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The Cost-Effectiveness of Radiofrequency Ablation for Barrett's Esophagus

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Abstract

Background & Aims—Radiofrequency ablation (RFA) reduces the risk of esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE) with high grade dysplasia (HGD), but its effects in patients without dysplasia are debatable. We analyzed the effectiveness and cost-effectiveness of RFA for the management of BE.

Methods—We constructed a decision analytic Markov model. We conducted separate analyses of hypothetical cohorts of patients with BE with dysplasia (HGD or low-grade [LGD]) and without dysplasia. In the analysis of the group with HGD, we compared results of the initial RFA to endoscopic surveillance with surgery when cancer was detected. In analyzing the group with LGD or no dysplasia, we compared 3 strategies: endoscopic surveillance with surgery when cancer detected (S1), endoscopic surveillance with RFA when HGD detected (S2), and initial RFA followed by endoscopic surveillance (S3).

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No potential conflicts to disclose.

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Results—Among patients with HGD, initial RFA was more effective and less costly than endoscopic surveillance. Among patients with LGD, when S3 was compared with S2, the incremental cost-effectiveness ratio (ICER) was \$18,231/quality-adjusted life year (QALY), assuming an annual rate of progression rate from LGD to EAC of 0.5%/year. For patients without dysplasia, S2 was more effective and less costly than S1. In a comparison of S3 with S2, the ICERs were \$205,500, \$124,796, and \$118,338/QALY using annual rates of progression of no dysplasia to EAC of 0.12%, 0.33%, or 0.5% per year, respectively.

Conclusions—Using updated data, initial RFA might not be cost-effective for patients with BE without dysplasia, within the range of plausible rates of progression of BE to EAC, and be prohibitively expensive, from a policy perspective. RFA might be cost effective for confirmed and stable LGD. Initial RFA is more effective and less costly than endoscopic surveillance in HGD.

Keywords

Barrett's esophagus; Esophageal adenocarcinoma; Radiofrequency ablation; Cost-effectiveness

Background & Aims

Although the incidence of esophageal adenocarcinoma (EAC) has increased by 500% over the past 40 years,¹ the management of Barrett's esophagus (BE), a precursor to EAC, has remained largely ineffective and controversial.^{2–5} Current strategies employ endoscopic surveillance with biopsy to detect early cancer or high-grade dysplasia (HGD).

Studies have demonstrated the ability of radiofrequency ablation to successfully ablate BE including dysplasia.^{4, 6–9} Shaheen et al. performed a multi-center randomized controlled trial which found that RFA could achieve a high rate of eradication of both dysplasia and intestinal metaplasia, and perhaps most importantly, reduce the risk of progression to EAC.⁷ However, these studies do not have the necessary follow-up duration to assess the long-term effectiveness of RFA, particularly in reducing more substantial outcomes such as invasive cancer rates or cancer mortality. Additionally, although the majority of the studies have been performed in patients with BE and dysplasia, the vast majority of patients with BE do not have dysplasia.^{10, 11} There are reports of increasing RFA utilization in patient without dysplasia in this setting of limited evidence and without clear support from medical society guidelines.¹²

A prior study by Inadomi et al.¹³ used a well established Barrett's esophagus disease model to analyze the cost-effectiveness of various endoscopic modalities including RFA treatment for BE with or without dysplasia. That analysis found that ablation could be the preferred management strategy for BE with HGD, but that the management of LGD and BE without dysplasia was less clear as it was highly contingent upon certain key factors such as the long-term effectiveness of ablation. The current analysis uses a new model that was constructed and developed using many of the assumptions, structure and model inputs of the previous Inadomi model.^{13, 14}

However, since the time of that publication, a significant amount of relevant and pivotal data have been published that could change the estimates of many of the model inputs and assumptions, which in turn could impact the results. These new data include recent publications that suggest that the progression rate to cancer in those with BE may be lower than previously thought.^{15, 16} The durability of RFA in those successfully treated to the point of no endoscopically detectable intestinal metaplasia (IM) appears more precarious than originally hoped for, as a large percentage of these patient required numerous follow-up “touch-up” treatments because of IM recurrences.^{17, 18} Additionally, the presence of buried crypts in a percentage of patients who appear to be successfully treated and eradicated of

both dysplasia and IM might worsen the future sensitivity of and effectiveness of endoscopic surveillance while providing a “false sense of security.”

The aim of our study was to analyze the effectiveness and cost-effectiveness of RFA for the management of BE with and without dysplasia, fully incorporating the aforementioned newer data into the disease model.

Materials and Methods

Model Design

A decision analytic Markov state transition model was constructed in TreeAge Pro (TreeAge, Williamstown, MA). Health states in the model included Barrett’s esophagus (no dysplasia, ND), LGD, HGD, completely eradicated intestinal metaplasia or dysplasia after RFA, buried crypt after RFA, post successful esophagectomy for cancer, inoperable or an incomplete resection of cancer, and death. Possible causes of death included age-related mortality, surgical mortality, EAC, and RFA complications. The Markov cycle length or time between state transitions was 1 month. The simulation began with a hypothetical cohort of 50-year-old individuals who were followed until age 80 or death. In each cycle, the simulated patient could stay in the same state, progress to the next state or cancer, or die from age-related all-cause mortality. All patients were assumed to have the correct diagnosis of BE including the presence of dysplasia at the start of the model simulation.^{7, 17} Separate model analyses were performed for cohorts consisting of HGD, LGD, or ND BE patients.

High Grade Dysplasia

The treatment strategies for BE patients with HGD consisted of: S1) endoscopic surveillance with esophagectomy when cancer was detected, and S2) initial RFA followed by endoscopic surveillance. Endoscopic surveillance continued at 3-month intervals for HGD patients. Patients who underwent RFA would have a circumferential RFA and additional potential focal RFA treatments administered at 2, 4, and 9 months following the initial therapy.⁷ In the second year, up to two additional focal or “touch up” RFAs would be performed for a percentage of patients requiring them.¹⁸ After RFA, patients with completely eradicated intestinal metaplasia or dysplasia received endoscopic surveillance at 1 year intervals in the base case analysis. The surveillance intervals for BE states that recurred after RFA were based on American Gastroenterological Association (AGA) guidelines.¹² RFA treatment could be ineffective with residual dysplasia, eradicate dysplasia but have residual intestinal metaplasia, seemingly eradicate both dysplasia and IM but have buried crypts of IM, or successfully ablate both dysplasia and intestinal metaplasia. Completely eradicated patients could progress to cancer but only after first having a recurrence of BE. However, patients with buried crypts could progress directly to cancer, as we theorized that the progression from BE to dysplasia to carcinoma was not detectable during post ablation surveillance. Patients found to have IM on post-RFA surveillance would undergo additional “touch-up” RFA annually in an attempt to maintain IM eradication with a percentage achieving remission.¹⁸ The model included complications of ablation, including perforation and stricture. Esophageal cancers that would undergo surgery were modeled to be either surgically resectable or unresectable based on published rates.^{19, 20}

Low Grade Dysplasia

There is considerable uncertainty regarding the natural history of LGD within BE. Significant inter-observer variability exists between pathologist’s interpretations²¹ and there have been reports of significant regression rates,^{21–23} which are difficult to confirm because of endoscopic sampling error. Therefore, for the purposes of this analysis, when we refer to the health state of low-grade-dysplasia within Barrett’s esophagus, we are describing LGD

that is *confirmed* and *stable*. *Confirmed* denoting review and agreement between more than one expert pathologist in the LGD assessment; *stable* signifying that LGD was found on more than one endoscopy spaced at least 6 months apart. This more stringent definition of LGD is consistent with the LGD health state in the model as regression was not incorporated into the model structure.

The management strategies for BE with *confirmed* and *stable* LGD included: S1) endoscopic surveillance with esophagectomy when cancer was detected; S2) endoscopic surveillance with RFA when diagnosed with HGD; and S3) initial RFA at LGD stage followed by endoscopic surveillance. Endoscopic surveillance continued at 6-month intervals for the first year from diagnosis of LGD, and at 12-month intervals thereafter. For the first strategy, every patient who was an operative candidate underwent esophagectomy when cancer was detected. For both RFA strategies (HGD or LGD), additional focal RFA was performed up to 3 times during the first year after the initial circumferential ablation. In subsequent years, when IM recurred after RFA, “touch up” RFA was performed with a percentage achieving remission.¹⁸ Similar to the HGD RFA strategy, treatment could be ineffective with residual dysplasia, eradicate dysplasia but have residual intestinal metaplasia, seemingly eradicate both dysplasia and IM but have buried crypts of IM, or successfully ablate both dysplasia and intestinal metaplasia. Completely eradicated patients were not assumed to be at risk of cancer but could progress to cancer if BE recurred.

No Dysplasia

Three management strategies for BE with ND were modeled: S1) endoscopic surveillance with esophagectomy when cancer was detected; S2) endoscopic surveillance with RFA when HGD was detected; S3) initial RFA at ND followed by endoscopic surveillance every 3 years. See Figure 1 for simplified schematic. The RFA treatments for ND were modeled to be functionally similar to those for the dysplastic states with up to three additional focal RFAs in the first year following initial circumferential ablation. Up to two additional focal or “touch-up” RFAs were performed in the second year and focal RFA was performed for patients found to have IM recurrence in subsequent years with a percentage achieving remission.¹⁸ For patients achieving complete eradication (both dysplasia and intestinal metaplasia) with RFA, surveillance endoscopy was performed every year if RFA was performed at HGD and every three years if RFA was performed at ND. Every patient diagnosed with cancer and who was an operative candidate underwent an esophagectomy. RFA therapy in IM could have the same outcomes as the dysplastic analyses including the possibility of buried crypts.

Parameter Estimates

Model parameters or inputs were estimated from the literature. Base-case values and ranges used in sensitivity analyses are summarized in Table 1.

Natural History: Model Transition Probabilities and Calibration

The transition probabilities between the various BE states are critical to the model’s validity. However, there is a wide range of estimates and uncertainty regarding transition rates between specific BE sub-states (e.g. from ND to LGD or LGD to HGD). The best quality and amount of data exist for the overall transition rate from BE to EAC. The transition probabilities between the BE sub-states were therefore calibrated to generate an overall BE to EAC transition rates of 0.12%, 0.33%, and 0.5% per year.^{15,16,24} Additionally, the transition rates derived from the calibration were also compared to the ranges of transition probabilities that were used for a previously validated US population simulation model of esophageal adenocarcinoma (EACMo)²⁵ that was calibrated to National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data as an additional check.

Costs and Utilities

Medicare reimbursement rates were used to estimate direct costs.²⁶ Published estimates of costs from prior years were converted to 2011 year dollars using the Consumer Price Index (U.S Bureau of Labor Statistics). The cost estimate for RFA in Table 1 of \$6,400 is a composite cost for the first year which would include the initial circumferential RFA and subsequent focal treatments and endoscopies.

Quality of life measures for various states in the model were adjusted to utility scores for the specific health states: cancer =0.5 and post-esophagectomy =0.97.^{13, 27–29} For the base-case analysis, all cost and expected life years were discounted at an annual rate of 3% to adjust for the relative value of present dollars or a present year of life.³⁰

Outcomes

The primary outcome of the analysis was the incremental cost-effectiveness ratio (ICER) per quality-adjusted-life years (QALY) between competing treatment strategies. A willingness to pay (WTP) of less than \$100,000/QALY was used as a threshold to determine cost-effectiveness. This threshold was derived from an analysis that estimated the ICER of hemodialysis which as inflation-adjusted to 2011 dollars.³¹ Outcomes assessed included cost, QALYs, and unadjusted life-years (life expectancy).

Analyses performed

A base-case analysis using best estimates for all model parameters and transition probabilities was performed. Because of the pivotal nature of the BE to EAC progression rate and the newly published estimates, we chose to have three base-case analyses corresponding to three progression rates which encompass a wide range of values (i.e. low, intermediate and high values).^{15,16,24} For the LGD cohorts, although there is uncertainty regarding progression rates which have a wide range of published values,^{21–23, 32} we assumed that progression rates were higher than ND; we assigned values that were 50% higher than the three rate for ND to EAC progression rates.

One-way sensitivity analyses were performed for ND cohort to investigate the effects of changes in model parameters on estimated outcomes across a wide range of values, including non-dysplastic BE to EAC progression rate, post ablation endoscopic surveillance interval for non-dysplastic patients, buried crypts rate, and cost of RFA. The ranges were based on published data. For sensitivity analysis other than the ND to EAC progression rate, an overall annual progression rate from ND to EAC of 0.33% was assumed as a base-case.¹⁶

Additionally, probabilistic sensitivity analysis was performed. Distributions for specific parameters or model input variables were assigned and 1000 iterations were performed to gain further insight into the optimal strategy under uncertain conditions within our defined willingness to pay threshold.

Results

Base-Case Results

The base-case analyses of the HGD and LGD cohorts are presented in Table 2. For the HGD analysis, the surveillance strategy with esophagectomy at the detection of cancer was dominated by the initial RFA strategy, resulting in 0.704 more QALYs and costing \$25,609. For the LGD patients, surveillance with esophagectomy for cancer was dominated by the surveillance with RFA at HGD, with the latter strategy resulting in 0.17 more QALYs and costing \$7,446 less. In LGD patients, when comparing initial RFA to surveillance with RFA

for HGD, the ICERs were \$46,153/QALY, \$18,231/QALY, and \$13,879/QALY corresponding to cancer progression rates of 0.19%, 0.5%, and 0.75%, respectively.

For the non-dysplastic (ND) cohort, surveillance with RFA at HGD was the most cost-effective strategy, assuming a willingness to pay (WTP) threshold of \$100,000 per QALY. Both RFA strategies (at HGD or initial at ND) dominated endoscopic surveillance with surgery at detection of EAC. Using overall ND to EAC progression rates of 0.12%, 0.33%, or 0.5% per year, when initial RFA at ND was compared to endoscopic surveillance with RFA at HGD, the corresponding ICERs were \$205,500, \$124,796, and \$118,338 per QALY, respectively (Table 2-iii).

In all the base case analyses, endoscopic surveillance was continued throughout the simulation, even in those patients completely eradicated (i.e. no remaining IM), which generated cost but also provided the opportunity for touch-up therapy. However, when endoscopic surveillance post successful RFA was eliminated from the model, the surveillance with RFA at HGD strategy produced 0.103 more QALYs at a cost of \$643 more, or initial RFA did not appear to be more effective although slightly less costly.

Sensitivity Analysis

The results of the key sensitivity analyses for the ND cohort are summarized in Table 3 and Figure 2. The ICERs calculated in the table compare initial RFA at ND to surveillance with RFA at HGD. Sensitivity analysis on the overall annual progression rate from ND to EAC found that initial RFA may not be cost-effective over the range of plausible progression rates.

The results of the model were not substantially affected by varying the buried crypt rates. If the first year cost of RFA is less than \$4500, then initial RFA for ND may become cost-effective (ICER < \$100K/QALY). Lower IM recurrence rates (<20% over 2.5 years) could also make initial RFA cost-effective. Additionally, if RFA efficacy was improved such that complete eradication could be achieved in >85% patients, initial RFA could be cost-effective.

Probabilistic sensitivity analyses (see results in Figure 3) found that at a WTP between \$0 and \$100,000 per QALY, RFA at HGD was preferred strategy in all of the simulations for HGD patients. For patients with LGD, initial RFA was the preferred strategy in the majority of trials. When WTP was less than \$18,000 per QALY, initial RFA was preferred. Among non-dysplastic patients, RFA at HGD was the preferred strategy in majority of the trials. Although the probability of being cost-effective decreased with increasing WTP, RFA at HGD was optimal in 76 % of trials at WTP of \$100,000. Endoscopic surveillance followed by esophagectomy when cancer is detected was never a preferred strategy at all WTP values.

Discussion

Our analysis finds that radiofrequency ablation of Barrett's HGD appears appropriate, as it is more effective and less costly than continued endoscopic surveillance with surgery when cancer is confirmed by biopsy.

The ablation of LGD costs more than continued surveillance with RFA when HGD is found, however the improvement in QALYs results in an ICER that is below our willingness to pay threshold of \$100,000/QALY making it the most plausible strategy in terms of cost-effectiveness. The ICER increased when the progression rates to cancer from LGD were lower, however the ICERs remained below our threshold. It is important to keep in mind

that there is significant uncertainty regarding LGD, both in terms of histologic agreement amongst pathologists and its natural history including regression and progression rates to cancer. For the functional purposes of representing LGD within the model for analysis, we chose to simplify the health state of LGD by assuming that there were no false positives (e.g. indefinite for dysplasia), no regression, and assuming that LGD would have a rate of progression to cancer approximately 50% greater than BE ND.^{21–23, 32–37} Consequently, our finding that initial ablation of LGD can be cost-effective applies to patients with a confirmed and stable LGD that has high level of certainty. This hypothetical LGD state might be one that has been confirmed by more than one pathologist and which has been stable (not regressed) over at least 2 or more endoscopies spaced at least 6 months apart. When comparing the ICERs for initial RFA strategies for LGD versus ND, there is a substantial difference with ICERs favorable in LGD while not so in ND. Much of the difference is a result of the increased costs in the LGD surveillance group generated by the numerous endoscopies from the heightened surveillance for LGD. The entire LGD cohort undergoes this surveillance including those that never progress to HGD. If guidelines for LGD surveillance were to change in the future (i.e. become less frequent), the cost of the surveillance strategy could drop and the ICER of initial RFA in LGD could substantially increase.

For BE without dysplasia, our analysis found that within a wide range of progression rates to cancer, initial ablation did not appear to be cost-effective when compared to surveillance with ablation when HGD is detected. Surveillance with surgery when cancer is detected was dominated by surveillance with ablation at HGD. We feel that these results for ND management are particularly timely as RF ablation in this group of patients is the most controversial and in the most need for additional data to inform decision making.

Inadomi et al published a cost-effectiveness analysis that studied various ablative therapies including radiofrequency ablation for BE with and without dysplasia.¹³ RFA for HGD dominated both esophagectomy and surveillance. RFA for LGD also dominated surveillance with esophagectomy for cancer. Initial RFA for BE without dysplasia was found to be cost-effective with a relatively low ICER.

Our analysis used a new model that incorporated many of the Inadomi model's structure, assumptions and inputs, but is simpler as it focused only on RFA as we felt that this was the ablation technique with the most data to support efficacy. Additionally, we incorporated numerous new data including lower rates of progression to cancer, more recent performance characteristics of RFA including durability and the need for touch up treatment for recurrences, and more concretely incorporated the possibility of buried crypts and their consequences. We found similar results for RFA in HGD. Our analysis also found initial RFA for LGD dominated surveillance with surgery for cancer. But when initial RFA was compared to surveillance with RFA when HGD was detected, it was more costly, but at a favorable ICER. The largest difference between the two studies was in the ND cohort analyses. Our ICER was well above \$100,000/QALY for a range of BE progression rates, whereas the prior analysis found that initial RFA would be cost-effective. Although the two models had somewhat differing structures, they were similar enough that we presume that the difference in results is primarily because of changes in model inputs.

Our analysis has limitations. As with any analysis that uses a disease model, limited data of the natural history and other model inputs lead to uncertainty in the model and raises legitimate concerns regarding the validity of the model results and projections. Although the team of investigators that participated in this analysis has extensive experience with disease models, including more complex versions, we chose to construct a model that was as simple as possible in order to maintain a high level of model transparency and minimize the "black box" phenomenon. Additionally, we performed sensitivity analysis, but also chose to

perform our base case analysis using three distinct progression rates from BE to EAC in acknowledgement of the uncertainty and pivotal aspect of this estimate. Although these measures do not eliminate model uncertainty, our methods hopefully help to fully delineate these areas within our analysis, serving as disclosure, but perhaps more importantly, to explore their impact.

Our modeling analysis also serves to highlight the key areas within BE radiofrequency ablation that need better data to confirm or change our findings. As better data for various model inputs become available, particularly if pivotal parameters change significantly from our current estimates, another analysis would be warranted.

As investigators with experience in disease modeling, we fully comprehend the limitations of an analysis such as this one. Even though our results were quite robust to varying levels of cancer progression rates, we believe that a multicenter randomized controlled trial for initial RF ablation versus surveillance in patients with BE without dysplasia is needed to confirm our model results and to inform clinical decision making. Such a study would require a large number of enrolled participants and a long follow-up period because the differences in endpoints such as mortality and cancer would be small between the two arms potentially requiring the use of surrogate endpoints such as dysplasia and other outcomes. Additionally, the continued long term follow-up of those patients ablated will provide much needed data regarding cancer progression and the need for surveillance, which significantly impacts the cost-effectiveness and patients preferences for RFA.

In conclusion, using updated data, including rates of cancer progression, our analysis found that for HGD, the initial RFA strategy is both more effective and less costly than endoscopic surveillance. Initial RFA for *Confirmed* and *Stable* LGD can be cost-effective. For BE without dysplasia, initial RFA may not be cost-effective within the range of plausible progression rates of BE to EAC and may be prohibitively expensive from a policy perspective.

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Abbreviations

BE	Barrett's esophagus
GERD	gastroesophageal reflux disease
EAC	Esophageal AdenoCarcinoma

References

1. American Cancer Society ACS. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012.
2. Bulsiewicz WJ, Shaheen NJ. The role of radiofrequency ablation in the management of Barrett's esophagus. *Gastrointest Endosc Clin N Am*. 2011; 21:95–109. [PubMed: 21112500]
3. Lyday WD, Corbett FS, Kuperman DA, et al. Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. *Endoscopy*. 2010; 42:272–8. [PubMed: 20146164]

4. Pouw RE, Wirths K, Eisendrath P, et al. Efficacy of radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia. *Clin Gastroenterol Hepatol*. 2010; 8:23–9. [PubMed: 19602454]
5. Shaheen NJ, Frantz DJ. When to consider endoscopic ablation therapy for Barrett's esophagus. *Curr Opin Gastroenterol*. 2010; 26:361–6. [PubMed: 20531183]
6. Ganz RA, Overholt BF, Sharma VK, et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. Multicenter Registry. *Gastrointest Endosc*. 2008; 68:35–40. [PubMed: 18355819]
7. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009; 360:2277–88. [PubMed: 19474425]
8. Sharma VK, Jae Kim H, Das A, et al. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. *Am J Gastroenterol*. 2009; 104:310–7. [PubMed: 19174783]
9. Velanovich V. Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned. *Surg Endosc*. 2009; 23:2175–80. [PubMed: 19263139]
10. 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. [PubMed: 9362182]
11. Weston AP, Krmpotich PT, Cherian R, et al. Prospective long-term endoscopic and histological follow-up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. *Am J Gastroenterol*. 1997; 92:407–13. [PubMed: 9068459]
12. Spechler SJ, Sharma P, Souza RF, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology*. 2011; 140:e18–52. quiz e13. [PubMed: 21376939]
13. Inadomi JM, Somsouk M, Madanick RD, et al. A cost-utility analysis of ablative therapy for Barrett's esophagus. *Gastroenterology*. 2009; 136:2101–2114. e1–6. [PubMed: 19272389]
14. Inadomi JM, Sampliner R, Lagergren J, et al. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. *Ann Intern Med*. 2003; 138:176–86. [PubMed: 12558356]
15. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med*. 2011; 365:1375–83. [PubMed: 21995385]
16. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut*. 2011
17. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy*. 2010; 42:781–9. [PubMed: 20857372]
18. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. *Gastroenterology*. 2011; 141:460–8. [PubMed: 21679712]
19. Hur C, Nishioka NS, Gazelle GS. Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus. *J Natl Cancer Inst*. 2004; 96:316–25. [PubMed: 14970280]
20. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med*. 2002; 347:1662–9. [PubMed: 12444180]
21. Wani S, Mathur S, Sharma P. How to manage a Barrett's esophagus patient with low-grade dysplasia. *Clin Gastroenterol Hepatol*. 2009; 7:27–32. [PubMed: 18986846]
22. Curvers WL, ten Kate FJ, Krishnadath KK, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol*. 2010; 105:1523–30. [PubMed: 20461069]
23. Wani S, Falk GW, Post J, et al. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology*. 2011; 141:1179–86. 1186, e1. [PubMed: 21723218]
24. Shaheen NJ, Crosby MA, Bozyski EM, et al. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology*. 2000; 119:333–8. [PubMed: 10930368]
25. Hur C, Hayeck TJ, Yeh JM, et al. Development, calibration, and validation of a U.S. white male population-based simulation model of esophageal adenocarcinoma. *PLoS One*. 2010; 5:e9483. [PubMed: 20208996]

26. Russell LB, Gold MR, Siegel JE, et al. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. *Jama*. 1996; 276:1172–7. [PubMed: 8827972]
27. de Boer AG, Stalmeier PF, Sprangers MA, et al. Transhiatal vs extended transthoracic resection in oesophageal carcinoma: patients' utilities and treatment preferences. *Br J Cancer*. 2002; 86:851–7. [PubMed: 11953814]
28. Fisher D, Jeffreys A, Bosworth H, et al. Quality of life in patients with Barrett's esophagus undergoing surveillance. *Am J Gastroenterol*. 2002; 97:2193–200. [PubMed: 12358232]
29. Gerson LB, Ullah N, Hastie T, et al. Patient-derived health state utilities for gastroesophageal reflux disease. *Am J Gastroenterol*. 2005; 100:524–33. [PubMed: 15743346]
30. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *Jama*. 1996; 276:1253–8. [PubMed: 8849754]
31. Winkelmayer WC, Weinstein MC, Mittleman MA, et al. Health economic evaluations: the special case of end-stage renal disease treatment. *Med Decis Making*. 2002; 22:417–30. [PubMed: 12365484]
32. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. *Clin Gastroenterol Hepatol*. 2006; 4:566–72. [PubMed: 16630761]
33. O'Connor JB, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. *Am J Gastroenterol*. 1999; 94:2037–42. [PubMed: 10445525]
34. Mirois M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. *Gut*. 1991; 32:1441–6. [PubMed: 1773946]
35. Reid BJ, Levine DS, Longton G, et al. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low- and high-risk patient subsets. *Am J Gastroenterol*. 2000; 95:1669–76. [PubMed: 10925966]
36. Sikkema M, Looman CW, Steyerberg EW, et al. Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. *Am J Gastroenterol*. 2011; 106:1231–8. [PubMed: 21577245]
37. Lim CH, Treanor D, Dixon MF, et al. Low-grade dysplasia in Barrett's esophagus has a high risk of progression. *Endoscopy*. 2007; 39:581–7. [PubMed: 17611911]
38. Provenzale D, Kemp JA, Arora S, et al. A guide for surveillance of patients with Barrett's esophagus. *Am J Gastroenterol*. 1994; 89:670–80. [PubMed: 8172136]
39. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol*. 1999; 94:2043–53. [PubMed: 10445526]
40. Gorelick AB, Inadomi JM, Barnett JL. Unsdated small-caliber esophagogastroduodenoscopy (EGD): less expensive and less time-consuming than conventional EGD. *J Clin Gastroenterol*. 2001; 33:210–4. [PubMed: 11500609]
41. Soni A, Sampliner RE, Sonnenberg A. Screening for high-grade dysplasia in gastroesophageal reflux disease: is it cost-effective? *Am J Gastroenterol*. 2000; 95:2086–93. [PubMed: 10950062]
42. Gold M. Panel on cost-effectiveness in health and medicine. *Med Care*. 1996; 34:DS197–9. [PubMed: 8969326]
43. Siegel JE, Weinstein MC, Russell LB, et al. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996; 276:1339–41. [PubMed: 8861994]
44. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology*. 2001; 120:1607–19. [PubMed: 11375943]
45. Fleischer DE, Overholt BF, Sharma VK, et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2. 5-year follow-up. *Gastrointest Endosc*. 2008; 68:867–76. [PubMed: 18561930]
46. Corley DA, Levin TR, Habel LA, et al. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology*. 2002; 122:633–40. [PubMed: 11874995]
47. Pera M, Trastek VF, Carpenter HA, et al. Barrett's esophagus with high-grade dysplasia: an indication for esophagectomy? *Ann Thorac Surg*. 1992; 54:199–204. [PubMed: 1637206]

48. van Sandick JW, van Lanschot JJ, Kuiken BW, et al. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. *Gut*. 1998; 43:216–22. [PubMed: 10189847]
49. Peters JH, Clark GW, Ireland AP, et al. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg*. 1994; 108:813–21. discussion 821–2. [PubMed: 7967662]
50. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg*. 1993; 105:383–7. discussion 387–8. [PubMed: 8445916]
51. Nguyen NT, Schauer P, Luketich JD. Minimally invasive esophagectomy for Barrett's esophagus with high-grade dysplasia. *Surgery*. 2000; 127:284–90. [PubMed: 10715983]
52. Gray NA, Odze RD, Spechler SJ. Buried metaplasia after endoscopic ablation of Barrett's esophagus: a systematic review. *Am J Gastroenterol*. 2011; 106:1899–908. quiz 1909. [PubMed: 21826111]
53. Sharma VK, Wang KK, Overholt BF, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. *Gastrointest Endosc*. 2007; 65:185–95. [PubMed: 17258973]
54. Roorda AK, Marcus SN, Triadafilopoulos G. Early experience with radiofrequency energy ablation therapy for Barrett's esophagus with and without dysplasia. *Dis Esophagus*. 2007; 20:516–22. [PubMed: 17958728]
55. Sharma VK, Kim HJ, Das A, et al. A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system). *Endoscopy*. 2008; 40:380–7. [PubMed: 18459074]
56. Hernandez JC, Reicher S, Chung D, et al. Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia. *Endoscopy*. 2008; 40:388–92. [PubMed: 18459075]
57. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Effective treatment of early Barrett's neoplasia with stepwise circumferential and focal ablation using the HALO system. *Endoscopy*. 2008; 40:370–9. [PubMed: 18494132]
58. Gondrie JJ, Pouw RE, Sondermeijer CM, et al. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. *Endoscopy*. 2008; 40:359–69. [PubMed: 18494131]
59. Vassiliou MC, von Renteln D, Wiener DC, et al. Treatment of ultralong-segment Barrett's using focal and balloon-based radiofrequency ablation. *Surg Endosc*. 2010; 24:786–91. [PubMed: 19711128]
60. Pouw RE, Gondrie JJ, Rygiel AM, et al. Properties of the neosquamous epithelium after radiofrequency ablation of Barrett's esophagus containing neoplasia. *Am J Gastroenterol*. 2009; 104:1366–73. [PubMed: 19491850]
61. Eldaif SM, Lin E, Singh KA, et al. Radiofrequency ablation of Barrett's esophagus: short-term results. *Ann Thorac Surg*. 2009; 87:405–10. discussion 410–1. [PubMed: 19161747]
62. 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. [PubMed: 9178668]
63. 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. [PubMed: 128642]
64. Ofman JJ, Shaheen NJ, Desai AA, et al. The quality of care in Barrett's esophagus: endoscopist and pathologist practices. *Am J Gastroenterol*. 2001; 96:876–81. [PubMed: 11280568]
65. Piotet E, Escher A, Monnier P. Esophageal and pharyngeal strictures: report on 1,862 endoscopic dilatations using the Savary-Gilliard technique. *Eur Arch Otorhinolaryngol*. 2008; 265:357–64. [PubMed: 17899143]

Figure 1.

Schematic of Strategies for BE ND Cohort. The ovals within the schematic depict the natural history of Barrett's esophagus as it progresses to esophageal adenocarcinoma. The rectangles are the three different strategies simulated and analyzed: Radiofrequency ablation (RFA) initially at Barrett's esophagus without dysplasia (ND); Surveillance with RFA when HGD is found; Surveillance with surgery when EAC is found.

Figure 2. One-way sensitivity analyses
 (ND Cohort analysis, Figures 2b to 2e: assuming BEND to EAC progression rate of 0.33)

Figure 3.
Probabilistic Sensitivity Analysis

Table 1**Model Inputs**

Parameters	Estimate, Base Case	Ranges used in sensitivity analysis	Source
Costs (2011 US\$)			
Cost of cancer (annual)	\$ 49,385		
Cost surveillance EGD	\$ 930		13, 38–41
Cost of post surgery state (annual)	\$ 1,496		13, 38, 39
Cost of RFA	\$ 6,400	\$3,500 – \$15,000	CMS, CPT Code 43228 *
Cost of focal RFA/"Touch up"	\$ 1,600		CMS, CPT Code 43228 *
Cost of esophagectomy	\$ 25,882		13, 38, 39, 41
Cost of ablation-related stricture	\$ 2,216		13, 38, 39
Cost of stricture complication	\$8,000		19
Cost of perforation during ablation	\$25,980		13, 38, 39
Discount rate	0.03		42, 43
Transition probabilities			
HGD to cancer	0.024		44
LGD to HGD			See Methods; Calibrated to overall progression rate from BE to EAC
LGD to cancer			
ND BE to LGD			
ND BE to cancer			
Efficacy of therapy			
%complete ablation of IM			
among HGD patients	0.74		7, 18
among LGD patients	0.81		7, 18
among ND patients	0.70	0.1 – 0.9	17, 45
% complete ablation of dysplasia			
among HGD patients	0.81		7, 18
among LGD patients	0.91		7, 18
Durability of therapy			
Recurrence rate of IM	0.25	0.02 – 0.4	7, 17, 18
among HGD and LGD patients at year 3			
Recurrence rate of IM	0.23		17, 45
among ND patients at year 2.5			
Recurrence rate of dysplasia	0.15		7, 18
among HGD patients at year 3			
Recurrence rate of dysplasia	0.10		7, 18
among LGD patients at year 3			
"Touch up" focal RFA success rate for IM recurrence	0.57		7, 18
Procedure characteristics			
Operative candidate, cancer	0.80		13

Parameters	Estimate, Base Case	Ranges used in sensitivity analysis	Source
Surgical resectability rate			
Surveillance	0.80		13, 19, 44, 46–51
No Surveillance	0.33		19, 20
Complications of therapy			
Buried crypt rate	0.05	0.0 – 0.28	52, 3, 4, 6, 8, 53–61
Complication rate from EGD	0.00013		19, 62, 63
Mortality from EGD complication	0.0016		19, 62, 63
Mortality from esophagectomy	0.05		13, 51
Stricture rate with RFA at year 3	0.076		64
Complication rate from stricture	0.18		65
Mortality from stricture complication	0.0009		65
Perforation with RFA	0.0005		13, 6, 45, 53–55, 57, 58

Abbreviation: EGD = esophagogastroduodenoscopy; IM = intestinal metaplasia; CEIM = complete eradication of IM

* CPT Code 43228-Esophagoscopy including Anesthesia time.

Table 2

Base Case Results

i) HGD						
BE HGD to EAC (% per year)	Strategy	Cost (USD)	QALYs	ICER (USD)	Unadjusted LYs	
1.0	Surveillance, Surgery Ca	71,288	16,036	-	23,015	
	Initial RFA HGD	45,679	16,740		24,172	
ii) LGD (Confirmed and Stable)						
BE LGD to EAC (% per year)	Strategy	Cost (USD)	QALYs	ICER (USD)	Unadjusted LYs	
0.19	Surveillance, Surgery Ca	24,971	16,984		24,609	
	Surveillance, RFA HGD	21,135	17,034		24,701	
	Initial RFA LGD	24,135	17,099	46,153	24,806	
	Surveillance, Surgery Ca	33,963	16,709		24,123	
0.5	Surveillance, RFA HGD	26,517	16,879		24,431	
	Initial RFA LGD	28,486	16,987	18,231	24,599	
	Surveillance, Surgery Ca	38,810	16,516		23,783	
0.75	Surveillance, RFA HGD	29,412	16,780		24,258	
	Initial RFA LGD	31,133	16,904	13,879	24,443	
iii) ND						
BE ND to EAC (% per year)	Strategy	Cost (USD)	QALYs	ICER (USD)	Unadjusted LYs	
0.12	Surveillance, Surgery Ca	11,587	17,050		24,725	
	Surveillance, RFA HGD	10,764	17,059		24,744	
	Initial RFA ND	19,806	17,103	205,500	24,816	
	Surveillance, Surgery Ca	19,315	16,873		24,411	
0.33	Surveillance, RFA HGD	16,435	16,932		24,524	
	Initial RFA ND	24,422	16,996	124,796	24,617	
	Surveillance, Surgery Ca	24,144	16,738		24,168	
0.50	Surveillance, RFA HGD	19,718	16,848		24,378	
	Initial RFA ND	27,410	16,913	118,338	24,463	

Table 3

Sensitivity analyses of selected parameters: ICERs for ND patients

Parameter	Initial RFA versus RFA at HGD (USD)	Results Change (WTP \$100,000)
ND to EAC progression		
0.05	445,600	-
0.1	245,400	-
0.3	129,600	-
0.5	118,600	-
Cost of Initial RFA Treatment		
\$3,500	88,000	Initial RFA cost-effective
\$5,000	118,600	-
\$10,000	173,300	-
\$15,000	234,600	-
Buried crypt rate		
0%	109,300	-
14%	167,400	-
28%	341,200	-
IM recurrence rate (over 2.5 years)		
5%	24,500	Initial RFA cost-effective
10%	43,500	Initial RFA cost-effective
20%	100,000	-
30%	211,900	-
40%	541,900	-
RFA efficacy (% complete eradication of IM)		
10%	491,700	-
30%	266,600	-
60%	146,800	-
90%	93,690	Initial RFA cost-effective