
Barrett's Esophagus: A New Look at Surveillance Based on Emerging Estimates of Cancer Risk

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OBJECTIVE: Surveillance of Barrett's patients is recommended, to detect dysplasia and early cancer. The reported risk for developing cancer varies substantially, however. Our previous analysis used an average cancer incidence of 1/75 patient-years (PY). Recent reports suggest that the risk may range from 1/251 to 1/208 PY in combined series of patients with long segment Barrett's esophagus (LSBE, >3 cm), and short segment Barrett's esophagus (SSBE), and up to 1% annually in patients with SSBE. Our goal was to consider these new estimates of cancer risk in a cost-utility analysis of surveillance of patients with Barrett's esophagus.

METHODS: Using our previously published model, we incorporated an average of the recent estimates of cancer risk (0.4% annually, 1/227 PY), and our primary data on quality of life after esophagectomy. We included actual variable (direct) costs and used a discount rate of 5%. From the perspective of an HMO, the model evaluates surveillance every 1-5 yr and no surveillance, with esophagectomy performed if high grade dysplasia is diagnosed, and calculates the incremental cost-utility ratios for each strategy.

RESULTS: The results suggest that, at our baseline, annual cancer risk surveillance every 5 yr is the only viable strategy. More frequent surveillance costs more and yields a lower life expectancy. The incremental cost-utility ratio for surveillance every 5 yr is \$98,000/quality-adjusted life year (QALY) gained, comparable to the incremental cost-effectiveness ratios of accepted practices (heart transplantation and screening for tuberculosis in selected populations, \$160,000/LY gained and \$216,000/LY gained, respectively).

CONCLUSIONS: Surveillance of Barrett's patients should extend life, with incremental cost-utility ratios that compare favorably with some accepted medical practices. Policy makers can compare the cost of surveillance to that of other accepted practices to determine their willingness to fund surveillance.

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INTRODUCTION

Barrett's esophagus, occurring in at least 700,000 adults in the United States (1, 2, 3) is a sequela of chronic gastroesophageal reflux. Patients with Barrett's esophagus are at increased risk for the development of esophageal adenocarcinoma. The estimated annual risk for adenocarcinoma ranges from 0.2% to 2.0% (3, 4, 5, 6, 7, 8, 9) (1/441-1/52 patient-years), a risk that is 30-125 times that of an age-matched population (3, 4, 5, 6, 7, 8, 9, 10). Once symptomatic carcinoma is diagnosed, the prognosis is

poor, with a 5-yr survival of approximately 17% after complete resection of tumor and of <1% for unresectable tumors (11, 12, 13, 14, 15, 16, 17). Because of this cancer risk, periodic endoscopic surveillance with biopsy has been recommended to detect dysplasia and early carcinoma (2, 18, 19). Most authorities recommend esophagectomy for high grade dysplasia.

Because there are no controlled trials that examine the efficacy of surveillance and subsequent esophagectomy for dysplasia or cancer, and because a randomized trial would be impractical (requiring thousands of patients with long periods of follow-up), we previously performed a cost-utility analysis comparing surveillance to no surveillance. We used a Markov model (20) and constructed a computer cohort simulation of 10,000 hypothetical 55-yr-old men with Barrett's esophagus (the mean age of patients diagnosed with Barrett's esophagus) (21). The model compared no surveillance to surveillance with biopsy every 1-5 yr, and considered both high grade dysplasia and cancer as indications for esophagectomy. Strategies in which esophagectomy was deferred for the development of cancer were inferior, costing more and yielding a lower life expectancy. Our results suggested that surveillance every 4 yr would provide the greatest gain in quality-adjusted life expectancy, with an incremental cost-utility ratio of \$276,700 quality-adjusted life year (QALY) gained. Surveillance every 5 yr also increased life expectancy, and had an incremental cost-utility ratio of \$27,400 (22), which compares favorably with the incremental cost-effectiveness ratios of other common medical practices such as mammography screening for breast cancer (\$22,000 per life year gained) (23). Our cost-utility analysis identified two parameters as critical for decisions about surveillance: the incidence of cancer and the quality of life after esophagectomy. In this article, we incorporate current estimates of cancer risk and the results of our quality of life measurements in patients with a history of Barrett's esophagus who have undergone esophagectomy. In addition, we consider the effects of surveillance on a cohort of patients with short-segment (<3 cm) Barrett's esophagus (SSBE). The cancer risk in this group has been reported to be as high as 1% (24) annually, within the range of reported values for patients with long segment Barrett's esophagus (>3 cm) (LSBE). However, the few reports on the cancer incidence in this group are limited by small numbers of patients who actually develop cancer and by short periods of follow-up. Because there is a great deal of uncertainty surrounding the cancer risk, particularly in SSBE patients, we examine the effects of varying this risk on decisions for surveillance and esophagectomy.

MATERIALS AND METHODS

We modified our previously published Markov (20) model. A Markov model is a mathematical model used to estimate life expectancy in medical applications. It is particularly useful for modeling clinical situations involving repeated risks over time, such as the annual risk for developing adenocarcinoma in patients with Barrett's esophagus. We developed a computer cohort simulation of 10,000 hypothetical 55-yr-old patients with Barrett's esophagus and no evidence of dysplasia by biopsy (22).

Structure of the Analysis

We considered six strategies for this cohort (Table 1). No endoscopic surveillance, but endoscopy is performed for the development of new or worsened dysphagia. Esophagectomy is performed only if cancer is diagnosed. The surveillance strategies involve endoscopic surveillance every 1-5 yr with biopsies. Esophagectomy is performed if high grade dysplasia is diagnosed.

Table 1. Strategies

No surveillance

No surveillance: esophagectomy for cancer

Surveillance

Surveillance every 5 yr: esophagectomy for high grade dysplasia

Surveillance every 4 yr: esophagectomy for high grade dysplasia

Surveillance every 3 yr: esophagectomy for high grade dysplasia

Surveillance every 2 yr: esophagectomy for high grade dysplasia

Surveillance every 1 yr: esophagectomy for high grade dysplasia

Strategies that defer esophagectomy for the development of cancer were not included in this analysis because our previous results suggested that they cost more and yield a lower life expectancy than strategies in which esophagectomy was performed for the development of high grade dysplasia (22). The simulation begins 1 yr after a baseline endoscopic biopsy demonstrates Barrett's esophagus but no dysplasia. The model assumes that cancer develops as a progression from Barrett's esophagus to low grade dysplasia, then to high grade dysplasia, and finally to cancer. Over time, patients with Barrett's esophagus and no evidence of dysplasia may remain in this health state or may progress toward cancer. They may move to a low grade dysplasia state, then to a high grade dysplasia state, and finally to a cancer state, or they may die (Table 2). The model also includes long term postsurgical states for the prognosis of patients after surgery (Table 2). The likelihood of entering each of these states, for each year, depends on annual transition probabilities derived from published literature (5, 6, 19). All patients diagnosed with low grade dysplasia undergo endoscopy and biopsy every 6 months. Patients diagnosed with high grade dysplasia who are surgical candidates at the time of diagnosis undergo esophagectomy.

Table 2. Markov States of Health

Biological conditions	Barrett's esophagus Low grade dysplasia High grade dysplasia Cancer
Biopsy results*	Barrett's esophagus Low grade dysplasia High grade dysplasia Cancer
Postsurgical states (long term)	No biopsy performed Complete resection of dysplasia Complete resection of cancer Partial resection of cancer
Inoperable state	Cancer but inoperable because of other illness
Dead state	

* Our model considers that endoscopy is not a perfect test. Patients may be underdiagnosed or overdiagnosed because of sampling error by the endoscopist or misinterpretation by the pathologist. Our model includes states of health that combine the true biological condition of the patient's esophageal mucosa with the histology reported from the endoscopic biopsy. A biopsy in patients with low grade dysplasia as their true biological condition may be interpreted as Barrett's mucosa in those who are underdiagnosed by endoscopy, as low grade dysplasia in those who are correctly diagnosed, or as high grade dysplasia or cancer in those who are overdiagnosed by endoscopy. Patients who do not undergo surveillance will not have a biopsy unless they become symptomatic and, therefore, their true biological condition may remain undetected until a biopsy is performed.

Data

We incorporated an average annual incidence of cancer of 0.4% (1/227 PY) based on recent reports in patients with Barrett's esophagus (SSBE and LSBE) (25, 26). In separate analyses, we consider the cancer risk of patients with SSBE. We incorporated the published value of 1% annually (1/104/PY) (24) to reflect literature reports. The other (noncost) parameters used in the model have been published earlier (22) and are shown in Table 3. Estimates were obtained from published reports. When published data were not available, we consulted experts in the field to obtain estimates. The assumptions underlying this model have been published in our earlier report (22).

Long-term Morbidity Post-esophagectomy

To measure the quality of life after esophagectomy, we performed a utility assessment of patients who had undergone esophagectomy for high grade dysplasia or cancer at Duke University. We evaluated patients who had undergone surgery ≥ 1 yr earlier. Utility assessment measures patient preferences for

health states and relates them to death. The time trade-off (TTO) (27), a typical utility measure, asks the respondent to choose between living a longer (time t) in a less healthy state (state i) or living a shorter period of time (time x) in a perfect or excellent state of health. Preference values are derived implicitly, based on individual responses to decision situations, e.g., "Would you rather live 10 years with an esophagectomy or 5 years in perfect health?" The time in the state of perfect health (time x) is varied until the respondent is indifferent between the two alternatives. At the point of indifference, h_i (preference value for state i) = x (time in perfect health) \div t (time in state i, the less healthy state). For example, if the individual believes that living 10 yr with an esophagectomy is equivalent to living 5 yr in perfect health, the TTO (27) score is 5/10 or 0.5. A score of 0 equates having an esophagectomy to being dead, whereas a score of 1 equates esophagectomy to a state of perfect health. The median quality of life for this group was 0.97 (interquartile range 25-75%, 0.83-1.0). We incorporated this value into our analysis as our baseline estimate of quality of life after esophagectomy. In sensitivity analysis, we varied this parameter from 0 (equivalent to being dead) to 1 (equivalent to a state of perfect health).

Costs

Our model used costs and not charges (28). Actual variable costs for endoscopic and surgical procedures and costs for inpatient postoperative care were obtained from the Transition System I: Clinical Cost Manager (Transition Systems, Boston, MA) at Duke University Medical Center (Table 3). As a proxy for costs, outpatient visits and physicians fees (charges) were adjusted to reflect actual reimbursement at Duke University (Table 3). Costs for terminal cancer care were obtained from hospice fees in North Carolina (Table 3).

TABLE 3

Natural History	Sources
On average, the incidence of adenocarcinoma in patients with Barrett's esophagus is 0.4%/yr (1/227 patient-yr).	(25, 26)
On average, the time period from endoscopically detectable esophageal cancer to symptomatic cancer is 4-5 yr.	(38)
Test Characteristics	
The following represent the accuracy (see Table 2) of endoscopic biopsy and pathologist's interpretation for detecting Barrett's mucosa, low grade dysplasia, high grade dysplasia, and cancer.	
The true biological condition of the mucosa is listed first, on the left, and the biopsy results are listed on the right.	
<i>False-negative rates</i>	
Biological Condition	Biopsy Results
Barrett's mucosa	Normal mucosa 12.5% *
Low grade dysplasia	Barrett's mucosa 17.5% *
High grade dysplasia	Low grade dysplasia 11.5% *
Cancer	High grade dysplasia 17.5% *
<i>False-positive rates</i>	
Normal mucosa	Barrett's mucosa 7.5%
Barrett's mucosa	Low grade dysplasia 14.5% *
Low grade dysplasia	High grade dysplasia 8.3% *
High grade dysplasia	Cancer 11.0% *
Endoscopic and Surgical Procedures	
Endoscopy	
Complications (perforation, respiratory arrest, myocardial infarction)	13/10,000 procedures (39)
Mortality (perforation not requiring surgery, respiratory arrest, myocardial infarction)	0.21/10,000 procedures (32)
Perforation requiring surgery	1.6/10,000 procedures (37)

Biological Condition	Biopsy Results	*
Surgical mortality		
Repair of esophageal perforation		
Cancer	19%	(40)
No cancer	9.5%	(40)
Elective esophagectomy (symptomatic cancer)	9.5%	(11, 12, 13, 14, 15, 16, 17)
Mortality From Esophageal Cancer		
Probability of complete resection of esophageal cancer		
Cancer detected by surveillance	75%	(11, 12, 13, 14, 15, 16, 17, 38, 40)
Cancer detected when symptomatic	49%	(11, 12, 13, 14, 15, 16, 17, 36)
Effectiveness of surveillance in reducing death from esophageal cancer	78%	(11, 12, 13, 14, 15, 16, 17, 38, 40)
Short- and Long-Term Morbidity		
Short term		
Endoscopy	-1 day	†
Endoscopy with complication	-1 wk	(41)
Elective surgery	-2 wk	(41)
Emergency surgery	-4 wk	(41)
Long term		
Quality adjustment for esophagectomy	0.97	‡
Costs		
Endoscopy	\$600	§
Endoscopy with complication	\$3,700	§
Esophagectomy	\$23,800	§
Perforation requiring surgery:		
Cancer	\$23,900	§
No cancer	\$7,700	§
Annual follow-up-postesophagectomy	\$1,000	§
Costs for terminal care of the patient with esophageal cancer:		
Gastrostomy tube	\$700-1200	§
Hospice care/yr	\$34,000	

* Antonioli DA, Upton MP (personal communication).

† Expert opinion.

‡ Time trade-off (TTO).

§ Actual variable costs, fees—Duke University Medical Center (Clinical Cost Manager), adjusted to 1995 dollars.

|| Estimates from hospice charges, North Carolina, 1996.

Analysis

We took the perspective of an HMO in our analysis and calculated the average lifetime cost per patient in each strategy, and the incremental cost-utility ratio. The incremental cost-utility ratio calculates the additional cost to obtain additional benefit in terms of quality-adjusted life years gained. Policy makers can use these ratios to compare the cost-effectiveness of surveillance of patients with Barrett's esophagus to that of other common medical practices.

The costs of a surveillance program typically occur early, in terms of procedures, complications, and surgery for dysplasia. The benefits of increased length of life occur years in the future. To adjust for this differential timing of outcomes, we employed the technique of "discounting" future costs and benefits, using standard discounting formulas from economics. Discounting considers that a dollar spent today is worth more than a dollar spent in the future. Because life years are valued relative to dollars, they are

also discounted. Discounting permits calculation of the present value of both costs and health consequences (29). Thus, it effectively biases against surveillance in which the cost and the risk of procedures and surgery occur early on, whereas benefits accrue far in the future. Most economic analyses include discount rates that range from 3% to 6%. We used 5% in our base case analysis so that we might compare our results with other published analyses. To conform to recent recommendations (30), however, we also performed an analysis using the recommended 3% rate (see Appendix 1).

Appendix 1 (Discount Rate 3%)

Strategy	Average Cost (\$)	Average Gain in Quality-Adjusted Life Expectance (yr)	Incremental Cost-Utility* Ratio Dollars/Quality-Adjusted Life Years Gained
No surveillance	5,651	15.59	†
Surveillance every 5 yr	18,627	15.78	69,861
Surveillance every 4 yr	20,223	15.77	‡
Surveillance every 3 yr	22,338	15.76	‡
Surveillance every 2 yr	25,353	15.75	‡
Surveillance every 1 yr	30,085	15.70	‡

Difference caused by rounding.

† Baseline strategy.

‡ Dominated—costs more, yet yields a lower life expectancy.

RESULTS

The results for both long and short segment patients with Barrett's esophagus (SSBE and LSBE) are shown in Figure 1. Each of the circles represents the results for a particular strategy. On the bottom left, no surveillance costs \$4,100 and provides 12.64 discounted yr of life. Moving to the right, surveillance every 5 yr costs \$13,900 and provides 12.74 yr of life. Thus, surveillance every 5 yr increases life expectancy by 0.10 yr at an additional cost of \$9,800. The incremental cost-utility ratio for this strategy is calculated by dividing the additional cost by the increase in quality-adjusted life expectancy ($\$9,800 \div 0.10 \text{ yr} = \$98,000$ per additional life year gained) and is shown on the top of the line connecting the two strategies (Fig. 1).

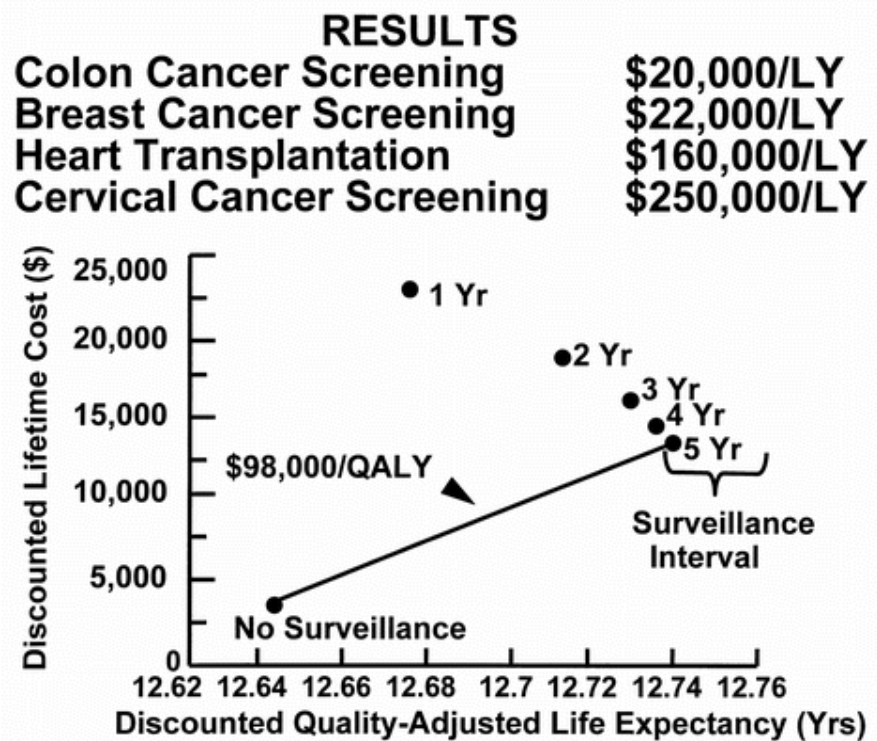


Figure 1. Cost-utility analysis (annual incidence of cancer 0.4%, discount rate 5%). Average discounted lifetime cost per patient and discounted quality-adjusted life years (QALY) for each strategy. The horizontal axis displays discounted quality-adjusted life expectancy in years, and the vertical axis displays the average lifetime cost per patient (discounted at the rate of 5%). Circles represent the results for each strategy. The incremental cost-utility ratio (additional cost/increase in quality-adjusted life expectancy) of moving to a more frequent surveillance interval is shown above the line connecting the strategies. See text for details.

The figure also shows that strategies of surveillance every 1-4 years are "dominated" by surveillance every 5 yr: they cost more yet yield a lower life expectancy because there are more endoscopies, endoscopic complications, and surgeries in these strategies.

Figure 2 shows the results for patients with SSBE for an annual incidence of cancer of 1%, as noted in one series of SSBE patients (24). If the incidence of cancer is 1%, surveillance every 2 yr provides the greatest gain in quality-adjusted life expectancy but has an incremental cost-utility ratio of nearly \$600,000/QALY. Less frequent surveillance (every 3-5 yr) has incremental cost-utility ratios ranging from \$26,600/QALY to \$121,600/QALY gained.

For comparison, the incremental cost-effectiveness ratio of screening for colorectal cancer with annual fecal occult blood testing and flexible sigmoidoscopy every 5 yr in an asymptomatic 50-yr-old has been estimated to cost \$20,000 per life year gained (31). Screening mammography in women aged 50-70 yr is estimated at \$22,000/LY gained (23). Heart transplantation and screening for tuberculosis in select populations have been estimated at \$160,000/LY (32) and \$216,000/LY (33) gained, respectively. Screening for cervical cancer with a Papanicolaou smear every 3 yr, a well accepted medical practice, has been estimated to cost \$250,000/LY gained (23).

Sensitivity Analyses

Because published estimates and the opinions of experts vary, we examined the effect of changing the value of each parameter through sensitivity analysis. Sensitivity analysis of all parameters revealed two critical values in the decision for surveillance and esophagectomy: the lifetime incidence of cancer and the quality adjustment for life after an esophagectomy. Estimates for the operative mortality associated with esophagectomy vary as well and, thus, we also included our sensitivity analysis on the this parameter.

The incidence of cancer has been reported to be as low as 0.2%/yr (1/441 patient-years) (4) and as high as 2.1%/yr (1/48 patient-years) (3), with most endoscopic series reporting values between 1% and 2% (1/48-1/99 patient-years) in patients with Barrett's esophagus (5, 6, 7, 8, 9). Our model incorporated

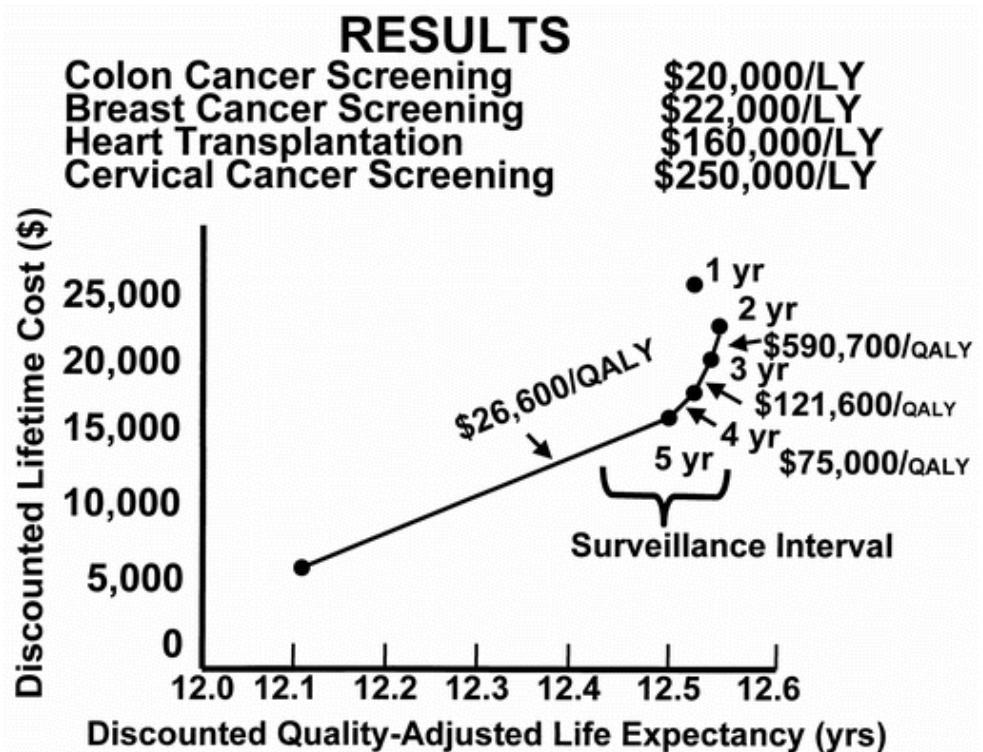


Figure 2. Cost-utility analysis (annual incidence of cancer 1%, discount rate 5%). Average discounted lifetime cost per patient and discounted quality adjusted life years (QALY) for each strategy. The horizontal axis displays discounted quality-adjusted life expectancy in years, and the vertical axis displays the average lifetime cost per patient (discounted at the rate of 5%). Circles represent the results for each strategy. The incremental cost-utility ratio (additional cost/increase in quality-adjusted life expectancy) of moving to a more frequent surveillance interval is shown above the line connecting the strategies. See text for details.

recent estimates (1/251 and 1/208 patient-years) and used 0.4%/yr (1 per 227 patient-years) for the baseline incidence of cancer, an average of these reported values (25, 26) for SSBE and LSBE patients. For a broad range of values for this parameter, Figure 3 illustrates the preferred strategy for different cancer incidences. The horizontal axis depicts the annual incidence of cancer. The horizontal bars depict the optimal interval for surveillance with esophagectomy for high grade dysplasia from different perspectives. Considering both length and quality of life (with an unlimited health care budget), the lower bar shows that if the incidence of cancer were <0.2% (1/420 patient-years), no surveillance would be the preferred strategy because the risks of surveillance and esophagectomy would outweigh any benefit in terms of length and quality of life. For a cancer incidence of 1%, or approximately 1/100 patient-years, the average annual cancer risk from recent prospective studies (26), surveillance every 2 yr would provide the greatest benefit. If the risk of cancer approaches 2% (5, 6, 7), or the reported 1/52-1/56 patient-years, surveillance every year would be the preferred strategy. The remaining bars display the preferred strategy based on the budget of those who make health policy. For a policy maker who is willing to pay up to \$300,000 to increase the length and quality of life of Barrett's esophagus patients by 1 yr, an amount similar to the cost-effectiveness ratio of cervical cancer screening, the model suggests that surveillance should be performed unless the incidence of cancer is <0.2% (1/420 patient-years). If the incidence of cancer approaches 2%, surveillance every year would cost less than \$300,000 per quality-adjusted life year (QALY) gained. For the policy maker who is willing to spend \$100,000/QALY gained, the model suggests that surveillance should be performed unless the incidence of cancer falls below our baseline of 0.4% (1/227 patient-years). If the incidence of cancer is 2%, or (1/48-1/56 patient-years), as some published reports suggest (3, 5, 6, 7), surveillance every 1-2 yr would cost less than \$100,000/QALY gained. For the policy maker who is willing to spend only \$50,000/QALY gained, our model suggests that surveillance should be performed unless the cancer risk falls below 0.6% (1/118 patient-years). If the incidence of cancer is 2% [1/48-1/56 patient-years (3, 5, 6, 7)], surveillance every 2 yr would cost less than \$50,000/QALY gained. Finally, the upper bar displays the results for a willingness to pay of \$25,000/QALY gained. If the incidence of cancer is <1% (1/100 patient-years), no surveillance would be the only viable strategy. Surveillance would cost more than \$25,000/QALY gained. If the incidence of cancer is 2% (3, 5, 6, 7) (1/48-1/56 patient-years), surveillance every 5 yr would cost less than \$25,000/QALY gained, comparable to screening for breast cancer.

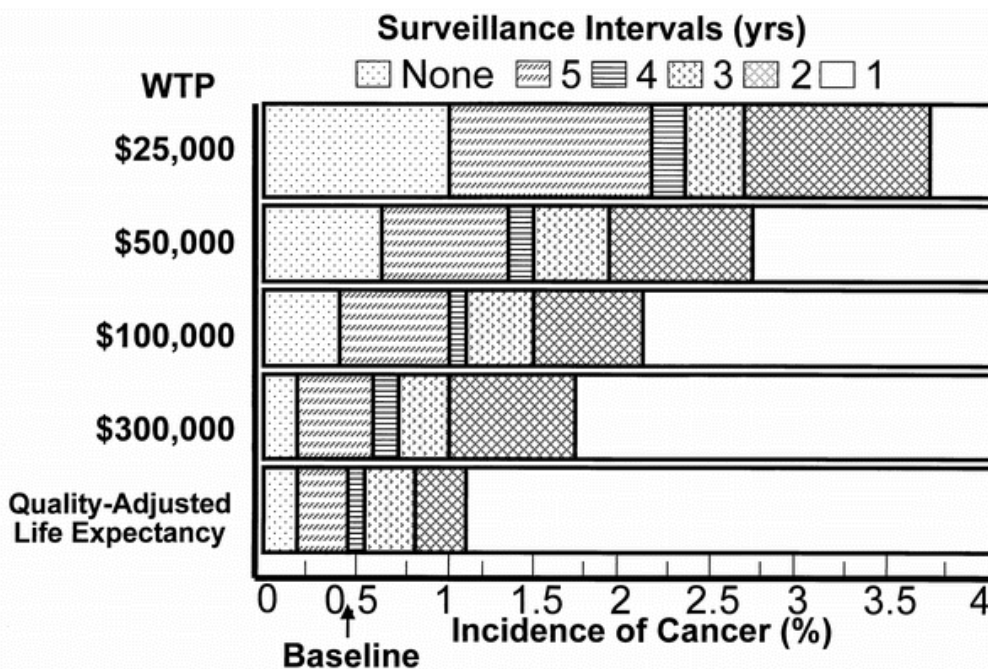


Figure 3. Annual incidence of cancer short segment Barrett's esophagus (SSBE) and long segment Barrett's esophagus (LSBE) patients. The effect of the incidence of cancer on surveillance with esophagectomy for high grade dysplasia from several perspectives: 1) the lower bar considers length and quality of life without restrictions; 2-5) the remaining bars depict the effect of cancer incidence on the cost-utility analysis from different perspectives of "willingness to pay" of the policy maker. See text for details. At a given incidence of cancer, e.g., 1.0%, less frequent surveillance is preferred as resources or willingness to pay is constrained.

For patients with SSBE, [Figure 3](#) provides information on effective and cost-effective strategies based on their estimated cancer risk. Although the cancer risk for patients with SSBE is largely unknown, some authorities suggest that the cancer risk (compared to that of patients with LSBE) is reduced because the amount of metaplastic mucosa at risk for cancer is reduced ([34](#)). [Figure 3](#) shows the preferred strategy based on cancer risk. Considering both length and quality of life, the lower bar shows that, if the cancer risk is only half of recent estimates in combined series (1/454 patient-years, 0.2%), then no surveillance would be the preferred strategy, as the risk of surveillance and esophagectomy would outweigh any benefit in terms of length and quality of life. As noted earlier, if the incidence of cancer is 1%, as reported in one series of SSBE patients ([24](#)), surveillance every 2 yr would provide the greatest quality-adjusted life expectancy. As the incidence of cancer increases, more frequent surveillance is preferred.

The remaining bars in [Figure 3](#) display the preferred strategy based on the budget of those who make health policy. For the policy maker who is willing to pay up to \$300,000 to increase the length and quality of life of Barrett's esophagus patients by 1 yr, the model suggests that if the incidence of cancer is as low as half of our baseline value of 0.2% (1/454 patient-years), then no surveillance would be the only strategy that would not exceed the \$300,000 budget. If the incidence of cancer approaches 1%, then surveillance every 2-3 yr would increase quality-adjusted life expectancy and cost less than \$300,000 per quality-adjusted life year gained. For the policy maker with \$100,000 to spend on surveillance, surveillance should be performed if the incidence of cancer is $\geq 0.4\%$. If the incidence of cancer is as high as 1%, then surveillance every 4-5 yr would increase quality-adjusted life expectancy and would be within the budget of the policy maker with \$100,000 per quality-adjusted life year gained to spend. For the policy maker who can spend \$50,000/QALY, surveillance every 5 yr would be the preferred strategy if the incidence of cancer is 1%. If the budget for surveillance is \$25,000/QALY, surveillance is the preferred strategy unless the cancer risk falls below 1% annually (1/100 PY), when no surveillance is the only strategy that does not exceed the \$25,000 limit.

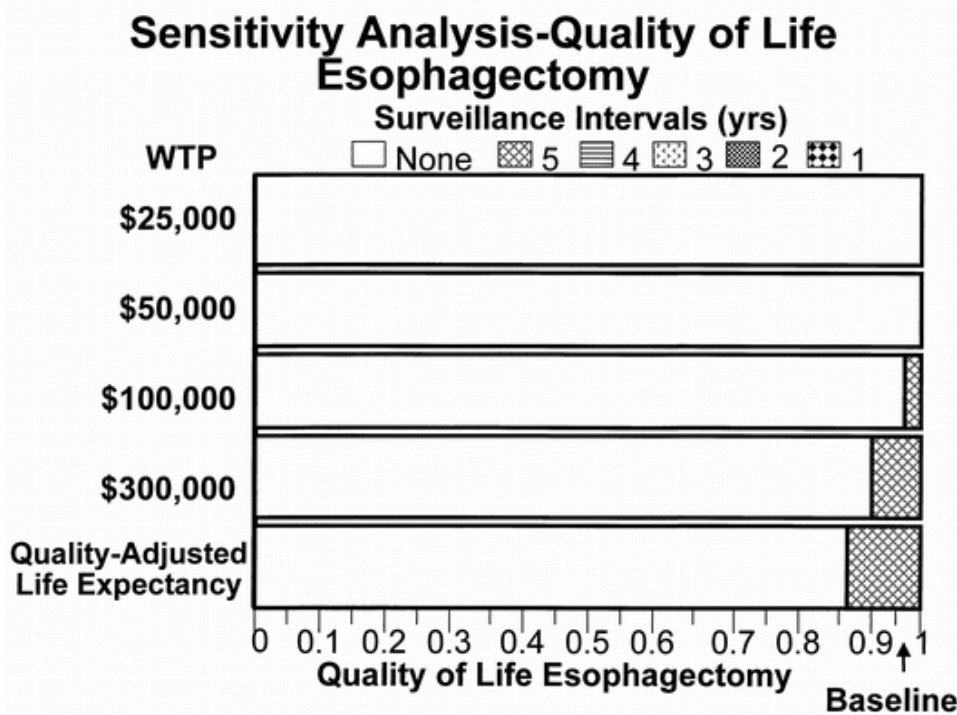


Figure 4. Quality adjustment—esophagectomy. The effect of quality of life with an esophagectomy on surveillance with esophagectomy for high grade dysplasia from several perspectives: 1) the lower bar considers both length and quality of life without restrictions; 2-5) the remaining bars depict the effect of quality of life on the cost-utility analysis from different perspectives of "willingness to pay" of the policy maker. See text for details.

[Figure 4](#) depicts the results of the sensitivity analysis for the quality of life with an esophagectomy. The results can be applied to both LSBE and SSBE patients. The horizontal axis depicts the quality of life adjustments. A quality adjustment of zero is considered equivalent to being dead, whereas a quality adjustment of 1 is equivalent to a state of perfect health. The horizontal bars depict the optimal interval for surveillance from different perspectives of willingness to pay. The lower bar depicts the optimal surveillance interval if we consider length and quality of life (with an unlimited budget). These results incorporate the long term morbidity

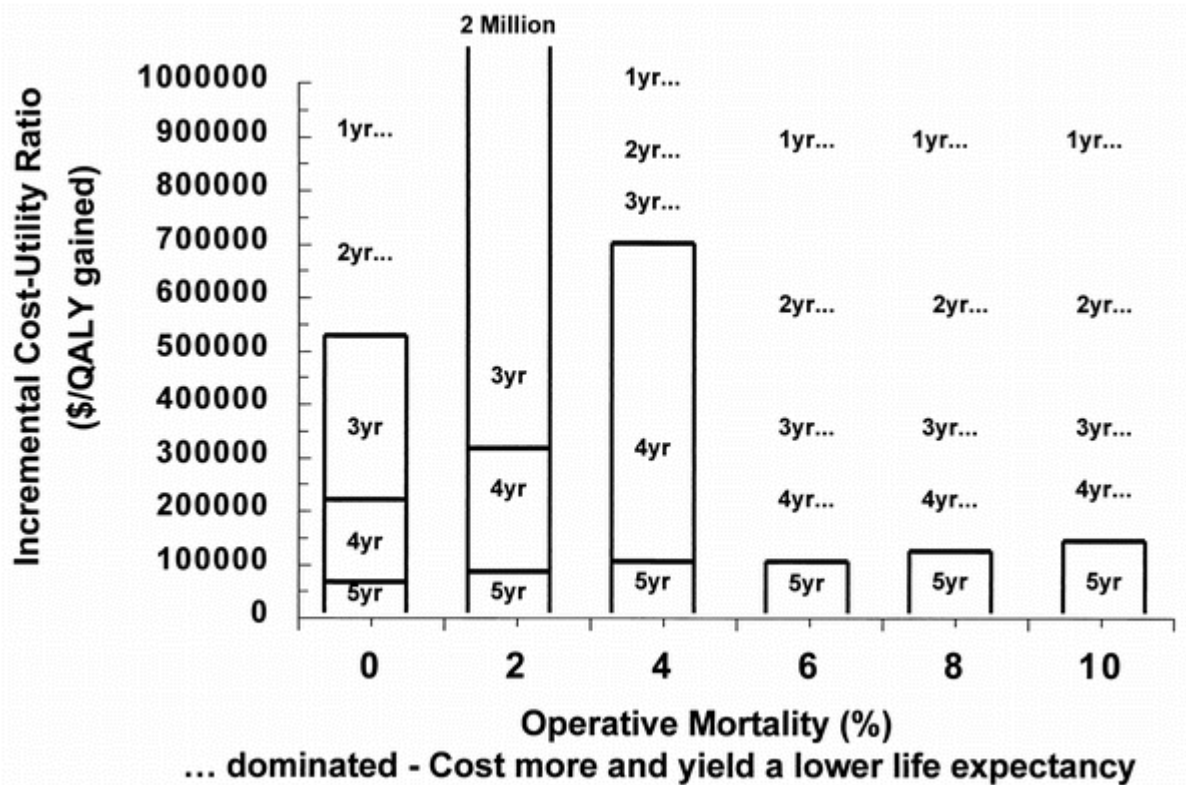


Figure 5. Sensitivity analysis—operative mortality (esophagectomy). The vertical axis lists the incremental cost-utility ratio. The horizontal axis lists the operative mortality associated with esophagectomy. Each of the vertical bars lists the alternative surveillance intervals for each level of operative risk. Strategies denoted by an asterisk (***) are dominated, costing more yet yielding a lower quality-adjusted life expectancy. See text for details.

associated with esophagectomy and short term morbidities of surveillance (endoscopy, endoscopic complications, and surgery). Based on our model, surveillance every 5 yr is the preferred strategy if the quality of life after esophagectomy is >0.87 (0 = dead, 1 = perfect health, 0.97 = baseline). For quality of life values that are <0.87 , no surveillance is preferred. The morbidity of esophagectomy and the inconvenience of repeated endoscopy outweigh the benefits of surveillance. The remaining bars depict different levels of willingness to pay for surveillance of \$300,000, \$100,000, \$50,000, and \$25,000/QALY gained. For a policy maker willing to spend up to \$300,000/QALY gained, the second bar shows that surveillance should be performed if the quality of life with an esophagectomy exceeds 0.90. For the policy maker who can spend only \$100,000/QALY gained, surveillance is indicated if the quality of life with an esophagectomy exceeds 0.97, our baseline value. Moving up, the next two bars show that for a willingness to pay of \$50,000/QALY or \$25,000/QALY, no surveillance is preferred. [Figure 4](#) emphasizes the importance of quality of life on the decision for surveillance. Unless the quality of life with an esophagectomy is quite good (0.87), the morbidity of esophagectomy outweighs any benefit in terms of cancer prevention and increased life expectancy.

The sensitivity analysis for the operative mortality associated with esophagectomy, applicable to both long segment and short segment Barrett's patients, is shown in [Figure 5](#). The operative mortality for esophagectomy has been reported to be as low as 0% ([35](#)) and as high as nearly 10% ([11](#), [12](#), [13](#), [14](#), [15](#), [16](#), [17](#)).

[Figure 5](#) shows that for an operative mortality of 0% or 2%, surveillance every 3 yr provides the greatest gain in quality-adjusted life expectancy but with incremental cost-utility ratios of \$530,000/QALY gained and \$2,000,000/QALY gained, respectively, is expensive compared with other accepted medical practices. More frequent surveillance is more expensive than surveillance every 3 yr and yields a lower quality-adjusted life expectancy. Surveillance every 4 yr has incremental cost-utility ratios of \$200,000

to \$300,000/QALY gained, similar to the cost-effectiveness ratio of cervical cancer screening (\$250,000/LY gained). For an operative mortality ranging from 0% to 2%, surveillance every 5 yr, also effective at reducing deaths from esophageal cancer, has incremental cost-utility ratios of approximately \$50,000/QALY gained, which is substantially less expensive. If the operative mortality associated with esophagectomy is 4%, surveillance every 4 yr would provide the greatest quality-adjusted life expectancy but, with an incremental cost-utility ratio of nearly \$700,000/QALY gained, would be expensive. More frequent surveillance would cost more, yet yield a lower life expectancy. For an operative mortality that ranges from 6% to 10%, surveillance every 5 yr is the only strategy that increased quality-adjusted life expectancy. The incremental cost-utility ratios range from \$80,000 to \$120,000/QALY gained, within the range for accepted medical practices. All other strategies are "dominated," costing more yet yielding a lower life expectancy. The figure shows that as the operative mortality associated with esophagectomy increases, less frequent surveillance is effective and cost-effective compared with accepted medical practices. More frequent surveillance is expensive and yields a lower quality-adjusted life expectancy because the operative risk associated with esophagectomy for high grade dysplasia outweighs any benefits in terms of length and quality of life.

DISCUSSION

Our previous analysis of surveillance of patients with Barrett's esophagus suggests that this practice is effective (22). Others have reported earlier diagnosis of esophageal cancer and improved survival among patients who undergo surveillance (36). In this era of limited resources, however, policy makers and health care managers will determine whether surveillance is cost-effective compared with other accepted medical practices. A definition of the term "cost-effective" is warranted here.

A recommended use of the term "cost-effective," for medical practices, has been that the additional benefit obtained from the practice under evaluation is worth the additional cost. This is in contrast to cost saving, in which the preferred medical practice reduces costs compared with the alternative, and has an equal or better outcome. "Cost-effective" requires a value judgement on the part of the decision maker, or a threshold of his or her "willingness to pay" for a particular program or treatment. To formalize this definition, it is important to clarify the construct called the *incremental* cost-effectiveness ratio—the principal vehicle for analyzing trade-offs among treatment alternatives and for making value judgments among different practices. Let us assume that cost A and cost B are the net medical costs associated with a candidate treatment, A, and the current, standard treatment B. Similarly, effectiveness score A and effectiveness score B represent the effectiveness of treatments A and B stated in units that are meaningful to the decision maker, *e.g.*, lives saved, life years gained, quality-adjusted life years (QALYs) gained. The incremental cost-effectiveness ratio of A relative to B = $(\text{cost A} - \text{cost B}) \div (\text{effectiveness score A} - \text{effectiveness score B})$. By indicating the dollar cost per unit of effectiveness gained, this ratio measures the economic efficiency of treatment A relative to treatment B, in providing improvements in health. For analyses in which quality-adjusted life years gained is the measure of effectiveness, the ratio is also known as an incremental cost-utility ratio, the term used in this article. These cost-effectiveness and cost-utility ratios alone, however, cannot identify the most cost-effective strategy. The ratios are necessary but not sufficient. They must be placed in a decision context, one that can be expressed in two alternative forms. In the first form, an explicit budget amount is stated. This is the amount that the policy maker has to spend on health care. In the second form, a list of medical practices (and their associated cost-effectiveness ratios) that the decision maker regards as acceptable, is used as a basis for comparison with the cost-effectiveness ratio of the practice or treatment under consideration. A practice is considered "cost-effective" if its incremental cost-effectiveness ratio is similar to, or less than, the ratios of other "accepted" practices.

First, we will consider an explicit budget. The policy maker with \$10,000,000 to spend on health care could use the incremental cost-utility and cost-effectiveness ratios to compare the cost-effectiveness of surveillance of patients with Barrett's esophagus to the cost-effectiveness of accepted practices such as fecal occult blood testing and flexible sigmoidoscopy, screening mammography, heart transplantation, screening for tuberculosis, and screening for cervical cancer. Our analysis suggests that if the incidence of cancer is at least (1/420 PY) 0.2% for either SSBE or LSBE patients, surveillance every 5 yr provides the greatest discounted quality-adjusted life expectancy. At our baseline cancer incidence of 0.4%,

surveillance every 5 yr has an incremental cost-utility ratio of slightly less than \$100,000 per QALY gained (\$98,000/QALY). If the entire \$10 million went to surveillance every 5 yr, ($\$10,000,000 \div \$98,000/\text{QALY}$ gained), an additional 102, quality-adjusted years of life would be added, on average, to the life expectancy of the cohort of patients with Barrett's esophagus. [Table 4](#) provides a perspective on the value of health care dollars spent in terms of life expectancy or life years gained for alternative medical practices. The table lists incremental cost-effectiveness and cost-utility ratios and the estimated gain in life expectancy for several medical practices. The table shows that as the incremental cost-effectiveness ratios increase, the gains in life expectancy decrease. For example, surveillance every 5 yr, with an incremental cost-utility ratio of 98,000/QALY, should increase the quality-adjusted life expectancy of the cohort with Barrett's esophagus by 102 yr. Cervical cancer screening with a Papanicolaou smear every 3 yr, with a substantially higher incremental cost-effectiveness ratio of 250,000/LY gained, will increase the life expectancy of the cohort of screened women, on average, by approximately 40 yr.

Table 4. Comparisons With Accepted Medical Practices

Strategies	Incremental CE or CU Ratios	Gain in Life Expectancy (yr)
Surveillance every 5 yr (annual incidence of cancer 0.4%)	\$98,000/QALY	$\$10 \text{ million} \div \$98,000/\text{QALY} = 102$
Surveillance every 2 yr (annual incidence of cancer 1%)	\$590,700/QALY	$\$10 \text{ million} \div \$590,700/\text{QALY} = 17$
Colon cancer screening	\$20,000/LY	$\$10 \text{ million} \div \$20,000/\text{LY} = 500$
Heart transplantation	\$160,000/LY	$\$10 \text{ million} \div \$160,000/\text{LY} = 63$
Cervical cancer screening	\$250,000/LY	$\$10 \text{ million} \div \$250,000/\text{LY} = 40$

CE = cost-effectiveness; CU = cost-utility; QALY = quality-adjusted life year; LY = life year.

The decision making process is also facilitated by comparing the incremental cost-utility ratio of surveillance every 5 yr with the incremental cost-utility and cost-effectiveness ratios of accepted medical practices, which is the other method for examining the cost-effectiveness of surveillance. For comparison: breast cancer screening with annual mammography (compared with every 1 1/3 yr for women aged 50-70 yr) has been estimated at \$22,000 per life year gained ([23](#)) and would be considered cost-effective compared with surveillance of patients with Barrett's esophagus because it has a lower cost per life year gained. This practice is more economically "efficient" in improving health. Heart transplantation for select individuals (patients <50 yr old with irremediable terminal cardiac disease and a <10% chance of surviving for 6 months) has an incremental cost-effectiveness ratio (compared with no transplantation) of \$160,000 per life year gained ([32](#)). Surveillance of patients with Barrett's esophagus would be considered to be cost-effective compared with this practice because it has a lower incremental cost-utility ratio.

Nonetheless, there are those who might consider an incremental cost-utility ratio of \$100,000 per quality-adjusted life year gained to be expensive. How might the cost of surveillance be decreased? We performed a sensitivity analysis on the cost of endoscopy. The results suggest that if endoscopy were free of charge (baseline \$600), surveillance every 5 yr would cost \$59,000 per quality-adjusted life year gained, which is approximately half of our baseline result of \$98,000 per QALY gained, but still more than a policy maker willing to spend \$50,000/QALY to increase quality-adjusted life expectancy by 1 yr. As the cost of endoscopy decreases, the incremental cost-utility ratio for surveillance decreases, as well. The cost of a surveillance program, however, has many components, including the cost of endoscopy, endoscopic complications, surgery, and cancer care. The cost of cancer care for the patient who develops terminal esophageal cancer is an expensive component of a surveillance program (baseline \$34,000/per patient yr). As the cost of cancer care increases, the incremental cost-utility ratio for surveillance decreases (as the goal of a surveillance program is to prevent cancer cases).

The cancer risk and the quality of life after esophagectomy are two critical components for decision making regarding surveillance. Our baseline analysis examines the cost-effectiveness of surveillance

using recent reports of cancer risk (0.4-0.5%/yr). If, however, the average annual cancer risk is 1%, as suggested by recent prospective studies of SSBE and LSBE patients (24, 26), then surveillance every 2 yr would provide the greatest quality-adjusted life expectancy, but (with an incremental cost-utility ratio of nearly \$600,000 per QALY gained) would be expensive compared with less frequent surveillance strategies. Surveillance every 4-5 yr would also increase length and quality of life, and the incremental cost-utility ratios (which range from \$26,600-\$75,000 per QALY gained) are comparable to those of other accepted medical practices (23, 32, 33). For the policy maker willing to spend only \$25,000/QALY on surveillance, all surveillance strategies would exceed the \$25,000 limit. No surveillance would be the only strategy that would not exceed the \$25,000 limit.

The quality of life after esophagectomy is another critical parameter in decisions about surveillance. Our measured results suggest that the quality of life after esophagectomy can be quite good (0.97, 0 = dead, 1 = perfect health). Figure 4 shows that if the quality of life after esophagectomy were 1.0 (equivalent to having perfect health), then surveillance every 5 yr would have an incremental cost-utility ratio of \$74,250 and would be within the budget of the policy maker with \$100,000 to spend on cancer prevention. If the quality of life after esophagectomy were <0.87, then no surveillance would be the preferred strategy. All other strategies would cost more and would yield a lower life expectancy.

The operative mortality associated with esophagectomy also varies in literature reports. Figure 5 shows that if the operative mortality associated with esophagectomy is $\leq 4\%$, surveillance every 3 or 4 yr is effective but is expensive compared with other accepted practices. Surveillance every 5 yr also increases quality-adjusted life expectancy and with incremental cost-utility ratios of approximately \$50,000/QALY gained is cost-effective compared with other accepted practices such as cervical cancer screening (\$250,000/LY gained) and heart transplantation in select groups (\$160,000/LY gained). For an operative mortality of 6-10%, surveillance every 5 yr is the only viable strategy, with incremental cost-utility ratios of \$80,000/QALY to \$120,000/QALY gained, which are in the range of other accepted practices. All other strategies cost more, yet yield a lower quality-adjusted life expectancy.

How can policy makers and clinicians use these results for decisions regarding surveillance of patients with Barrett's esophagus? Those who make health policy and have a limited health care budget can use these results to fund this effective, accepted practice based on their level of "willingness to pay" or their budgetary constraints. The policy maker can also use the results to compare the incremental cost-utility ratio of surveillance of patients with Barrett's esophagus to the incremental cost-utility and cost-effectiveness ratios of other accepted medical practices and, thus, can set priorities for funding. In an era in which clinicians and managed care organizations must work together to promote practices that are effective at acceptable costs, the incremental cost-utility ratio for surveillance of patients with Barrett's esophagus can be used to demonstrate that surveillance compares favorably with accepted medical practices.

This analysis considers only endoscopic surveillance with biopsy as a surveillance tool and esophagectomy as therapy for high grade dysplasia. If other promising surveillance modalities such as balloon cytology (37) are found to be sensitive and specific for diagnosing dysplasia and cancer in Barrett's patients, they can be incorporated into the model as surveillance techniques. The reduced cost of balloon cytology compared with endoscopy may lower the incremental cost-utility ratio of surveillance even further. Newer therapies for high grade dysplasia, such as photodynamic therapy, may be effective in the long term eradication of dysplasia and in cancer prevention. As data on the effectiveness of this and other therapies become available, they can be incorporated into the model along with their associated costs, providing a tool for technology assessment. Because the quality of life after esophagectomy is such a critical parameter for decision making, effective alternative therapies that maintain an excellent quality of life are almost certain to enhance the benefits of surveillance.

CONCLUSIONS

In summary, decisions regarding surveillance and esophagectomy ultimately depend on the perspective of the decision maker. Patients must be willing to undergo surveillance and esophagectomy and policy makers must determine whether the costs of surveillance are worth the benefits obtained. Our baseline analysis, which uses recent estimates of cancer risk (0.4%, 1/227 PY), suggests that surveillance every 5

yr with esophagectomy for high grade dysplasia increases both length and quality of life and has an incremental cost-utility ratio that is similar to that of accepted medical practices. As new methods of surveillance and new effective therapies for treating dysplasia and cancer become available, they too can be incorporated into the analysis. Their risks, benefits, and associated costs can be critically examined and their role in management of patients with Barrett's esophagus determined.

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References

1. U.S. Bureau of the Census. Statistical Abstract of the United States: 1991 (111th ed). Washington, DC, 1991.
2. Spechler SJ. Barrett's esophagus: What's new and what to do. *Am J Gastroenterol* 1989;84:220-3.
3. Skinner DB. The incidence of cancer in Barrett's esophagus varies according to series. In: Giuli R, McCallum RW, eds. Benign lesions of the esophagus and cancer: Answer to 210 questions. New York: Springer-Verlag, 1989:764-5.
4. Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med* 1985;74:857-9.
5. Robertson CS, Mayberry JF, Nicholson DA, et al. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. *Br J Surg* 1988;75:760-3.
6. Hameeteman W, Tytgat GNJ, Houthoff HJ, et al. Barrett's esophagus: Development of dysplasia and adenocarcinoma. *Gastroenterology* 1989;96:1249-56.
7. Ovaska J, Miettinen M, Kivilaakso E. Adenocarcinoma arising in Barrett's esophagus. *Dig Dis Sci* 1989;34:1336-9.
8. Sampliner RE, Kogan FJ, Morgan TR, et al. Progression-regression of Barrett's esophagus. *Gastroenterology* 1985;88:1567.
9. Williamson WA, Ellis FH, Gibb SP, et al. Barrett's esophagus: Prevalence and incidence of adenocarcinoma. *Arch Intern Med* 1991;151:2212-6.
10. Spechler SJ, Robbins AH, Rubins HB, et al. Adenocarcinoma and Barrett's: An overrated risk? *Gastroenterology* 1984;87:927-33.
11. Cedarquist C, Nielsen J, Berthelsen A, et al. Cancer of the esophagus. II. Therapy and outcomes. *Acta Chir Scand* 1978;144:233-40.
12. Skinner DB. En bloc resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1983;85:59-71.
13. Ellis FH, Gibb SP, Watkins E. Esophagogastrectomy—A safe, widely applicable and expeditious form of palliation for patients with carcinoma of the esophagus and cardia. *Ann Surg* 1983;198:531-40.
14. Galandiuk S, Hermann RE, Gassman JJ, et al. Cancer of the esophagus. The Cleveland Clinic experience. *Ann Surg* 1986;198:101-8.
15. DeMeester TR, Zaninotto G, Johansson KE. Selective therapeutic approach to cancer of the lower esophagus and cardia. *J Thorac Cardiovasc Surg* 1988;95:42-54.
16. Wu YK, Huang KC. Chinese experience in the surgical treatment of carcinoma of the esophagus. *Ann Surg* 1979;190:361-5.
17. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma. I. A critical review of surgery. *Br J Surg* 1980;67:381-90.
18. The role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal tract. Guidelines for clinical application. Manchester: American Society for Gastrointestinal Endoscopy, 1986.
19. Spechler SJ. Endoscopic surveillance for patients with Barrett's esophagus: Does the cancer risk justify the practice? *Ann Intern Med* 1987;106:902-4.
20. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983;3:419-58.
21. Spechler SJ, Goyal RK. Barrett's esophagus. *N Engl J Med* 1986;31:362-71.
22. Provenzale D, Kemp JA, Sanjeev A, et al. A guide for surveillance of patients with Barrett's esophagus. *Am J Gastroenterol* 1994;89:670-80.
23. Tengs TO, Meyer G, Siegel JE, et al. Oregon's medicaid ranking and cost-effectiveness: Is there any relationship? *Med Decis Making* 1996;2:99-107.
24. Sharma P, Morales TG, Bhattacharyya A, et al. Dysplasia in short-segment Barrett's esophagus: A prospective 3-year follow-up. *Am J Gastroenterol* 1997;92:2012-6.
25. Sprung DJ, Apter MN, The Gastroenterology Group, Orlando, FL. Occurrence of dysplasia in Barrett's esophagus—A community based study. *Am J Gastroenterol* 1996;91:70.
26. Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: A prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol* 1997;92:212-5.
27. Torrance GW. Utility approach to measuring health-related quality of life. *J Chron Dis* 1987;40:593-600.

28. Finkler SA. The distinction between cost and charges. *Ann Intern Med* 1982;96:102-9.
 29. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;113:147-54.
 30. Gold MR, Siegel JE, Russell LB, et al. Cost-effectiveness in health and medicine. Oxford: Oxford University Press, 1996.
 31. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: Clinical guidelines and rationale. *Gastroenterology* 1997;112:594-642.
 32. Pennock JL, Pyer PE, Reitz BA, et al. Cardiac transplantation in perspective for the future: Survival complications, rehabilitation, and cost. *J Thorac Cardiovasc Surg* 1982;83:168-77.
 33. Berwick DM, Cretin S, Keeler E. Cholesterol, children, and heart disease: An analysis of alternatives. New York: Oxford University Press, 1980:272-3.
 34. Spechler SJ. Short and ultrashort Barrett's esophagus—What does it mean? *Semin Gastrointest Dis* 1997;8:59-67.
 35. Streitz JM Jr, Ellis FH Jr, Tilden RL, et al. Endoscopic surveillance of Barrett's esophagus: A cost-effectiveness comparison with mammographic surveillance for breast cancer. *Am J Gastroenterol* 1998;93:911-5.
 36. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus: Does it help? *J Thorac Cardiovasc Surg* 1993;105:383-8.
 37. Falk GW, Chittajallu R, Goldblum JR, et al. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* 1997;112:1787-97.
 38. Guanrei Y, Songliang Q, He H, et al. Natural history of early esophageal squamous carcinoma and early adenocarcinoma of the gastric cardia in the People's Republic of China. *Endoscopy* 1988;20:95-8.
 39. Silvis SE, Nebel O, Rogers G, et al. Endoscopic complications. Results of the 1974 American Society for Gastrointestinal Endoscopy survey. *JAMA* 1976;235:928-30.
 40. Sabiston DC, ed. *Textbook of surgery*, 13th ed. Philadelphia: WB Saunders, 1986:749-53.
 41. United States Government. *Federal Register: Rules and Regulations*. Washington, DC: U.S. Government Printing Office 1989:169-36533-46.
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