

Screening and Surveillance for Barrett Esophagus in High-Risk Groups: A Cost–Utility Analysis

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Background: Once-in-a-lifetime screening for Barrett esophagus has been proposed for patients with gastroesophageal reflux disease (GERD), but there is little evidence of its cost-effectiveness.

Objective: 1) To determine the cost-effectiveness of screening high-risk groups for Barrett esophagus and providing surveillance to patients with Barrett esophagus and dysplasia or to all patients with Barrett esophagus and 2) to compare the results with the cost-effectiveness of no screening or surveillance.

Design: A decision analytic model was developed to examine no screening or surveillance and screening and surveillance for Barrett esophagus with dysplasia only or Barrett esophagus without dysplasia every 2 to 5 years. Low- or high-grade dysplasia received surveillance every 6 or 3 months, respectively.

Data Sources: Published literature and the Health Care Financing Administration.

Target Population: 50-year-old white men with symptoms of GERD.

Time Horizon: 50 years of age until 80 years of age or death.

Perspective: Third-party payer.

Outcome Measure: Incremental cost-effectiveness ratio.

Results of Base-Case Analysis: Screening with surveillance limited to patients with Barrett esophagus with dysplasia required \$10 440 per quality-adjusted life-year (QALY) saved compared to no screening or surveillance. The incremental cost-effectiveness ratio of surveillance every 5 years in patients with Barrett esophagus without dysplasia compared to surveillance of patients with Barrett esophagus with dysplasia was \$596 000 per QALY saved.

Results of Sensitivity Analysis: The annual incidence of adenocarcinoma must exceed 1 case per 54 patient-years of follow-up (1.9%) for surveillance of Barrett esophagus without dysplasia every 5 years to yield an incremental cost-effectiveness ratio less than \$50 000 per QALY saved.

Conclusions: Screening 50-year-old men with symptoms of GERD to detect adenocarcinoma associated with Barrett esophagus is probably cost-effective. However, subsequent surveillance of patients with Barrett esophagus but no dysplasia, even at 5-year intervals, is an expensive practice.

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Current guidelines from the American College of Gastroenterology recommend surveillance to detect cancer and dysplasia in patients with Barrett esophagus, a columnar-cell metaplasia that replaces the native squamous-cell epithelium of the distal esophagus (1). The costs and benefits of surveillance have been evaluated in retrospective studies (2–5) and formal decision analyses (6, 7). Barrett esophagus alone does not cause symptoms that would prompt endoscopic evaluation, and the question of whether screening strategies to detect Barrett esophagus are reasonable and, if so, in which patients is unresolved (8). Adding to the uncertainty is emerging evidence from prospective studies that the incidence of cancer in patients with Barrett esophagus may be considerably lower than previously reported (9, 10). In the absence of randomized, controlled trials of screening and surveillance in Barrett esophagus, the costs and benefits of strategies to decrease mortality rates from cancer are unknown.

We used decision analysis to determine whether current recommendations for screening of patients with gastroesophageal reflux disease (GERD) represent cost-effective care. The cohort that we modeled consisted of white men 50 years of age who have symptoms of GERD, because this group is at high risk on the basis of epidemiologic evidence demonstrating an increased risk for esophageal adenocarcinoma compared with other groups (11–14). Specifically, we examined strategies for screening patients

with symptoms of GERD for the presence of Barrett esophagus, dysplasia, or cancer and compared these strategies with no screening for Barrett esophagus. Secondary objectives were 1) to determine whether more benefit was provided by the initial screening examination or by subsequent surveillance, 2) to evaluate different intervals of surveillance in patients with Barrett esophagus, and 3) to identify clinical variables critical to the determination of cost-effectiveness.

METHODS

Patients

The hypothetical cohort consisted of white men 50 years of age who had symptoms consistent with GERD (heartburn or acid regurgitation). These patients were assumed not to have symptoms or signs that would otherwise prompt endoscopic evaluation (dysphagia, anemia, weight loss, or bleeding) and had not been previously screened for Barrett esophagus. The analysis assumed that Barrett esophagus was defined by salmon-colored mucosa of any length at endoscopy and intestinal metaplasia on histologic examination. Intestinal metaplasia of the gastroesophageal junction in the absence of endoscopic identification of Barrett esophagus was not examined. It was assumed that all patients modeled for participation in screening and surveillance would be surgical candidates for esophagectomy and would consent to undergo this operation if esophageal can-

cer was diagnosed. The analysis followed the cohort until 80 years of age or death.

Model

A decision analysis model was created by using DATA 4.0 software (TreeAge, Williamstown, Massachusetts). A Markov model was used to analyze patients with symptomatic GERD (15, 16). **Figure 1** shows a simplified outline of the structure of the Markov model. The actual model contains more than 7000 nodes (branch points) that encompass the natural history of patients with GERD compared to strategies of screening and surveillance for Barrett esophagus, dysplasia, and cancer. (The Appendix [available at www.annals.org] provides further information on model assumptions, including structure, transitions, utilities, and sensitivity analysis.)

Natural History

Costs and quality-adjusted life-years (QALYs) without screening and surveillance for Barrett esophagus and adenocarcinoma of the esophagus were examined. Cancer would be diagnosed only if symptoms (dysphagia, weight loss, bleeding, or pain) prompted endoscopic evaluation. Depending on the stage of cancer at the time of diagnosis, palliation (esophageal stent or chemoradiation) or surgical resection could be attempted. Patients with unresectable disease accrued costs of hospice or palliative care. Patients in whom resection was attempted could die after the procedure or survive. Patients who survived surgery could be cured of cancer or experience persistent or recurrent cancer, rates of which depended on the stage of cancer at diagnosis. Death from causes other than adenocarcinoma of the esophagus was incorporated in an age-dependent manner.

Screening and Surveillance

The natural history analysis was compared to screening with two surveillance strategies. Both strategies used screening endoscopy at 50 years of age and biopsy done to confirm Barrett esophagus if abnormalities were seen at endoscopy. Identification of adenocarcinoma by the initial screening examination prompted esophagectomy or palliation, depending on the stage of tumor. Palliation was associated with costs of endoscopic stenting or chemotherapy and radiation. Surgery could result in perisurgical death, persistent or recurrent cancer, or cure.

The first strategy limited surveillance to patients with Barrett esophagus with dysplasia at the initial examination. White men with symptoms of GERD would undergo screening endoscopy at 50 years of age; if Barrett esophagus without dysplasia or no Barrett esophagus was diagnosed, further surveillance would not be performed. Patients with Barrett esophagus with dysplasia would undergo surveillance endoscopy every 6 months for low-grade dysplasia or every 3 months for high-grade dysplasia as long as dysplasia was noted at least once during the preceding 12 months. Detection of cancer would prompt esophagectomy or palliation, depending on stage of disease at diagnosis.

Context

Barrett esophagus, a complication of gastroesophageal reflux disease (GERD), is associated with an increased risk for esophageal cancer. Some have proposed endoscopic screening for Barrett esophagus, followed by surveillance for cancer in patients with the disorder.

Contribution

The authors modeled the cost-effectiveness of screening 50-year-old white men with GERD. Screening followed by surveillance in patients with Barrett esophagus and dysplasia cost \$10 440 per quality-adjusted life-year (QALY). Surveillance of patients with Barrett esophagus but no dysplasia every 5 years would cost an additional \$596 000 per QALY.

Implications

One-time screening for Barrett esophagus in 50-year-old men with GERD is reasonably cost-effective if surveillance is limited.

—The Editors

The second strategy also evaluated screening of white men with symptoms of GERD at 50 years of age. Patients with Barrett esophagus with dysplasia underwent surveillance as in the first strategy; however, those with Barrett esophagus without dysplasia were separately modeled to undergo surveillance endoscopy at intervals of 2, 3, 4, or 5 years. If intestinal metaplasia was not found on two consecutive surveillance endoscopies, surveillance ceased. Cancer was managed as in the first strategy.

Endoscopy and biopsy was modeled to be an imperfect test: that is, false-positive and false-negative results would occur, thereby missing some cases of dysplasia or cancer and overdiagnosing other states. Procedure-related morbidity and mortality for surgery and endoscopy were included in the analysis. Adjustment for patient preferences for the various health states (utilities) was incorporated into the model. Differential rates of cure from cancer were assigned depending on the stage at diagnosis. Death from causes other than adenocarcinoma of the esophagus was incorporated in an age-dependent manner. All costs and benefits were discounted at 3% annually (0% to 5% annually in the sensitivity analysis).

Transitions

Transitions between health states of the Markov model were derived from the published literature. To assess key variables, the MEDLINE and EMBASE databases from 1970 to 2001 and abstracts from major gastroenterological scientific meetings from 1999 to 2001 were searched by using the terms *Barrett's esophagus*, *esophageal neoplasms*, *adenocarcinoma*, *precancerous conditions*, and *gastroesophageal reflux disease*. If no data existed for a specified transition, the authors reached consensus. In addition to

the base-case scenario, sensitivity analyses were performed using variations around each of the transitions supported by the literature (Table 1).

Costs and Utilities

Costs, not charges, were the basis for inputs used in this analysis. Costs included direct costs of care for delivery of services and were derived from published literature and 2001 data from the Health Care Financing Administration. Data on inpatient resource use from the Health Care Financing Administration were based on diagnosis-related groups and Current Procedural Terminology codes, whereas outpatient data were based on ambulatory payment classification and Current Procedural Terminology codes. Costs of endoscopy included biopsies and histologic interpretation.

Costs are shown in Table 1. A third-party insurer perspective was taken (58–60). Patient preferences for different health states (utilities) were derived from the published literature, and outcomes were adjusted to derive QALYs (6, 7). Utilities were derived from expert opinion by using a time-tradeoff technique (7) and from responses by patients who had undergone esophagectomy for high-grade dysplasia or cancer (6). Costs of time lost from work and support

required from family or friends and intangible losses due to pain and suffering were not incorporated.

Sensitivity Analysis

All assumptions for the model were varied over a wide range of values in a series of one-way sensitivity analyses. Published rates from the literature were used if available. In the absence of published data, baseline rates were halved and doubled with adjustment by consensus from the authors. Monte Carlo simulation was used to create a multi-way sensitivity analysis.

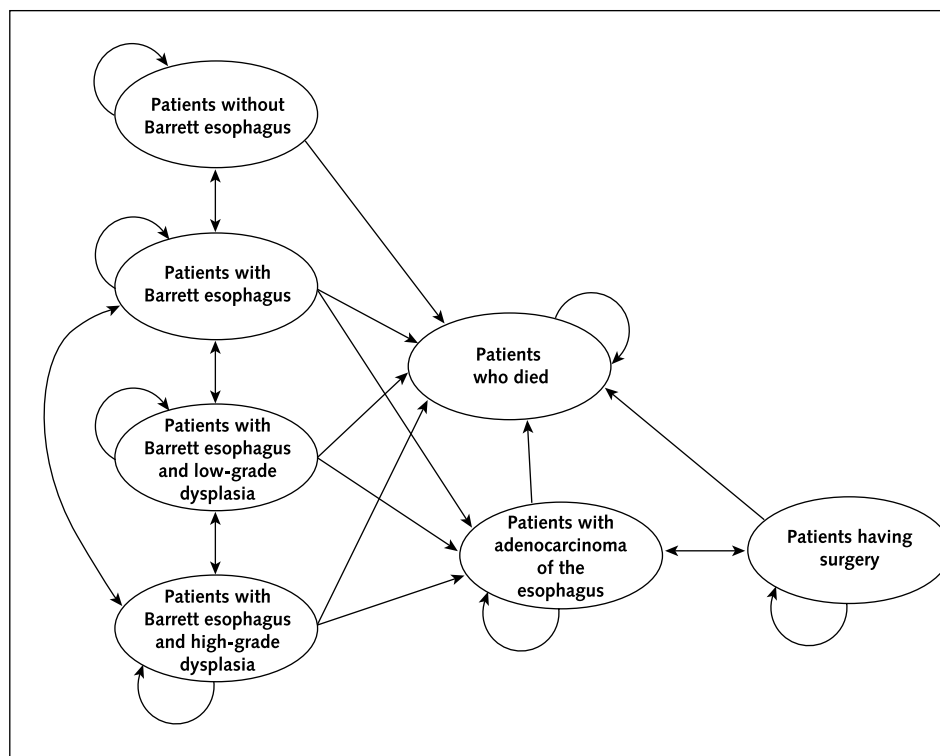
Surgery for High-Grade Dysplasia

In the base-case strategy, the diagnosis of high-grade dysplasia prompted the frequency of endoscopic surveillance to be increased to every 3 months; esophagectomy was performed only if cancer was detected. Sensitivity analysis incorporated a competing management strategy in which high-grade dysplasia diagnosed at screening or surveillance endoscopy was treated by esophagectomy.

Surveillance Intervals for Dysplasia

The base-case scenario modeled surveillance endoscopy with biopsy every 3 and 6 months for high-grade

Figure 1. Markov model.



Patients in this analysis can reside in seven major states: Patients without Barrett esophagus; patients with Barrett esophagus, without dysplasia or cancer; low-grade dysplasia, in which patients have Barrett esophagus and low-grade dysplasia; high-grade dysplasia, in which patients have Barrett esophagus and high-grade dysplasia; cancer, in which patients have adenocarcinoma of the esophagus; status after surgery, in which patients have undergone esophagectomy for adenocarcinoma of the esophagus; and death from adenocarcinoma of the esophagus, complications of surgery or endoscopy, or other causes. Because there may be errors in diagnosis, the first five states also contain substates that refer to the diagnosed state of the patients in addition to the actual health state. The arrows indicate the possible transitions from one state to another in each cycle. The base-case analysis examined the effect of esophagectomy for detection of cancer only, whereas sensitivity analysis examined esophagectomy for cancer or high-grade dysplasia.

Table 1. Model Assumptions

Variable	Value	Range	Reference
Prevalence			
Barrett esophagus	0.1	0.05–0.15	13, 17–21
Low-grade dysplasia	0.01	0.0054–0.012	17, 22–24
High-grade dysplasia	0.007	0.00036–0.01	9, 17, 22, 23, 25, 26
Cancer in Barrett esophagus	0.067	0.04–0.15	11, 14, 27–31
Annual rate of progression			
Development of Barrett esophagus	0.005	0.002–0.01	—*
No dysplasia to low-grade dysplasia	0.05	0.01–0.078	22–24, 27, 32
No dysplasia to high-grade dysplasia	0.01	0.0028–0.083	9, 22, 24, 26, 33
Low-grade dysplasia to high-grade dysplasia	0.05	0.01–0.074	22, 26, 30, 32
No dysplasia to cancer	0.005	0.001–0.01	30
Low-grade dysplasia to cancer	0.025	0.005–0.05	30
High-grade dysplasia to cancer	0.055	0.01–0.1	9, 22, 30, 34, 35
Incidence of cancer in Barrett esophagus	0.005	0.001–0.009	11, 22, 23, 26–30, 32, 35–37
Annual rate of regression			
Barrett esophagus to normal	0.0175	0.001–0.02	38
Low-grade dysplasia to no dysplasia	0.63	0.5–0.8	24, 26
High-grade dysplasia to no dysplasia	0.1	0.01–0.15	26, 34
High-grade dysplasia to low-grade dysplasia	0.07	0.05–0.1	9, 26, 34
Treatment of cancer			
Resectability			
Unscreened patients	0.5	0.1–0.7	39–41
Screened patients	0.95	0.85–1.0	18, 39, 41
Surgical mortality			
Unscreened patients	0.05	0.025–0.15	40, 42–44
Screened patients	0.027	0–0.1	42, 44–50
Cure of cancer			
Unscreened patients	0.2	0.1–0.43	39–41, 46, 51, 52
Screened patients	0.8	0.6–0.9	9, 39, 41, 45, 51–53
Death			
Unresectable cancer	0.9	0.8–1.0	—*
All other causes	Varies		54
Complications of endoscopy			
Death	0.000021	0–0.00005	55, 56
Other complication	0.0013	0–0.005	55, 56
Endoscopic and biopsy characteristics†			
Normal, Barrett esophagus	0.01	0.001–0.05	—*
Normal, low-grade dysplasia	0.005	0.001–0.01	—*
Normal, high-grade dysplasia	0.005	0.001–0.01	—*
No dysplasia, low-grade dysplasia	0.145	0.01–0.2	6, 7
No dysplasia, high-grade dysplasia	0.01	0–0.02	—*
No dysplasia, cancer	0.01	0–0.02	—*
Low-grade dysplasia, no dysplasia	0.175	0.01–0.2	6, 7
Low-grade dysplasia, high-grade dysplasia	0.083	0.01–0.1	6, 7
Low-grade dysplasia, cancer	0.05	0.01–0.1	—*
High-grade dysplasia, low-grade dysplasia	0.115	0.01–0.2	6, 7
High-grade dysplasia, cancer	0.11	0.01–0.2	6, 7
Cancer, low-grade dysplasia	0.05	0.01–0.1	6, 7
Cancer, high-grade dysplasia	0.175	0.01–0.2	6, 7
Utilities			
Cancer	0.5	0–1	—*
Postesophagectomy state	0.97	0.8–1.0	6, 7
Costs, \$			
Endoscopy with biopsies	830	350–1200	6, 7, 25, 57‡
Esophagectomy	19 000	8500–25 000	6, 25‡
Endoscopic palliation	2000	1000–5000	6, 7‡
Annual postsurgical care	1000	500–2000	6, 7‡
Care of incurable cancer	34 000	10 000–50 000	6, 7‡
Clinic visit	50	25–100	6, 7‡

* Authors' consensus.

† Information listed as actual state, diagnosed state.

‡ Data from the Health Care Financing Administration.

dysplasia and low-grade dysplasia, respectively. Less aggressive surveillance for dysplasia was also examined in a sensitivity analysis, lengthening surveillance to every 6 months for high-grade dysplasia and every 12 months for low-grade dysplasia.

Screening at a Younger Age

Screening of 40-year-old white U.S. men with symptoms of GERD was analyzed. The Appendix (available at www.annals.org) provides detailed information on the assumptions for the sensitivity analyses.

Outcomes

The primary outcome of the analysis was the incremental cost per QALY saved between competing strategies of management (incremental cost-effectiveness ratio). Additional outcomes reported include mean cost per patient, mean QALYs saved per patient, number of adenocarcinomas of the esophagus, deaths from cancer, and procedure-related deaths per 1000 patients in each of the strategies.

Role of the Funding Sources

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RESULTS

Natural History

The model was first tested without screening or surveillance to determine whether the results matched those of published data. With use of baseline assumptions, the annual incidence of adenocarcinoma of the esophagus among patients with Barrett esophagus was 541.9 per 100 000, corresponding to a rate of 1 case of cancer per 185 patient-years of follow-up. Without screening or surveillance, the base-case scenario yielded 37 cases of adenocarcinoma of the esophagus per 1000 patients. These cancers incurred to per-patient costs of \$104 and 16.466 QALYs.

Screening and Surveillance

The first strategy consisted of one-time screening at 50 years of age and performing surveillance only in patients with Barrett esophagus with dysplasia. This strategy cost \$1748 per patient, yielded 16.624 QALYs, and produced an incremental cost-effectiveness ratio of \$10 440 per QALY saved compared with no screening. Per 1000 patients, 17 deaths from cancer would be averted and 0.8 death would be incurred through endoscopic and surgical

procedures compared to no screening or surveillance (Table 2).

The second strategy, in which surveillance for Barrett esophagus without dysplasia was performed every 5 years, cost \$2053 per patient and yielded 16.624 QALYs. Per 1000 patients, this strategy estimated that 0.5 fewer cancer death but 0.12 more procedural death would occur compared to screening with surveillance limited to patients with Barrett esophagus with dysplasia. The incremental cost-effectiveness ratio of this strategy compared to surveillance limited to patients with Barrett esophagus with dysplasia was \$596 000 per QALY saved.

A benchmark value often used to identify medical interventions that society deems a worthwhile investment is \$50 000 per QALY saved. The incremental cost-effectiveness ratio of performing surveillance in patients with Barrett esophagus without dysplasia every 5 years remained greater than \$50 000 per QALY saved unless the incidence of adenocarcinoma among patients with Barrett esophagus exceeded 1 case per 54 patient-years of follow-up.

More frequent surveillance intervals for Barrett esophagus without dysplasia were associated with a small increase in QALYs (16.624, 16.625, and 16.626 for 4-year, 3-year, and 2-year intervals, respectively) but higher costs (\$2153, \$2309, and \$2587 per patient).

Figure 2 shows the costs and benefits of screening and different surveillance intervals compared to no surveillance. The incremental cost-effectiveness ratio for surveillance intervals more frequent than every 5 years was consistently greater than \$380 000 per QALY saved.

We also calculated the cost-effectiveness of each strategy compared with a common baseline of no screening or surveillance (Table 2). If withholding surveillance from patients with Barrett esophagus without dysplasia is an unacceptable strategy, surveillance every 5 years in this subgroup is associated with an incremental cost-effectiveness ratio of \$12 336 compared to no screening or surveillance.

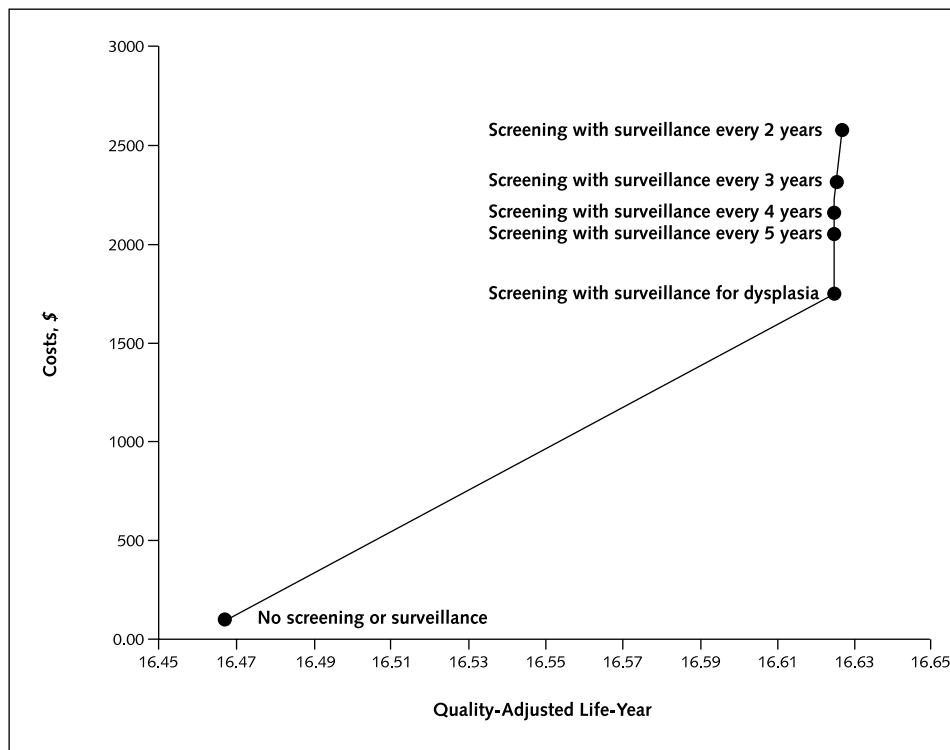
Table 2. Results of Screening Strategies*

Strategy	Per Patient with GERD				Per 1000 Patients with GERD		
	Cost	Quality-Adjusted Life-Years	Incremental Cost-Effectiveness Ratio	Cost-Effectiveness†	Cases of Cancer	Deaths from Cancer	Procedural Deaths
	\$			\$	← n →		
No screening or surveillance	104	16.466	–	–	36.6	35.5	0.08
Screening with surveillance							
Surveillance for patients with dysplasia only	1748	16.624	10 440	10 440	36.4	18.3	0.77
Surveillance for patients with no dysplasia							
Every 5 y	2053	16.624	596 184	12 336	35.1	17.8	0.89
Every 4 y	2153	16.624	383 860	12 946	34.7	17.6	0.93
Every 3 y	2309	16.625	381 543	13 894	34.1	17.4	0.98
Every 2 y	2587	16.626	414 233	15 579	33.2	17.1	1.06

* GERD = gastroesophageal reflux disease.

† Compared with no screening or surveillance.

Figure 2. Cost and benefit of screening and surveillance compared to no screening or surveillance.



Sensitivity Analyses

One-Way Sensitivity Analyses

Each variable in the model was subjected to a sensitivity analysis using the range in Table 1. Table 3 shows the results of one-way sensitivity analyses. The incremental cost-effectiveness ratio of screening with surveillance limited to Barrett esophagus with dysplasia compared to no screening or surveillance varied more than 25% for the following variables: probability of cure from cancer with esophagectomy, incidence of cancer in Barrett esophagus (specifically, the rate of progression from high-grade dysplasia to cancer), prevalence of Barrett esophagus and of cancer in the group studied, and the utility associated with the postesophagectomy state. The most influential variables included the prevalence of Barrett esophagus and the annual incidence of cancer among patients with Barrett esophagus. The incremental cost-effectiveness ratio for screening with surveillance limited to patients with dysplasia ranged from \$9000 to \$62 000 per QALY saved (prevalence of Barrett esophagus, 1% to 15%) compared with \$9000 to \$17 000 per QALY saved (1 case of cancer per 114 to 889 patient-years of follow-up) for no screening and surveillance.

Monte Carlo Analysis

All variables in the model were varied simultaneously by using Monte Carlo analysis consisting of 1000 simulations. Table 4 shows mean costs and QALYs. The propor-

tion of runs in which a more intensive surveillance strategy compared to a less expensive strategy achieved an incremental cost-effectiveness ratio less than \$50 000 per QALY saved, and the proportion with an incremental cost-effectiveness ratio less than \$100 000 per QALY saved, are reported. In 99% percent of simulations, the incremental cost-effectiveness ratio for screening with surveillance limited to dysplasia was less than \$50 000 per QALY saved compared to no screening and surveillance, whereas the incremental cost-effectiveness ratio was less than \$100 000 per QALY saved in all 1000 runs. Surveillance for Barrett esophagus without dysplasia required \$527 000 to \$672 000 per QALY saved, depending on the surveillance interval. The incremental cost-effectiveness ratio for these strategies was less than \$50 000 per QALY saved 0% to 2% of the time and was less than \$100 000 per QALY saved in only 7% to 13% of simulations.

Surgery for High-Grade Dysplasia and Cancer

The strategy in which esophagectomy was performed only when cancer was diagnosed dominated (that is, cost less and yielded more QALYs) the strategy in which esophagectomy was performed for both high-grade dysplasia and cancer. Threshold analysis revealed that the strategy using esophagectomy for both high-grade dysplasia and cancer yielded more QALYs if the annual incidence of cancer

among patients with Barrett esophagus exceeded 0.0075 (1 case of cancer per 133 patient-years of follow-up) and produced an incremental cost-effectiveness ratio less than \$50 000 per QALY saved only if the rate were greater than 0.0082 (1 case of cancer per 122 patient-years of follow-up).

Less Aggressive Surveillance for Dysplasia

Increasing the surveillance interval in patients with dysplasia to 6 months for high-grade dysplasia and 12 months for low-grade dysplasia improved the incremental cost-effectiveness ratio of screening with surveillance for dysplasia alone compared to no screening and surveillance to \$10 133 per QALY saved. However, this strategy yielded fewer QALYs (16.23) than did the base-case scenario. In addition, the incremental cost-effectiveness of

surveillance for Barrett esophagus without dysplasia increased to \$440 000 to \$1 500 000 per QALY saved, depending on the surveillance interval.

Screening at a Younger Age

Screening at 40 years of age instead of 50 years of age resulted in fewer incremental QALYs with screening and surveillance for Barrett esophagus with dysplasia compared to no screening and surveillance (0.07 QALY saved by screening at 40 years of age versus 0.16 QALY saved by screening at 50 years of age). The incremental cost-effectiveness ratio of providing screening with surveillance in Barrett esophagus with dysplasia increased to \$17 064 per QALY saved compared to no screening and surveillance.

Table 3. One-Way Sensitivity Analysis

Variable	Input		Incremental Cost-Effectiveness Ratio of Screening with Surveillance for Dysplasia, \$*
	Minimum	Maximum	
Cost, \$			
Terminal cancer	10 000	50 000	9956–10 763
Endoscopy with biopsies	350	1200	7369–12 807
Endoscopic palliation	1000	5000	10 439–10 443
After surgery	500	2000	9669–11 983
Surgery	8500	25 000	9023–11 250
Clinic visit	25	100	10 440–10 440
Discount rate	0.03	0.05	10 440–12 844
Annual probability			
Development of Barrett esophagus	0.002	0.01	10 437–10 444
No dysplasia to low-grade dysplasia	0.01	0.078	10 197–10 867
No dysplasia to high-grade dysplasia	0.0028	0.083	8724–10 760
No dysplasia to cancer	0.001	0.01	9355–12 211
Low-grade dysplasia to high-grade dysplasia	0.01	0.074	10 430–10 458
Low-grade dysplasia to cancer	0.01	0.05	10 075–10 781
High-grade dysplasia to cancer	0.01	0.1	8536–16 728
Resolution of Barrett esophagus	0.001	0.02	10 210–10 475
Low-grade dysplasia to no dysplasia	0.5	0.8	10 399–10 479
High-grade dysplasia to no dysplasia	0.01	0.15	10 078–10 553
High-grade dysplasia to low-grade dysplasia	0.05	0.1	10 390–10 503
Prevalence			
Barrett esophagus	0.01	0.15	8663–61 602
Cancer	0.004	0.015	8016–11 894
High-grade dysplasia	0.00036	0.01	10 435–10 453
Low-grade dysplasia	0.0054	0.012	10 235–10 529
Cure of cancer			
Without screening	0.1	0.43	10 349–10 656
With screening	0.6	0.9	9009–14 823
Diagnosis of cancer			
Without screening	0	0.5	8197–11 006
With screening	0.7	1	10 162–11 114
Death			
From cancer	0.8	1	10 354–10 546
From endoscopy	0	0.00005	10 392–10 507
Surgery without screening	0.025	0.15	10 439–10 444
Surgery with screening	0	0.1	10 080–11 584
Surgical resectability			
Without screening	0.1	0.7	10 386–10 467
With screening	0.85	0.99	9991–11 758
Sensitivity of endoscopy to detect Barrett esophagus	0.8	1	10 188–10 598
Utility			
Cancer	0	1	10 336–10 546
Postesophagectomy state	0.8	1	9978–14 151

* Compared with no screening or surveillance.

Table 4. Monte Carlo Analysis*

Strategy	Mean Cost	Mean QALY	Mean ICER	ICER†	
				ICER < \$50 000	ICER < \$100 000
	\$		\$	%	
No screening	242	16.418	–		
Screening with surveillance					
Surveillance for patients with dysplasia	1827	16.586	9400	99	100
Surveillance for patients with no dysplasia					
Every 5 y	2230	16.587	672 000	0	7
Every 4 y	2364	16.587	670 000	1	12
Every 3 y	2559	16.587	650 000	2	13
Every 2 y	2875	16.588	527 000	1	11

* ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
 † Proportion of Monte Carlo simulations that achieved an ICER < \$50 000 or < \$100 000 per QALY saved.

DISCUSSION

This study demonstrates the potential benefit of strategies of screening and surveillance for Barrett esophagus and associated adenocarcinoma of the esophagus among white men with symptoms of GERD. Performing a single screening examination at 50 years of age and limiting surveillance to patients with Barrett esophagus with dysplasia is associated with an incremental cost-effectiveness ratio of \$10 440 compared to no screening or surveillance. Surveillance for patients with Barrett esophagus without dysplasia may increase the total number of QALYs saved but is expensive (\$300 000 to \$600 000 per QALY saved). The majority of benefit provided by any strategy stems from the initial screening examination to detect asymptomatic cancers and subsequent surveillance for patients with dysplasia. Surveillance for high-grade dysplasia dominates esophagectomy unless the incidence of cancer in Barrett esophagus is greater than 1 per 122 to 133 patient-years of follow-up. The analysis is sensitive to the prevalence of Barrett esophagus and adenocarcinoma of the esophagus at the time when screening is performed, the incidence of cancer among patients with Barrett esophagus, the proportion of cases cured by early detection of cancer through screening and surveillance, and the utility experience by patients in whom esophagectomy is performed.

Decision analysis has been used to examine strategies aimed at decreasing the rate of death from adenocarcinoma of the esophagus. The published studies have limited analysis to screening of symptomatic patients with GERD or surveillance in patients with established Barrett esophagus. Soni and colleagues (25) examined screening alone at 60 years of age in patients with GERD; esophagectomy was performed in those with high-grade dysplasia or cancer. Screening was shown to be cost-effective compared with no screening, requiring \$24 700 per life-year saved, although surveillance of patients with Barrett esophagus was not addressed. In two studies, Provenzale and associates found that a 5-year surveillance interval dominated surveillance intervals of 1 to 4 years for patients with Barrett esophagus without dysplasia (6, 7).

Our study differs from previously published studies in that we examined screening and surveillance simultaneously. Simultaneous evaluation allows comparison of the cost and benefit of screening for prevalent cancers with that of surveillance for incident cancers. Our findings show that the benefit accrued from screening is greater than that of surveillance, since the prevalence of adenocarcinoma of the esophagus in patients presenting for endoscopy with symptoms of GERD is greater than the subsequent annual incidence of cancer in patients with identified Barrett esophagus. An additional difference is that previous studies had cancer progress through a sequence of low-grade, then high-grade, dysplasia, whereas we allowed cancer to develop from diagnosed states of Barrett esophagus with low-grade dysplasia or no dysplasia. Finally, esophagectomy for high-grade dysplasia was previously considered the standard of care; however, recent evidence suggests that continued surveillance in this subgroup may be a valid option, as modeled in our study (9).

Our results demonstrate that unless incremental cost-effectiveness ratios between competing strategies are calculated, each screening strategy appears to be cost-effective compared to no screening or surveillance. The inclusion of a strategy in which surveillance was limited to patients with dysplasia shows that early detection of prevalent cancers provides the majority of benefit. Continued surveillance of patients with Barrett esophagus without dysplasia offers relatively little benefit because of the low incidence of esophageal adenocarcinoma.

The results of sensitivity analysis highlight areas that require further clinical research. These areas include identifying groups at risk for Barrett esophagus and adenocarcinoma of the esophagus, determining the risk for cancer among patients with Barrett esophagus, decreasing the cost of screening and surveillance programs by use of physician extenders or less expensive methods of office-based endoscopy (33), and defining the effect of various health states (for example, diagnosis of Barrett esophagus with and without dysplasia and the postesophagectomy state) on quality of life. Symptoms of GERD may not be the most

sensitive marker of Barrett esophagus (13, 14, 17, 18). The duration, severity, and frequency of GERD symptoms are strongly associated with the development of adenocarcinoma of the esophagus. However, up to 40% of patients who have cancer do not report having had frequent symptoms of heartburn for at least 1 year, when measured more than 5 years before the diagnosis of adenocarcinoma (12). Thus, although the presence of GERD symptoms identifies a group of patients at higher risk for cancer, the absence of symptoms does not eliminate the risk. Nonetheless, our data suggest that a strategy using screening endoscopy in white men with symptoms of GERD may be cost-effective to reduce mortality from esophageal adenocarcinoma.

Our findings highlight the low rate of progression to cancer in patients with established Barrett esophagus. Although some studies report an incidence as high as 1 case of cancer per 56 to 72 patient-years of follow-up (22, 26, 35), larger studies have shown a considerably lower incidence, even in patients in whom high-grade dysplasia has been diagnosed (9, 11, 23, 27–29, 32, 36). Emerging evidence indicates that publication bias is a potential source of the previously reported high risk for cancer among patients with Barrett esophagus (10). Further clinical data on the progression of high-grade dysplasia to adenocarcinoma in Barrett esophagus are needed to clarify decision making about surgery. The ability to identify groups at high risk for progression is essential to improve the cost-effectiveness of surveillance. Both the initial prevalence of cancer and subsequent incidence in patients with Barrett esophagus could greatly vary the cost-effectiveness of surveillance.

The issue of screening patients for Barrett esophagus (“once-in-a-lifetime endoscopy”) remains contentious. We found that even at a low prevalence of cancer, the benefit of an initial screening examination may be worth the cost compared with no screening (\$10 440 per QALY gained). This strategy is inexpensive because only one examination is required in the majority of patients, surveillance is limited to those at the highest risk for cancer, and the disadvantages associated with discounting are limited owing to the close proximity of intervention and benefit. However, the incremental cost-effectiveness ratio of providing surveillance even at intervals of 5 years in patients without dysplasia may be prohibitive (>\$500 000 per QALY gained). The presence of Barrett esophagus does not appear to detract from quality of life, as measured by generic instruments (61); however, patient preferences (utilities) for management have not been assessed. To resolve this issue, the utility associated with a diagnosis of Barrett esophagus should be defined so that the potential negative effect of having this disease diagnosed may be incorporated in future analyses. If withholding surveillance in patients with Barrett esophagus without dysplasia is unacceptable because of the utility impairment of living with Barrett esophagus or medicolegal issues, surveillance in this subgroup should be performed no more often than every 5 years.

In conclusion, our study confirms that among 50-year-old men with symptoms of GERD, one-time screening endoscopy for Barrett esophagus and adenocarcinoma of the esophagus is probably cost-effective. However, surveillance for Barrett esophagus without dysplasia, especially strategies involving intervals more frequent than 5 years, is associated with incremental cost-effectiveness ratios that are much higher than those of other accepted medical interventions. Future research should be directed toward identifying groups at high risk for Barrett esophagus and adenocarcinoma of the esophagus and subgroups of patients with Barrett esophagus in whom progression to cancer is likely, as well as defining the effect of Barrett esophagus and the postesophagectomy state on quality of life.

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APPENDIX

Model Assumptions

In a Markov model, a mathematical simulation in which patients move among various states of health and disease over time (15, 16), each health state (for example, healthy, Barrett esophagus without dysplasia, or cancer) is associated with a different set of costs and benefits, such as life-years. Utilities, or patient preferences for the various health states, are used to adjust the benefit of certain health states, such as adenocarcinoma, to reflect the fact that these states are less desirable than other states. The results of the model are reported as a cost–utility analysis to recognize this adjustment of benefit and are expressed as cost per quality-adjusted life-year (QALY). The proportion of the cohort residing in any one state is governed by the transitions into and out of that state, which may remain constant (Markov chain) or vary with time (Markov process). The model used variables to specify transitions between health states, the diagnostic accuracy of endoscopy and biopsy, costs, and patient preferences (utilities).

Table 1 shows the values for the base-case analysis and range used in the sensitivity analysis. The manner in which these variables are used in the model is described below.

Transitions

The initial conditions of the model were set by prevalence of each health state at the time that the study population was first evaluated (50 years of age in the base-case scenario). At that time, the sample was distributed into the states of no Barrett esophagus, Barrett esophagus without dysplasia, Barrett esophagus with low-grade dysplasia, Barrett esophagus with high-grade dysplasia,

adenocarcinoma, status after esophagectomy, or dead. At the end of each cycle of the model (1 year), the sample was redistributed among the various health states on the basis of the rate of change between one state to another. Patients could progress from no dysplasia to low-grade dysplasia, high-grade dysplasia, or cancer. Serial progression from low-grade dysplasia to high-grade dysplasia to cancer was not required; cancer could develop directly from low-grade dysplasia, high-grade dysplasia, or no dysplasia. In addition, patients could regress from high-grade dysplasia to low-grade dysplasia or no dysplasia, or from low-grade dysplasia to no dysplasia (Figure 1). The individual transitions were used to construct an overall transition to cancer among patients with Barrett esophagus. Because this overall transition was derived from multiple studies, the model was validated by running a simulation in which no screening or surveillance was performed and comparing the results with those in published literature. Inclusion of the individual transitions between states of Barrett esophagus with and without dysplasia and cancer allowed full use of the available data from previous studies. Moreover, it provided a framework by which management decisions could be stratified by presence or absence of dysplasia.

Efficacy of Surveillance To Decrease Mortality from Esophageal Adenocarcinoma

Although no randomized, controlled trials comparing surveillance with no surveillance in patients with Barrett esophagus have been reported, several retrospective series have been published. These studies consistently demonstrate substantial benefit from performance of endoscopy in terms of stage of tumor at the time of diagnosis and survival (39, 41, 51, 52). The proportion of patients in whom resection is attempted, the surgical mortality rate, and the proportion of patients in whom esophagectomy is curative in this model were derived from these data.

Diagnostic Error

Incorporation of the sensitivity and specificity of endoscopy with biopsy and histological interpretation allowed separation of the outcome, based on the actual health state, and costs of management, based on the diagnosed health state. Performance of endoscopy could detect the actual health state of a patient or lead to an incorrect diagnosis in which management would be based on the diagnosed health state. Transitions were also modeled to occur in the absence of endoscopy and thus could occur without detection, leaving management to be based on the last diagnosed health state. Multiple endoscopies with biopsies within a given cycle increased the probability that the actual health state would be detected but also increased the risk for complications of endoscopy. Diagnostic characteristics of endoscopy with biopsy were obtained from published literature (6, 7).

Utilities

The outcome of the analysis was expressed as a cost–utility (cost per QALY saved with one strategy compared to another). This was done to reflect the supposition that certain health states are preferred over others. Two studies have reported patient preferences (utilities) for the postesophagectomy state; none have reported utilities for the state of cancer itself. One study based the utility of the postesophagectomy state on the consensus of expert

physicians caring for patients with esophageal cancer (7), whereas another used responses from patients who had undergone esophagectomy for Barrett esophagus with high-grade dysplasia or cancer through a time–trade-off exercise (6). The lower bound for the postesophagectomy utility in the sensitivity analysis was based on the physician-based assessment; the baseline case used the patient-derived estimate; and the upper bound used a utility of 1.0, or perfect health.

Sensitivity Analyses

Monte Carlo Simulation

The distribution and expected value of variables are specified in a Monte Carlo analysis. The distribution may be parametric or nonparametric. In this study, the cost data were skewed; we therefore defined them to conform to a “triangular” distribution in which the minimum, maximum, and modal values were programmed. All other variables, including prevalence, incidence, and the diagnostic accuracy of endoscopy with biopsy, were defined to be normally distributed. Over the course of multiple runs, values for each variable were randomly selected from the distribution specified, and every variable was simultaneously varied within the model. The output of the analysis contained details of each simulation and summary of the costs and outcomes. The results included the mean cost, outcome (expressed as QALYs), and the incremental cost-effectiveness of providing the next more intensive surveillance strategy.

Since incremental cost-effectiveness ratios are not calculable in the case of a dominant strategy (one that is more effective and less costly), standard deviations may be misleading owing to the skewed nature of the results. Therefore, a “confidence interval” consisting of the proportion of simulations whose outcomes were within a certain range was calculated. Specifically, the proportion of simulations in which the incremental cost-effectiveness ratio of

the next more intensive surveillance strategy was \$1 to \$50 000 per QALY saved and the proportion in which the incremental cost-effectiveness ratio was \$1 to \$100 000 per QALY saved were reported.

Surgery for High-Grade Dysplasia

The model was modified to allow esophagectomy to be performed for a diagnosis of high-grade dysplasia in addition to diagnosis of cancer. The remainder of transitions, costs, and utilities were unchanged from the base-case scenario. An erroneous diagnosis of high-grade dysplasia or cancer (that is, low-grade dysplasia or no dysplasia was actually present) would result in esophagectomy, thereby incurring unnecessary costs and potential morbidity or mortality.

Less Aggressive Surveillance for Dysplasia

The model was altered to provide surveillance endoscopy with biopsy every 6 months for a diagnosis of high-grade dysplasia and every 12 months for a diagnosis of low-grade dysplasia (as opposed to 3 and 6 months, respectively, used in the base case). All other variable inputs remained constant with respect to the base-case analysis.

Screening at a Younger Age

Previous studies have found a lower prevalence of esophageal cancer in patients younger than 50 years of age (62, 63). We used a prevalence of 0.007 in our sensitivity analysis. In addition, no published studies have effectively examined the effect of age at diagnosis of Barrett esophagus on the incidence of cancer. Thus, we modeled the incidence of cancer in our sensitivity analysis to vary with the duration of disease.