Screening for and Surveillance of Barrett's Esophagus:
a cost-effectiveness assessment

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Screening for and surveillance of Barrett's esophagus: a cost-effectiveness assessment

Screening en surveillance van Barrett-slokdarm: een kosteneffectiviteitsanalyse

Thesis

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General Introduction

ESOPHAGEAL CANCER

Incidence

Gastrointestinal (GI) cancers constitute more than 25% of all cancers in the world. In 2018, almost five million new GI cancer patients were identified, of whom more than 10% with esophageal cancer.[1] Currently, esophageal cancer is the seventh most common cancer in the world (***Figure 1***). The age-adjusted incidence rate of the cancer varies by country from 0.33 to 18.7 per 100,000 individuals. In addition to the geographical region, the incidence of esophageal cancer depends strongly on age and gender. More than 90% of patients with esophageal cancer are older than 50 years old, and the overall risk of getting esophageal cancer in men is 4.4 times higher than in women.[2, 3]

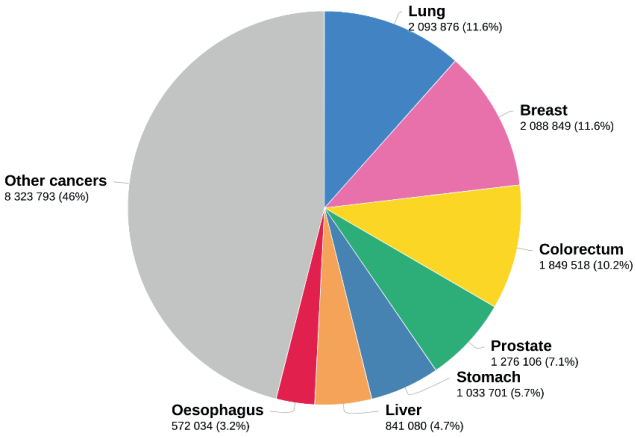

Figure 1. Estimated number of new cases in 2018, worldwide, all cancers, both sexes, all ages[1]

Mortality

Esophageal cancer is responsible for more than 5% of all cancer-related deaths in the world.[4, 5] Esophageal cancer has a poor prognosis, and the five-year survival rate of patients with the disease is 15-20% which varies a lot by cancer stage at diagnosis.[6] Early detection and treatment of patients with esophageal cancer may improve the survival rate and quality of life of patients. However, more than 65% of esophageal cancer patients are diagnosed with localized or distant stages, which have a 19.8% and 3.4% five-year survival rate, respectively.[7] In 2018, more than half a million people died due to esophageal cancer, of whom about 400,000 in Asia, 45,000 in Europe, 28,000 in Africa, and 18,000 in North America.[1] ***Figure 2*** shows the mortality rate of esophageal cancer by each country in the world, varying from 0.33 in the Solomon Islands to 18.8 in Kenya per 1,000 individuals.

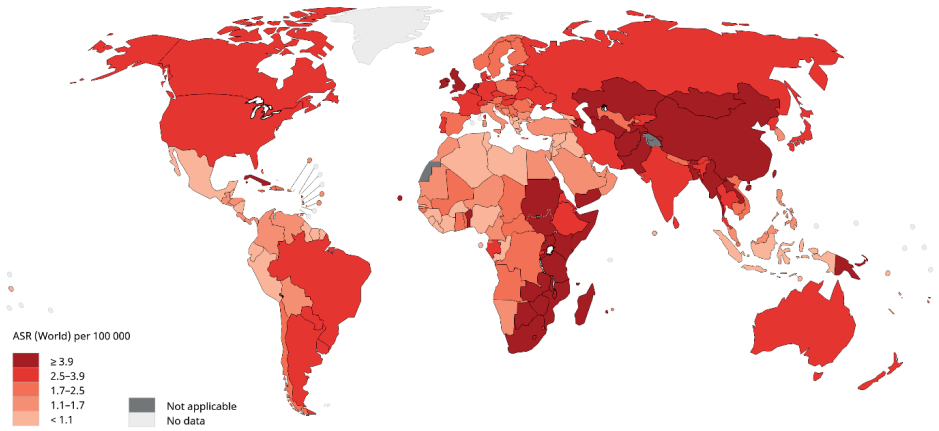

Figure 2. Estimated age-standardized esophageal cancer mortality rates in 2018 for both sexes[1]

Types of esophageal cancer

There are two main subtypes of esophageal cancer: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). The etiological and risk factors of these cancers are substantially different. ESCC develops from squamous cells that line the surface of the middle and upper parts of the esophagus, while EAC develops from glandular tissue near the gastroesophageal junction. ESCC is the most common type worldwide; however, this doesn't hold for all countries. EAC is the dominant type of esophageal cancer in several Western countries, including the Netherlands and the US.[8, 9] EAC incidence and mortality have increased significantly in recent decades (***Figure 3***). This increase was particularly evident in high-income

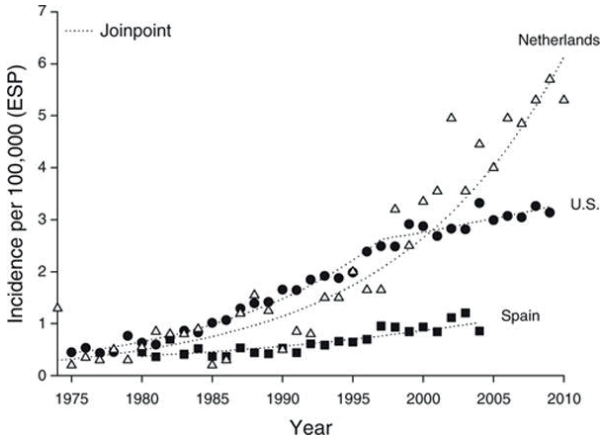

Figure 3. Esophageal adenocarcinoma (EAC) incidence rate trends over time for the United States, Spain, and the Netherlands[10]

countries such as the Netherlands and the US, in which an average annual increase of 9.6% and 6.1% was seen between 1975 to 2009, respectively.[10] Countries located in Northern and Western Europe, North America and Oceania, have the highest EAC incidence rates. [8, 9]

BARRETT'S ESOPHAGUS

Various risk factors are associated with EAC, of which Barrett's esophagus (BE) is the most important one.[5] BE is a condition in which normal squamous epithelium is replaced by intestinal columnar epithelium in the esophagus. According to the length of intestinal metaplasia, a distinction can be made between short-segment and long-segment BE (<3 cm and ≥3 cm of intestinal metaplasia, respectively).[11] The intestinal columnar epithelium in BE may also develop dysplasia. Based on the presence and severity of dysplasia, BE is classified as non-dysplastic (ND), low-grade dysplasia (LGD), or high-grade dysplasia (HGD). BE is the only known precursor lesion of EAC and has been reported to increase the risk of developing cancer to 0.1-6% annually, depending on the length of BE, as well as the presence and severity of dysplasia.[9, 12, 13]

Most people with BE show no symptoms and stay undiagnosed over their lifetime. Therefore, the epidemiology of BE is difficult to define precisely. Studies have reported different estimates for BE prevalence, varying from 0.5% to 6.8% depending on the study population.[14-17] BE is two to three times more prevalent in men than women and is associated with older age, white race, obesity, tobacco use, and gastroesophageal reflux disease (GERD) symptoms.[11]

The incidence of BE has increased over the last decades, which is probably one of the reasons that EAC incidence has increased as well, and that BE has become the focus of screening and surveillance programs to prevent EAC.[16]

SCREENING FOR BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

Because of the presence of BE as a slow-growing precursor lesion, EAC is amenable to screening. The goal of screening would be to detect patients with BE early, and then offer them surveillance to ensure timely diagnosis and treatment of HGD and/or EAC. Currently, screening the general population for BE and EAC is not recom-

mended anywhere in the world, because even in high-risk countries, the average risk of developing EAC is low and therefore, the harms of screening may outweigh the benefits.[18-22] Furthermore, there is not enough robust evidence available to show the effectiveness of screening for BE and EAC. However, targeted screening of well-defined high-risk populations is recommended by several clinical practice guidelines in the world.[18-22] For example, the American College of Gastroenterology (ACG) recommends to consider the screening of men with chronic or frequent symptoms of GERD, and two or more of the following risk factors using an upper GI endoscopy: central obesity, current or past history of smoking, age more than 50 years and a history of BE or EAC in a first-degree relative.[19]

Upper GI endoscopy, with the collection of random four-quadrant biopsies every 2 cm in case of any visible abnormality in the esophagus, is the common screening test for BE and EAC.[23] The sensitivity of diagnostic upper GI endoscopy for esophageal cancer has been reported to be more than 90% in general clinical practice.[24] In addition to upper GI endoscopy, other advanced techniques such as endosonography, confocal microendoscopy, and autofluorescence endoscopy, have been introduced to enhance detection of dysplasia; however, these techniques are not used commonly.[25-28]

Although GI endoscopy is considered to be a safe procedure, it carries a low risk of adverse events. Approximately 1 in 200 to 1 in 10,000 people who have undergone upper GI endoscopy have experienced those events, including perforation, bleeding, infectious, and adverse sedation events.[29] Therefore, less invasive methods such as Cytosponge have been introduced for screening for BE and EAC. The Cytosponge is a minimally invasive cell sampling device that consists of a sponge within a soluble capsule attached to a piece of string. When patients swallow the Cytosponge, the capsule is dissolved, and the sponge is expanded to collect the surface esophageal cells for laboratory analysis.[30]

SURVEILLANCE OF BARRETT'S ESOPHAGUS

Once BE is diagnosed, standard-of-care is to closely follow-up BE patients through regular endoscopic surveillance. BE surveillance can detect dysplasia or invasive carcinoma. Routine upper GI endoscopic surveillance for patients with BE is recommended by several organizations including American, Australian, Dutch and British GI societies.[18-20, 22, 31-34] Generally, if there is no dysplasia, surveillance is recommended, while in the presence of dysplasia, surveillance or endoscopic

Table 1. Recommendation of different guidelines for the management of non-dysplastic Barrett's esophagus (NDBE) and low-grade dysplasia (LGD) patients

Guideline	Year	Management recommendations for	
		NDBE	LGD
European Society of Gastrointestinal Endoscopy[18]	2017	< 1 cm: no surveillance. 1-3 cm: surveillance every 5 years. 3-10 cm: surveillance every 3 years. ≥ 10 cm: refer to a BE expert center.	Surveillance after 6 months: - If no dysplasia→ surveillance every year for 2 years, if no dysplasia persists, surveillance as NDBE patients, thereafter. - If LGD → endoscopic ablation therapy should be offered.
Netherlands Association of Gastroenterologists and Hepatologists[31]	2018	3 cm: surveillance every 5 years. 3-10 cm: surveillance every 3 years. ≥ 10 cm: refer to a BE expert center.	Surveillance after 6 months: - If no dysplasia → surveillance every year for 2 years, if no dysplasia persists, surveillance as NDBE patients, thereafter. - If LGD → surveillance every year. If LGD persists under surveillance, endoscopic eradication therapy can be considered for long-segment LGD.
British Society of Gastroenterology[22, 32]	2014, 2017	Intestinal metaplasia (IM) at the cardia: no surveillance. < 3 cm, without IM or dysplasia: repeat endoscopy, if it confirms the diagnosis, no surveillance. < 3 cm, with IM: Surveillance every 3-5 years ≥ 3 cm, with IM: Surveillance every 2-3 years.	Surveillance after 6 months: - If no dysplasia → surveillance at 6 months, if no dysplasia persists, surveillance as NDBE patients, thereafter - If LGD → endoscopic ablation therapy should be offered. If ablation is not performed, surveillance every 6 months.
American College of Gastroenterology[19]	2016	Surveillance every 3 to 5 year.	Repeat surveillance after optimization of acid suppressant therapy: - If no dysplasia → surveillance at 1 year, if no dysplasia persists, surveillance as NDBE patients, thereafter. -If LGD → The preferred modality: endoscopic eradication therapy. If ablation is not performed, surveillance every year.
American Society for Gastrointestinal Endoscopy[36, 37]	2012, 2018	Surveillance every 3–5 years.	Endoscopic eradication therapy. If ablation is not performed, surveillance in 6 months and every year thereafter.

Table 1. Recommendation of different guidelines for the management of non-dysplastic Barrett's esophagus (NDBE) and low-grade dysplasia (LGD) patients (*continued*)

Guideline	Year	Management recommendations for	
		NDBE	LGD
American Gastroenterological Association[33, 35]	2011, 2016	Surveillance every 3–5 years.	Surveillance after 8-12 weeks. - If no dysplasia → surveillance as NDBE patients. - If LGD is confirmed → endoscopic eradication therapy. If ablation is not performed, surveillance every 6 months for one year, then annually.
Australian guideline[34]	2015	< 1 cm without IM: No surveillance < 3 cm with IM: Surveillance every 3-5 years. < 3 cm without IM: surveillance after 3-5 years, if no IM, no surveillance is needed. ≥ 3 cm: Surveillance every 2-3 years	Surveillance every 6 months. - If two consecutive 6 monthly endoscopies show NDBE → less frequent follow-up schedule. - Endoscopic ablation should be considered where LGD is definite, multifocal, and present on more than one occasion.

BE: Barrett's esophagus, IM: intestinal metaplasia, LGD: low-grade dysplasia, NDBE: non-dysplastic BE

treatment is recommended. However, there are discrepancies in guidelines' recommendations, particularly in terms of LGD management (treatment or surveillance) and intervals for surveillance of BE patients without dysplasia (***Table 1***). For example, AGA recommends surveillance every three to five years for NDBE patients regardless of the extent of intestinal metaplasia. In comparison, Dutch guidelines recommend surveillance every three years for NDBE ≥3 cm and every five years for NDBE <3 cm. For LGD patients, AGA recommends a repeat endoscopy after 2 months, followed by endoscopic eradication therapy (EET) for those with confirmed LGD, while the Dutch guidelines recommend a surveillance endoscopy after 6 months and then every year.[31, 33, 35]

MISCAN-EAC MODEL

One of the reasons for the discrepancies in guidelines around the world is the lack of clinical studies evaluating the effectiveness of surveillance. At this stage, because clinical guidelines recommend BE surveillance, randomized clinical trials are no longer deemed ethical. But even if clinical studies had been performed, it would have been impossible to evaluate and compare all different possible surveillance strategies. This is where decision modeling comes into play. Decision modeling provides us with the opportunity to assess the health impact of interventions such as screening for the presence of BE or EAC, or surveillance of BE patients. Furthermore, decision modeling can estimate the costs of implementation of the intervention, which enables us to optimize the use of available healthcare resources. Although modeling has some uncertainties, this approach can definitely improve decision making in healthcare settings. Decision tree, (cohort and microsimulation) Markov and discrete event models are the most common models used in the decision modeling studies.

In this thesis, we have used the MIcrosimulation SCreening Analysis Esophageal adenocarcinoma (MISCAN-EAC) model developed in the Department of Public Health at Erasmus MC University Medical Center (Rotterdam, The Netherlands) in collaboration with University of Washington (Seattle, WA). The MISCAN-EAC is a discrete-event microsimulation model that simulates the population individual by individual from birth to death, and each person can evolve through discrete disease states. The model has three components: 1. demography component which simulates each individual's birth and death due to other diseases; 2. natural history component which simulates EAC development through BE in the population; 3. screening and treatment component which can interrupt the development of EAC.

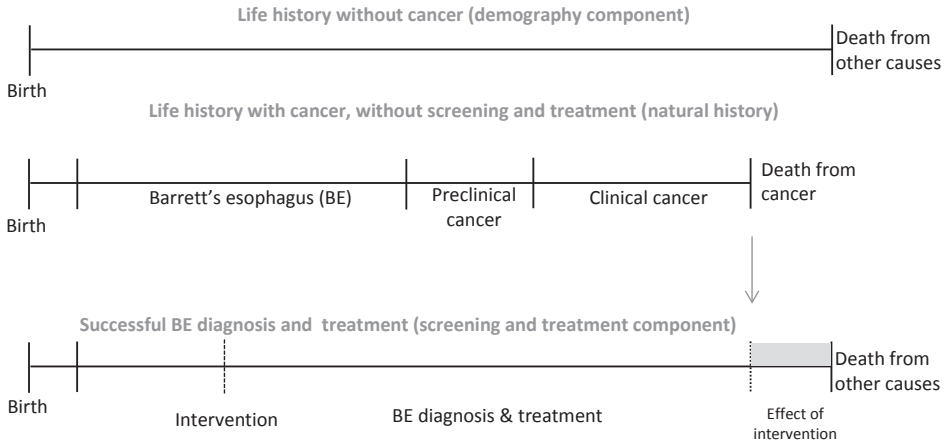

Figure 4. Modeling natural history, screening and treatment interventions for an example individual

Figure 4 presents these components for an example individual and shows a positive result of screening. Life history of an individual would change if EAC occurs, and therefore without any intervention, the patient would die due to cancer earlier than expected without cancer. If a screening program can detect and treat the precursor lesion (BE) successfully, EAC would be prevented, and consequently, the patient would live longer.

We have developed MISCAN-EAC models for the US and the Netherlands. The structure of the model is very similar; however, the natural history of each model has been calibrated to different calibration targets. Both models simulate the following health states: no BE (with or without GERD symptoms), NDBE, LGD, HGD, preclinical (asymptomatic, undiagnosed) EAC, clinical (symptomatic, diagnosed) EAC, and death. However, each model uses a different staging system for EAC (***Figure 5***). See more details in **Model Appendix**.

COST-EFFECTIVENESS ANALYSIS

Decision models can generate a wealth of information about the benefits, harms, and costs of different screening and surveillance strategies. One way to choose the optimal strategy among those possible strategies is by using cost-effectiveness analysis. Cost-effectiveness is a concept showing the relationship between the total costs of implementing a healthcare intervention, and its effect on health outcomes. A summary measure that is often used is the ratio of the net total costs of the inter-

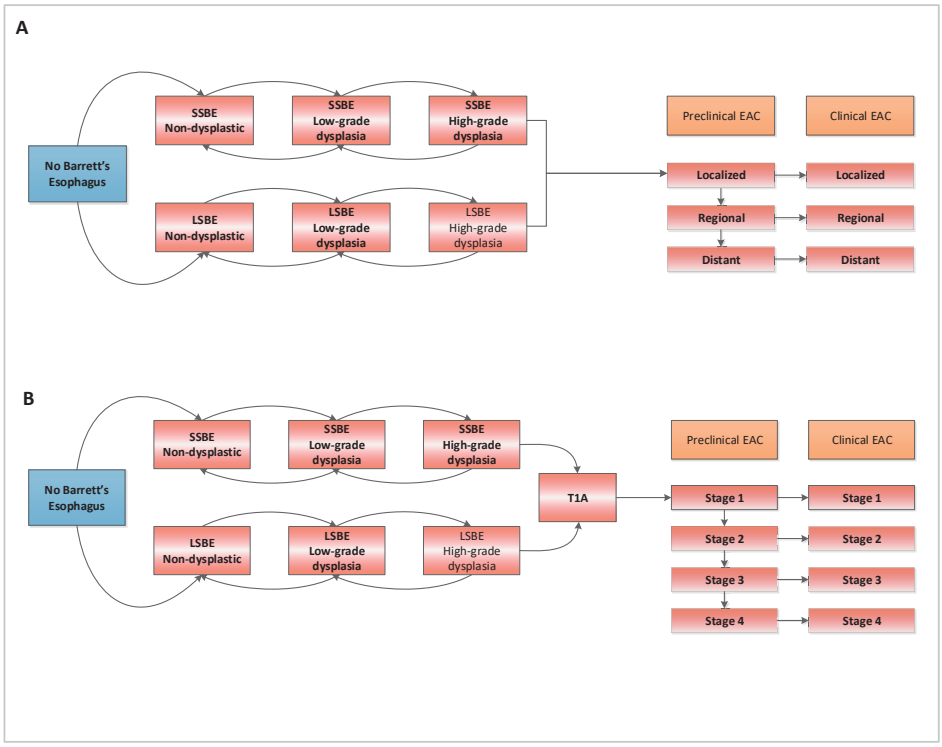

Figure 5. The structure of US MISCAN-EAC Model (**A**) and Dutch MISCAN-EAC model (**B**)
EAC: esophageal adenocarcinoma, LSBE: long-segment Barrett's esophagus, SSBE: short-segment Barrett's esophagus, T1a: esophageal adenocarcinoma T1a

vention over the net quality-adjusted life years gained. This ratio can be determined through a cost-effectiveness analysis comparing the situation with intervention to a situation without intervention as an average cost-effectiveness ratio. Alternatively, an incremental cost-effectiveness analysis evaluates multiple interventions where each intervention is compared with the next effective one, which is called the incremental cost-effectiveness ratio (ICER).

Different choices and assumptions need to be made in cost-effectiveness analysis, such as the perspective of the analysis and discounting rates for future costs and effects. In recent recommendations for conducting cost-effectiveness analysis, the Second Panel of Cost-Effectiveness in Health and Medicine has underscored the importance of considering future healthcare cost both related and unrelated to the condition of primary interest.[38] In most cost-effectiveness analyses for cancer screening and surveillance, unrelated health effects and associated costs are partly considered. If we do not consider the future unrelated health effects and costs due

to competing risk factors, the health benefits of an intervention may be overrepresented, while costs are underestimated, which may bias decision making based on cost-effectiveness outcomes.

GAPS IN BE MANAGEMENT

As described above, there are inconsistent recommendations concerning the management of BE patients caused by important gaps in knowledge about the optimal strategy for the surveillance of BE patients. In particular, uncertainty exists about the optimal interval for BE patients without dysplasia, and about whether patients with LGD should continue receiving surveillance or should be offered EET instead. Furthermore, there is no recommendation in the current guidelines concerning the stopping age of surveillance. There is also a policy-practice gap in BE management resulting in more intensive surveillance for BE patients than recommended.[39-42] Besides, there is a knowledge gap on using an alternative screening test for BE and EAC, and the impact of including future unrelated health effects and costs on cost-effectiveness estimates for the screening strategies.

In this thesis, we address these knowledge gaps in two parts. The first part is focused on screening for BE, and we evaluated the cost-effectiveness of using a minimally invasive method to screen high-risk people for BE. Then we assessed the impact of including unrelated health effects and costs on our cost-effectiveness estimates. In the second part, we synthesized the literature on the cost-effectiveness of surveillance recommendations and evaluated several ways to further improve the cost-effectiveness of surveillance by optimizing several aspects of BE management, including optimal management of BE patient with LGD or no dysplasia, and stopping age of surveillance of BE patients without dysplasia. Subsequently, we evaluated how the mismatch between recommended and practiced surveillance of BE patients can impact cost-effectiveness estimates.

AIMS AND RESEARCH QUESTIONS

This thesis is subdivided into two parts. The first part aims to evaluate the cost-effectiveness of an alternative screening test for BE and to evaluate the potential impacts of including unrelated health effects and associated costs on cost-effectiveness estimates. The overall aim of the second part is to determine the optimal BE man-

agement strategies from a cost-effectiveness perspective. The research questions of the studies described in the chapters of this thesis are as follows:

Part 1: Screening

Research question 1: Could the use of a minimally invasive cell sampling device for screening of patients with gastroesophageal reflux disease (GERD) symptoms for Barrett's esophagus be cost-effective? (chapter 2)

Research question 2: Does the inclusion of unrelated health effects and costs impact the cost-effectiveness of screening for GI cancers? (chapter 3)

Part 2: Surveillance

Research question 3: Is surveillance of individuals with precursor lesions of colorectal, esophageal, gastric, and pancreatic cancers cost effective? (*chapter 4*)

Research question 4: Which management strategy is optimal for patients with BE and low-grade or no dysplasia? (*chapter 5)*

Research question 5: What is the optimal age of last surveillance for patients with BE and no dysplasia considering their competing comorbidities? (*chapter 6*)

Research question 6: How does the current policy-practice gap in surveillance of patients with BE affect the costs and benefits of the BE management program in the Netherlands? (*chapter 7*)

In *chapter 8*, the results of the studies conducted to answer the questions above are interpreted and further discussed. We will also discuss the direction of future research in this field.

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Part 1

Screening for Barrett's esophagus

2

Cost-effectiveness of screening patients with gastroesophageal reflux Disease for Barrett's esophagus with a minimally invasive cell sampling device

Published as:

Heberle CR, Omidvari AH, Ali A, et al. Cost-effectiveness of screening patients with gastroesophageal reflux Disease for Barrett's esophagus with a minimally invasive cell sampling device. Clinical Gastroenterology and Hepatology. 2017;15(9):1397-1404.

ABSTRACT

Background

It is important to identify patients with Barrett's esophagus (BE), the precursor to esophageal adenocarcinoma (EAC). Patients with BE usually are identified by endoscopy, which is expensive. The Cytosponge, which collects tissue from the esophagus noninvasively, could be a cost-effective tool for screening individuals with gastroesophageal reflux disease (GERD) who are at increased risk for BE. We developed a model to analyze the cost effectiveness of using the Cytosponge in first-line screening of patients with GERD for BE with endoscopic confirmation, compared with endoscopy screening only.

Methods

We incorporated data from a large clinical trial of Cytosponge performance into 2 validated microsimulation models of EAC progression (the esophageal adenocarcinoma model from Massachusetts General Hospital and the microsimulation screening analysis model from Erasmus University Medical Center). The models were calibrated for US Surveillance, Epidemiology and End Results data on EAC incidence and mortality. In each model, we simulated the effect of a 1-time screen for BE in male patients with GERD, 60 years of age, using endoscopy alone or Cytosponge collection of tissue, and analysis for the level of trefoil factor 3 with endoscopic confirmation of positive results. For each strategy we recorded the number of cases of EAC that developed, the number of EAC cases detected with screening by Cytosponge only or by subsequent targeted surveillance, and the number of endoscopies needed. In addition, we recorded the cumulative costs (including indirect costs) incurred and quality-adjusted years of life lived within each strategy, discounted at a rate of 3% per year, and computed incremental cost-effectiveness ratios (ICERs) among the 3 strategies.

Results

According to the models, screening patients with GERD by Cytosponge with follow-up confirmation of positive results by endoscopy would reduce the cost of screening by 27% to 29% compared with screening by endoscopy, but led to 1.8 to 5.5 (per 1000 patients) fewer quality-adjusted life years. The ICERs for Cytosponge screening compared with no screening ranged from $26,358 to $33,307. For screening patients by endoscopy compared with Cytosponge the ICERs ranged from $107,583 to $330,361. These results were sensitive to Cytosponge cost within a plausible range of values.

Conclusions

In a comparative modeling analysis of screening strategies for BE in patients with GERD, we found Cytosponge screening with endoscopic confirmation to be a cost-effective strategy. The greatest benefit was achieved by endoscopic screening, but with an unfavorable cost margin.

INTRODUCTION

Since 1975 the incidence of esophageal adenocarcinoma (EAC) has increased more than six-fold in the United States, with comparable increases in several other western countries.[1] The prognosis for diagnosed esophageal cancer patients is poor, with five-year relative survival rates as low as 18.4%.[1] Barrett's Esophagus (BE) is a metaplastic precursor condition to EAC with an estimated prevalence of 5.6%.[2] BE can be detected via endoscopy and may be managed with surveillance to detect treatable high-grade dysplasia (HGD) or early EAC. However, more than 90% of diagnosed EACs do not arise from patients in BE surveillance programs.[3] This statistic highlights the need for better strategies for early detection in order to reduce the morbidity and mortality associated with EAC.

GERD symptoms are a known risk factor for BE and EAC.[4-6] GERD prevalence in the western world has been estimated at 10-20%.[7] Screening GERD patients for BE has the potential to reduce EAC incidence, but costs of endoscopic screening in a large population may be prohibitively high.

As a potential alternative to standard endoscopic screening, we consider a novel minimally-invasive screening method, the cytosponge, which allows tissue to be sampled from the surface of the esophagus non-endoscopically. A biomarker, Trefoil Factor 3 (TFF3), is currently utilized to diagnose BE from the collected tissue.[8-10] Cytosponge screening may be available at a significantly lower cost than endoscopy and can be administered in a primary care setting without need for sedation.

The largest clinical trial (BEST2) to assess cytosponge performance to date was published, and we incorporated these latest data into our modeling approach. We used a comparative modeling approach with two previously validated models both calibrated to high quality US population Surveillance, Epidemiology and End Results (SEER) data on EAC incidence and mortality.

METHODS

CISNET-EAC models

Analyses were conducted using two independent microsimulation models of the natural history of EAC: the Esophageal AdenoCarcinoma Model (EACMo) from the Massachusetts General Hospital (Boston, MA) (**MGH model**), and the Microsimulation Screening Analysis model from Erasmus University Medical Center (Rotterdam,

The Netherlands) and University of Washington (Seattle, WA) (**Erasmus/UW model**). Both models incorporate the full natural history of EAC, starting from normal health and progressing through non-dysplastic BE, low-grade dysplasia, and high-grade dysplasia before reaching cancer. Both models have previously been calibrated to SEER data on EAC incidence and mortality, stratified by age, year, and historic stage.[11] During the calibration process, the MGH model approximates the BE prevalence for males and females respectively in 2010 to be approximately 2.6% and 1.1%; the Erasmus/UW model estimation is 1.4% and 0.5%.[11] Additionally, both models were extended in a previous comparative modeling exercise to incorporate detailed simulations of BE surveillance and treatment of HGD using endoscopic eradication therapy (EET).[12] The models were developed independently and incorporate different parameters and structural assumptions regarding the natural history of EAC. However, the models are part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) consortium and have undergone extensive comparative modeling validation exercises. Full details of the respective models are available online.[13,14]

Population of interest

We simulated a 1950 birth cohort of US males starting from age 20. At age 60, the population of interest was restricted to those who had displayed GERD symptoms and had not been diagnosed with EAC. This group was then screened for BE according to one of three strategies: cytosponge-first screening, endoscopy-only screening, or no screening. Patient cohorts in all strategies were followed until death or age 100. Quality-adjusted life-years, EAC cases, EAC deaths, endoscopies, EET sessions, and total lifetime costs of treatment and surveillance were recorded starting from the time of the initial screen.

Screening strategies

Three strategies were included in this analysis. In the natural history or no screening strategy, no intervention took place until patients were found to have cancer because of symptoms, at which point they received standard treatment. In the cytosponge screening strategy, patients with GERD symptoms were given a one-time cytosponge screen for BE at age 60. Patients with positive screening results were subject to confirmation by endoscopy. The false negative and false positive probabilities for the initial cytosponge screen, conditional on dysplastic grade, were derived from the BEST2 trial (***Table 1***). If either the cytosponge test or the confirmation endoscopy was negative, there was no further follow-up. In the endoscopic screening strategy, GERD-symptomatic patients at age 60 were given an immediate

diagnostic endoscopy. Performance characteristics for endoscopy were estimated from the literature (***Table 1***). Negative results received no follow-up.

Table 1. Common Input Parameters

Parameter/Model Inputs		Value	Source
Endoscopy parameters			
BE ND false negative rate		0.125	23
BE false positive rate		0.075	23
Complication rate		0·00013	24,25
Cost of Endoscopy		$745	26
Cytosponge parameters			
Bleed rate		0.002	20*
BE false negative rate (no dysplasia)		0.21	20
BE false negative rate (low grade dysplasia)		0.195	20
BE false negative rate (high grade dysplasia)		0.158	20
BE false positive rate		0.076	20
Cost of Cytosponge		$182	16, **
Key RFA treatment parameters			
RFA initial treatment cost		$5630	26
RFA touchup treatment cost		$1012	26
Post-treatment recurrence rate		0.10	27,28
Eradication rate of dysplasia with persistence of intestinal metaplasia	HGD	0.17	27,28
	LGD	0.19	27,28
Eradication rate of dysplasia and Intestinal metaplasia	HGD	0.68	27,28
	LGD	0.72	27,28
	ND	0.81	27,28

BE: Barrett's Esophagus. ND: No dysplasia *Bleed rate estimated from adverse events reported in BEST2. **Personal communication with Medtronic representatives.

Management of BE

Detailed clinical aspects of BE surveillance and endoscopic eradication therapy were incorporated into our models in a previous analysis.[12] For this analysis, we assumed all diagnosed high-grade dysplasia patients were treated with endoscopic eradication that included possible endoscopic mucosal resection and radiofrequency ablation (RFA) therapy; touch-up RFA treatment was given to patients who had dysplasia recurrence after initial treatment. Possible outcomes of initial treatment were complete eradication of BE (including dysplasia), eradication of dysplasia only, and treatment failure. Patients with diagnosed low-grade dysplasia or non-dysplastic BE were not treated immediately, but underwent surveillance at regular intervals (every year for low-grade dysplasia, every three years for non-dysplastic BE), with

treatment administered upon a diagnosis of high-grade dysplasia. This treatment and surveillance strategy is consistent with recent AGA guidelines.[15] Key parameters governing endoscopic eradication treatment in the models can be found in ***Table 1***.

Costs

Cost-effectiveness analysis was conducted from the societal perspective. Costs for cancer treatment were derived from the literature. Costs for endoscopy and for EET of BE with HGD were estimated on Medicare reimbursement rates; see ***Table 1***. As cytosponge is a new technology and not yet commercially available, there is little empirical data to inform its cost in a clinical setting. For the base case we estimated an expected cost of $182 based on a combination of direct communication with Medtronic representatives regarding the cost of the device itself (estimated $55) as well as Medicare facility payments for comparable diagnostic tests.[16] Given the uncertainty of this parameter and its importance to our analysis, we conducted a pivotal sensitivity analysis using a wide range of plausible estimated cytosponge costs from $0 up to $1,000.

Quality of Life Adjustments

Quality of life utilities for EAC by stage were estimated from the literature, as were decrements for endoscopy, EET, and complications including stricture or perforation.

Outcomes

For each strategy we recorded the number of clinical EAC cases developed, the number of EAC cases detected by the initial screen or by subsequent targeted surveillance, and the number of endoscopies needed. Additionally, we recorded the cumulative costs (including indirect costs) incurred and quality-adjusted years of life lived within each strategy, discounted at a rate of 3% per year, and computed incremental cost-effectiveness ratios (ICERs) between the three strategies. All outcomes were computed per 1000 GERD-symptomatic patients at start of screening.

Sensitivity Analyses

We performed one-way sensitivity analyses on several key parameters, including cytosponge cost, cytosponge performance characteristics, initial effectiveness of EET, rates of recurrence after EET, gender, and the age of initial screening. Additionally, we performed a cost-effectiveness analysis from an alternative perspective in which patient time spent undergoing screening or treatment was incorporated into the total cost. A detailed description of the parameters used in these analyses can be found in the ***Supplementary Materials***, including ***Supplementary Tables 1 and 4***.

Finally, in the MGH model, a probabilistic sensitivity analysis (PSA) was performed, simultaneously varying a large number of parameters including performance characteristics of cytosponge and endoscopy, complication rates, recurrence rates, direct costs, and utilities. Distributions for each parameter were estimated from the literature. 1000 runs of 10 million patients each were performed using parameter sets sampled from the estimated distributions via a Metropolis algorithm. A distribution for cytosponge cost was not included in the PSA; instead, the cost of cytosponge cost was varied across the full $0-$1000 range for each PSA run. Full details of the probabilistic and one-way sensitivity analyses can be found in the ***Supplementary Materials.***

RESULTS

Base Case

Detailed base-case results are shown in ***Table 2***. The natural history (no screening) strategy resulted in the worst health outcomes, with 13.75 to 16.25 total cancers and 15,076 to 15,078 quality-adjusted life-years (QALYs) (ranges reflect differences between models). Endoscopic screening offered the largest benefit, with 6.8 to 12.44 total cancers and 15,101 to 15,116 QALYs. The Cytosponge-first screening showed results that were in-between, with 8.18 to 13.15 cancers and 15,099 to 15,110 QALYs. However, greater benefits were accompanied by higher total costs. Costs were $703,690 to $762,043 using the natural history strategy, $1,485,205 to $1,597,713 using the Cytosponge strategy, and $2,089,549 to $2,185,741 using the endoscopy strategy.

Table 2. Main results of the simulation models.

	MGH			Erasmus/UW		
	Natural History	Cytosponge	Endoscopy	Natural History	Cytosponge	Endoscopy
Total Clinical EAC	16.25	8.82	7.09	13.75	5.13	3.06
Total Screen-Detected EAC	0.00	4.33	5.35	0.00	3.05	3.74
Total EAC	16.25	13.15	12.44	13.75	8.18	6.8
Endoscopies	0	757	1,826	0	1197	2296
Cost (discounted)	$762,043	$1,485,205	$2,089,549	$703,690	$1,597,713	$2,185,741
QALY (discounted)	15,078	15,099	15,101	15,076	15,110	15,116

All results are reported per 1000 GERD patients at start of screening.

Both models found the Cytosponge to be cost effective compared with no screening in the base-case analysis, with an ICER of $26,358 to $33,307 (***Figure 1***). Both models found that endoscopic screening was not cost effective when Cytosponge-first screening was available as an alternative; the ICER for endoscopic screening compared with the Cytosponge was $107,583 to $330,361 greater than our willingness-to-pay threshold of $100,000. The large cost difference between the Cytosponge and endoscopic screening was driven primarily by the total number of endoscopies needed. The models predicted 757 to 1197 screening or surveillance endoscopies would be needed using the Cytosponge strategy, compared with 1826 to 2296 using the endoscopic screening strategy.

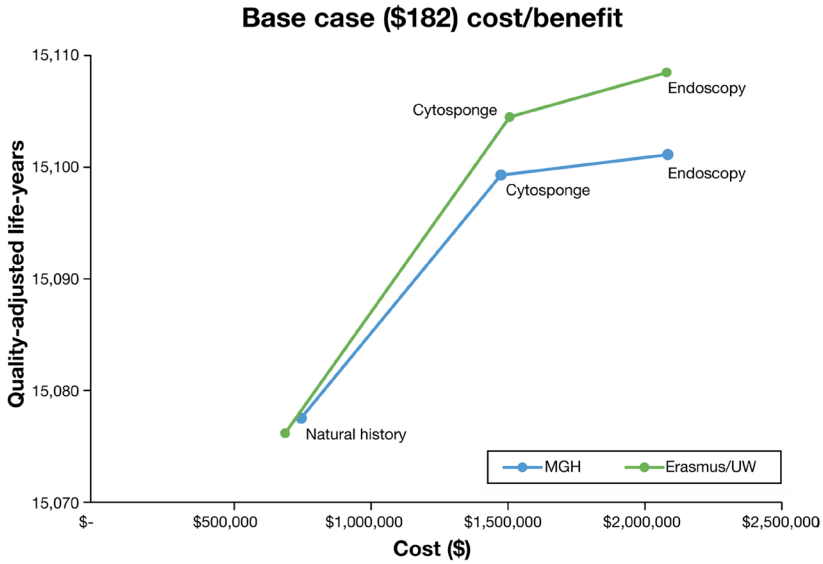

Figure 1. Cost/benefit curves for the MGH (blue) and Erasmus/UW (green) models. All numbers are reported per 1000 GERD patients at start of screening.

Sensitivity Analyses

Results of a 1-way sensitivity analysis on the Cytosponge cost are shown in ***Figure 2***. Endoscopic screening becomes cost effective (given a $100,000 willingness-to-pay-threshold) when the total cost of the Cytosponge exceeds $604 (MGH) or $224 (Erasmus/UW). Furthermore, endoscopic screening is a dominant strategy when the Cytosponge cost exceeds $684 (MGH) or $565 (Erasmus/UW). Thus, our results are sensitive to the Cytosponge cost within the range deemed plausible for this analysis; it is notable, however, that the Cytosponge remains cost effective over a majority of this range.

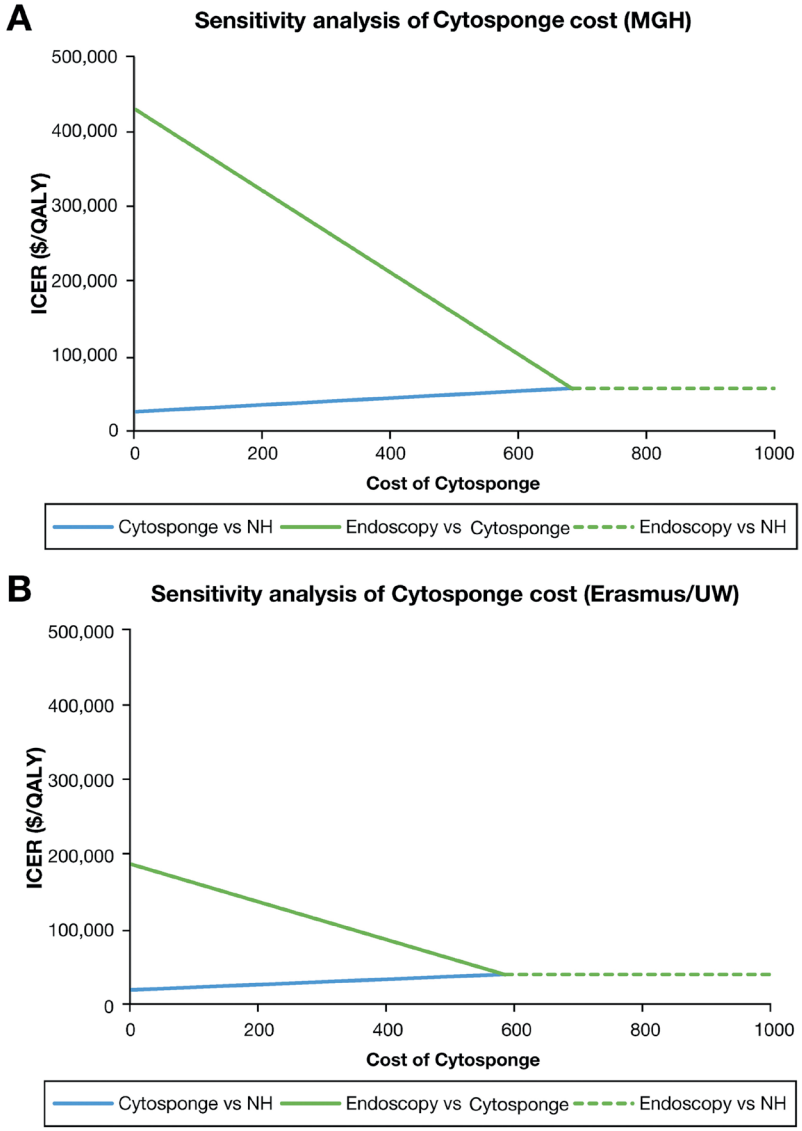

Figure 2. Sensitivity analysis of cytosponge cost performed with the MGH and Erasmus/UW models. ICERs corresponding to the efficiency frontier are shown at each point.

Results of all other 1-way analyses are provided in the ***Supplementary Materials*** and ***Supplementary Tables 3 and 4***. In an analysis of screening for 60-year-old women with GERD symptoms, the Cytosponge remained cost effective (ICER, $86,850–$89,674 compared with natural history) despite the lower incidence of EAC in women. Endoscopic screening was strictly dominated in this analysis. Our findings were somewhat sensitive to estimates of the performance characteristics of

the Cytosponge and RFA characteristics. With low estimates of Cytosponge sensitivity and specificity, the Cytosponge remains cost effective (ICER, $29,172–$34,758). However, comparing endoscopy with the Cytosponge we found an ICER of $64,031 to $191,076, therefore endoscopy may be a viable strategy given a willingness-to-pay threshold of $100,000 if the diagnostic accuracy of the Cytosponge is sufficiently poor. In addition, endoscopy may be viable if the recurrence rates after EET are low or if the effectiveness is high, with endoscopy to Cytosponge ICERS of $83,686 to $314,574 and $98,227 to $303,055, respectively. Our findings were robust to inclusion of indirect costs, sex, and choice of initial screening age (ages, 50, 60, or 70 y); in each analysis, the Cytosponge remained cost effective whereas endoscopic screening exceeded the willingness-to-pay threshold.

Finally, a probabilistic sensitivity analysis was performed using the MGH model. With a fixed Cytosponge cost of $182 and a willingness-to-pay threshold fixed at $100,000, our results were consistent across all runs. The Cytosponge was found to be cost effective with an ICER ranging from $32,567 to $36,353 compared with natural history; endoscopic screening was not cost effective with an ICER ranging from $234,762 to $423,809 compared with the Cytosponge. When the Cytosponge cost was increased to $500, the strategy remained cost effective in all PSA runs, with an ICER ranging from $47,326 to $51,822 compared with natural history. The ICER for endoscopic screening compared with the Cytosponge remained greater than the willingness-to-pay threshold in all runs, ranging from $106,630 to $206,272. Further details including alternate analyses with other willingness-to-pay thresholds and Cytosponge costs can be found in the ***Supplementary Materials, Supplementary Tables 2 and 3,*** and ***Supplementary Figure 1***, ***Supplementary Figure 2***, ***Supplementary Figure 3***, ***Supplementary Figure 4***.

DISCUSSION

Our comparative modeling analysis finds that, for male 60-year old patients with GERD symptoms, an initial cytosponge screen may be a cost-effective way to reduce the incidence and mortality of esophageal adenocarcinoma. Cytosponge screening could results in significant cost savings compared to screening with endoscopy. These findings are consistent with those of a previous UK modeling analysis which used preliminary cytosponge data.[17]

This cost savings is driven in part by the large difference in the estimated cost of a single endoscopy compared to administration of a cytosponge screen. An additional

driver of cost reduction in the cytosponge strategy is the reduction in the number of false positive results; although the estimated false positive rate for cytosponge was higher than that of endoscopy, the combined false positive rate for cytosponge with endoscopic confirmation is lower than that of a single endoscopy. This leads to a reduction to the number of people who enter surveillance and thus to the total number of endoscopies and EET sessions.

A significant strength of our analysis is the comparative modeling approach. Although the two models share a number of common inputs (including costs of all procedures, test performance characteristics, estimates of EET effectiveness, and SEER incidence and mortality as calibration targets), they were developed and calibrated independently, use different mathematical methods, and make different quantitative and structural assumptions regarding the natural history of EAC development. For example, the models rely on different estimates of BE prevalence, and the Erasmus/UW model incorporates regression while the MGH model does not. Although both models are calibrated to SEER incidence data, this constrains only the overall progression rate to EAC in the total population, leaving room for differences in the relative risk of BE or cancer development associated with GERD symptoms. Detailed profiles of both models as well as a broad comparative overview are available online.[13,14] The consistency of our model results in this analysis suggests a degree of robustness in our findings to the uncertainties that these model differences represent.

In our analysis we have considered the use of cytosponge only as a method of first-line screening for BE using the TFF3 biomarker. We did not consider cytosponge-based surveillance strategies, as BE surveillance requires discrimination between non-dysplastic BE, low grade dysplasia, and high grade dysplasia, in order to determine appropriate surveillance intervals and treatment options. Currently this level of detail requires endoscopic diagnosis. However, with additional biomarkers or panels, cytosponge tissue collection could potentially allow for the accurate identification of dysplasia, which could significantly alter the role of cytosponge in EAC prevention.

We chose to compare cytosponge with no screening or endoscopic screening as endoscopy with biopsy is the current standard for diagnosis of BE. Other low-cost, minimally-invasive alternatives to conventional endoscopy such as unsedated transnasal endoscopy and tethered capsule endoscopy are promising and potentially disruptive technologies that are accruing clinical evidence and may be viable options in the future.[18,19]

A significant limitation of our analysis is the dependence of our results on estimates of uncertain parameters, including screening-related test-performance characteristics, complications, quality of life adjustments, and parameters governing the natural history of EAC such as the independently optimized estimates of BE prevalence during the development of each model. To mitigate this limitation, we used the most reliable and up to date parameter estimates available in the literature, and performed both one-way sensitivity analyses and probabilistic sensitivity analysis. Further, our use of a comparative modeling approach provides a check against structural uncertainty in our knowledge of EAC natural history.

Another limitation is the uncertainty regarding the cost of the cytosponge. It is possible that the cost of the cytosponge could be significantly different from our base-case estimate once implemented in clinical practice. We addressed the limitation with multiple sensitivity analyses, both one way and probabilistic (MGH only). However, results continue to be robust at twice the cost of the base-case estimate of $182; it is not until the cost of the cytosponge exceeds $684 (MGH) or $565 (Erasmus/UW) that endoscopy becomes the dominant strategy.

Our analysis did not incorporate adherence rates; we assumed perfect compliance with the specified screening strategies as well as with all follow-up surveillance and treatment. Thus the effectiveness of both cytosponge and endoscopic screening are likely somewhat exaggerated in our models. In measures of acceptability, cytosponge has generally outperformed endoscopy in trials conducted to date.[20-22] Additionally, cytosponge screening can be performed in a brief outpatient visit, compared to endoscopy which in the US is typically performed with sedation. Cytosponge may therefore have higher adherence rates compared to endoscopy, particularly among patients who have difficulty taking time off work or arranging post-procedure transportation. Thus in practice the differences in effectiveness between cytosponge and endoscopic screening may be smaller (or more favorable to cytosponge) than estimated by our models.

Our analyses focused on cohorts of men with GERD symptoms. Limited numbers of female patients in the BEST2 study make it difficult to inform the performance characteristics of cytosponge for this cohort. Nonetheless, we conducted a sensitivity analysis which indicated cytosponge screening would be cost-effective for 60-year-old women with GERD symptoms. This finding should be read as provisional until adequate data become available to inform a more robust analysis.

In conclusion, our comparative modeling analysis finds that a cytosponge-first strategy may be a cost-effective way to screen for BE and reduce the harms associated with esophageal adenocarcinoma in patients with GERD symptoms. Additionally, both models found endoscopic screening to be a non-cost-effective approach. These findings were consistent in both models but were sensitive to the cost of cytosponge.

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Chapter 2 Supplementary Materials

PROBABILISTIC SENSITIVITY ANALYSIS

Overview

A probabilistic sensitivity analysis (PSA) was conducted to assess the robustness of our findings to uncertainty in model parameters. Parameter distributions were estimated from the literature and expert opinion. Sets of parameters were generated jointly from these distributions using the Metropolis-Hastings algorithm[1] to avoid parameter sets with low combined probability. 10000 parameter sets were generated; the last 1000 were used as inputs to the MGH model for runs of 10M patients each. Cost-effectiveness calculations were performed for each run, at various values of cytosponge cost and willingness-to-pay.

Estimation of Parameter Distributions

The distributions used in the PSA are listed in ***Supplementary Table 1***. Distributions are specified as Beta(alpha, beta) or Normal(mean, standard deviation).

The BEST2 trial provides data which allows us to fit beta distributions for cytosponge performance characteristics directly. For the performance characteristics of endoscopy, we used point-estimates found in the literature as means, and fitted distributions with variances based on the analogous cytosponge parameters. Distributions for utility adjustments are similarly based on point-estimates from the literature, with variance calculated based only on the order of magnitude of the point-estimate.

We use conditional beta distributions for parameters such as post-recurrence histology where exactly one of several possibilities must occur. This allows us to generate random values for the relevant probabilities that are guaranteed to sum to one.

Costs (with the exception of cytosponge) were calculated based on Medicare reimbursement rates. We assume the variation in reimbursement rates is small and use a standard deviation of 25 dollars.

Results

Given a base case price of $182 for cytosponge and a willingness-to-pay (WTP) threshold of $100,000/QALY, cytosponge is cost-effective and endoscopy is beyond the WTP threshold in 100% of runs. The ICER for cytosponge compared to natural history remained in a relatively small range, $32,567 to $36,354, indicating that our

results are robust to the estimated uncertainties in the included parameters. The ICER for endoscopy compared to cytosponge ranged from $234,762 to $423,809.

For each PSA run, we chose a 'best' strategy by first identifying the set of strategies which were cost-effective (i.e., on the efficiency frontier with an ICER below WTP), then selecting among those the strategy which yielded the greatest number of QALYs. By these criteria, cytosponge was the best strategy in 100% of runs with the fixed values of cytosponge cost and WTP mentioned above.

We conducted a further sensitivity analysis in which the PSA was repeated at values of cytosponge cost between $0 and $1000; for each cost point, we determined the proportion of runs in which cytosponge, endoscopy, or natural history was the best strategy. These proportions are plotted in ***Supplementary Figure 1***. Cytosponge was the best strategy in all runs for every value of cytosponge cost below $519. Above a cytosponge cost of $671, endoscopy is always the best strategy. Between these two values the cytosponge/endoscopy comparison is subject to heightened uncertainty.

All previous analyses were conducted with a fixed WTP threshold of $100,000. We examined the impact of this choice of threshold by varying the WTP from $0 to $250,000 and performing PSA at values in between. We plot the proportion of runs favoring each strategy at each point in ***Supplementary Figure 2***. Natural history is the favored strategy if willingness-to-pay is very low, between $0 and about $50,000. Between $52,000 and $106,000 cytosponge is favored in all PSA runs, while above $206,000 endoscopy is always favored, leaving a sizable range of varying degrees of uncertainty. For instance, at a WTP of $125,000, cytosponge is favored 83% of the time, endoscopy 17%. At $150,000, endoscopy is favored in a majority of runs (63%) compared to cytosponge (37%). Thus if societal willingness-to-pay is higher than estimated in our base case analysis, our findings may be subject to considerable uncertainty.

ONE-WAY SENSITIVITY ANALYSES

In addition to the PSA we performed multiple one-way sensitivity analyses on selected parameters, including choice of screening cohort (male or female GERD patients; age 50, 60, or 70), cytosponge performance characteristics, effectiveness and recurrence rates associated with endotherapy, and inclusion or exclusion of indirect patient time costs in total cost estimates. For each analyses the effect on the ICERs of cytosponge compared to natural history, endoscopy compared to natural

history, and endoscopy compared to cytosponge are shown in ***Supplementary Tables 2 and 3***.

Cytosponge and EET Parameters

For cytosponge specificity the upper and lower bounds were taken from the 95% confidence intervals reported by the BEST2 trial.[2] The exact parameter values used for this analysis as well as for the probabilities of recurrence after EET and of initial EET effectiveness are shown in ***Supplementary Table 4***. In the Erasmus/UW model, we found our results to be sensitive to Cytosponge performance characteristics and EET effectiveness and recurrence; endoscopy became cost effective when the model was run with low estimates of Cytosponge sensitivity and specificity, low estimates of EET recurrence, and high estimates of EET effectiveness. In the MGH model, results were robust for all Cytosponge and EET parameters.

Choice of Screening Cohort

The base case population cohort began by screening male patients with GERD symptoms at age 60; we performed additional analyses of male 50 year olds, male 70 year olds, and female 60 year olds, in each case screening those with GERD. Cytosponge remained cost-effective for screening male GERD patients regardless of the screening age considered, and endoscopy remained not cost-effective. Both models conclude that for female GERD, implementing cytosponge screening at age 60 would be cost-effective. The ICER for cytosponge compared to natural history in this analysis was substantially higher (range $86,850 to $89,674) than in the all-male base case but remained below the willingness-to-pay threshold. This result should be read as provisional as the data used to inform cytosponge performance characteristics were based on a predominantly male cohort.

Indirect Costs

Large scale screening efforts can impose considerable time costs on patients (and potential escorts after sedation), including travel time, wait time, the time of the procedure itself, and recovery time. In order to more fully capture the total burden of the interventions under consideration, we performed an alternative analysis in which we incorporated estimates of patient time costs for endoscopic screening, cytosponge screening, endoscopic eradication therapy, and treatment for EAC. Time costs were then converted to US dollars by multiplying by the US median wage of $17.40 per hour.[3]

Because estimates of EAC time cost are not directly available, we used comparable estimates for gastric and colorectal cancer as proxies. The patient time cost of gas-

tric cancer has been estimated at 351.3 hours in the first year after diagnosis and 512.2 hours in the final year of life; we adopted these as costs for the first and last year of EAC.[4] For the time cost of care between the first and final year of cancer, we followed a previous analysis which assumed a monthly time cost equivalent to $27 (2007 dollars) for colorectal cancer.[5] Adjusting for inflation to the year 2015 yielded a monthly continuing EAC cost of $31.16.

We assumed the time costs associated with an upper endoscopy were comparable to those of colonoscopy, as the procedures are similar. A study of colonoscopy time costs found that patients spent a median of 1.1 hours in transit, 2.8 hours at the center (including wait and procedure time), and 17.7 hours from completion of the procedure until returning to normal activity.[6] It is recommended that endoscopy patients arrange for a friend or family member to transport them to and from the facility. This imposes an additional time burden which we accounted for by doubling the transit time and time at center. Finally, the recovery time is an overestimate of patient time lost as it in some cases includes time the patient spent sleeping overnight. To adjust for this, we adjust the recovery time down by a third, arriving at a total endoscopy time cost of 19.6 hours. Finally, we assumed the time cost of endoscopic eradication therapy was the same as that of diagnostic endoscopy.

The time cost of cytosponge screening will depend on its exact implementation within clinical practice; if offered during an annual physical, the incremental time cost may be negligible. As a conservative estimate, we assumed cytosponge screening would be offered as a standalone intervention, so that the patient will spend on average 1·1 hours traveling and 1.4 hours waiting, similar to a colonoscopy patient.[6] In contrast to colonoscopy or upper endoscopy, no sedation is required for the cytosponge procedure, so that it is unnecessary for anyone to accompany the patient. Finally, we assumed the procedure time to be 0.3 h, resulting in a total time cost of 2.8 hours.

Cost-effectiveness results for this alternative analysis including indirect cost are shown alongside the base case results in ***Supplementary Figures 3 and 4***. Despite the substantial effect this perspective has on procedure costs, our conclusions are largely unaffected; we find cytosponge to be cost-effective with an ICER of $40,934 to $48,749 compared to natural history while endoscopy is not cost-effective. This is in part because the time costs of screening, surveillance, and endoscopic eradication treatment are partially offset by reductions in EAC and its heavy associated time costs.

Supplementary Table 1: Probability Sensitivity Analysis Parameters and Distributions

		Parameter	Distribution	Source
Cytosponge Parameters		False Positive	Beta(34, 411)	[2]
		False Negative ND	Beta(78, 294)	[2]
		False Negative LGD	Beta(14, 63)	[2]
		False Negative HGD	Beta(16, 85)	[2]
		Complication Rate	Beta(2, 998)	[2]
Endoscopy Parameters		False Negative	Beta(31, 214)	
		False Positive	Beta(33, 405)	
		Cost	Normal(745·36, 25)	[7]
		Complication Rate	Beta(275, 211135)	[8]
RFA Costs		Cost of Initial Treatment	Normal(5630, 25)	[7]
		Cost of Touchups	Normal(1012, 25)	[7]
Histology After Post-CE-IM Recurrence Event by Pre-RFA Health State	Pre-RFA NDBE	Post-recurrence NDBE	Beta(110, 9)	[9,10]
		Post-recurrence LGD*	Beta(7, 2)	[9,10]
		Post-recurrence HGD*	Beta(2.5, 0.5)	[9,10]
		Post-recurrence EAC*		[9,10]
	Pre-RFA LGD	Post-recurrence NDBE	Beta(78, 17)	[9,10]
		Post-recurrence LGD*	Beta(13, 4)	[9,10]
		Post-recurrence HGD*	Beta(2,2)	[9,10]
		Post-recurrence EAC*		[9,10]
	Pre-RFA HGD	Post-recurrence NDBE	Beta(64, 29)	[9,10]
		Post-recurrence LGD*	Beta(14, 15)	[9,10]
		Post-recurrence HGD*	Beta(9, 6)	[9,10]
		Post-recurrence EAC*		[9,10]
Probability of Recurrence Event After RFA by Pre-RFA Health State		Pre-RFA NDBE	Beta(47, 621)	[9,10]
		Pre-RFA LGD/IND	Beta(46, 437)	[9,10]
		HGD	Beta(42, 374)	[9,10]
Effectiveness by Pre-RFA Health State	Pre-RFA HGD	CE-D	Beta(607, 107)	[11]
		CE-IM given CE-D	Beta(122, 485)	[11]
	Pre-RFA LGD	CE-D	Beta(581, 52)	[11]
		CE-IM given CE-D	Beta(123, 458)	[11]
	Pre-RFA NDBE	CE-IM	Beta(941, 220)	[11]
Complications		Perforation Rate	Beta(5,19995)	[11]
		Stricture Rate	Beta(27, 513)	[11]

Supplementary Table 1: Probability Sensitivity Analysis Parameters and Distributions (*continued*)

	Parameter	Distribution	Source
Quality of Life Adjustments	Local EAC Utility	Beta(46, 9)	
	Regional EAC Utility	Beta(59, 31)	
	Distant EAC Utility	Beta(38, 59)	
	Unstaged EAC Utility	Beta(59, 35)	
	Post-treatment EAC Utility	Beta(15, 1)	
	Endoscopy Penalty	Beta(15, 7642)	
	EET or Stricture Penalty	Beta(132, 22750)	
Cancer Costs	Localized – First Year	Normal (46752, 2806.1224)	[12]
	Localized – Last Year	Normal (51274, 3207.1428)	[12]
	Regional – First Year	Normal (59667, 3835.7)	[12]
	Regional – Last Year	Normal (61606, 2534.1836)	[12]
	Distant – First Year	Normal (45303, 5572.9591)	[12]
	Distant – Last Year	Normal (67526, 2826.0204)	[12]
	Continuing Care	Normal(3102, 416.84)	[12]
	Unstaged	Average of Local/ Regional/Distant	[12]

*Post-recurrence histology probabilities are implemented as conditional beta distributions. EAC histology probability is calculated as 1 minus the sum of probabilities of the other states.
ND: No Dysplasia, LGD: Low Grade Dysplasia, HGD: High Grade Dysplasia, EGD: Esophagogastroduodenoscopy, RFA: Radiofrequency Ablation, NDBE: No Dysplasia Barret's Esophagus, CE-D: Complete Eradication of Dysplasia, CE-IM: Complete Eradication of Intestinal Metaplasia

Supplementary Table 2: Base values and sensitivity parameters

	Base value			Lower value			Upper value		
Durability of successful treatment									
Annual recurrence probability	**Pre-treatment histology**			**Pre-treatment histology**			**Pre-treatment histology**		
	NDBE	LGD	HGD	NDBE	LGD	HGD	NDBE	LGD	HGD
	7.0%	10.7%	10.0%	3.5%	5.4%	5.0%	14.0%	21.5%	20.0%
Effectiveness of the initial treatment									
Success of therapy in pre-treatment HGD patients									
CE – IM and CE-D	0.680			0.644			0.889		
Non CE-IM, CE-D	0.171			0.178			0.037		
Success of therapy in pre-treatment LGD patients									
CE – IM and CE-D	0.724			0.678			0.981		
Non-CE-IM, CE-D	0.194			0.211			0.000		
Success of therapy in pre-treatment ND patients									
CE – IM	0.811			0.685			0.984		
Non CE-IM	0.189			0.315			0.016		
Cytosponge Performance characteristics									
Specificity	92.4%			90.0%			95.0%		
ND Sensitivity	79.0%			74.5%			83.0%		
LGD Sensitivity	80.5%			69.9%			88.7%		
HGD Sensitivity	84.2%			75.6%			90.7%		

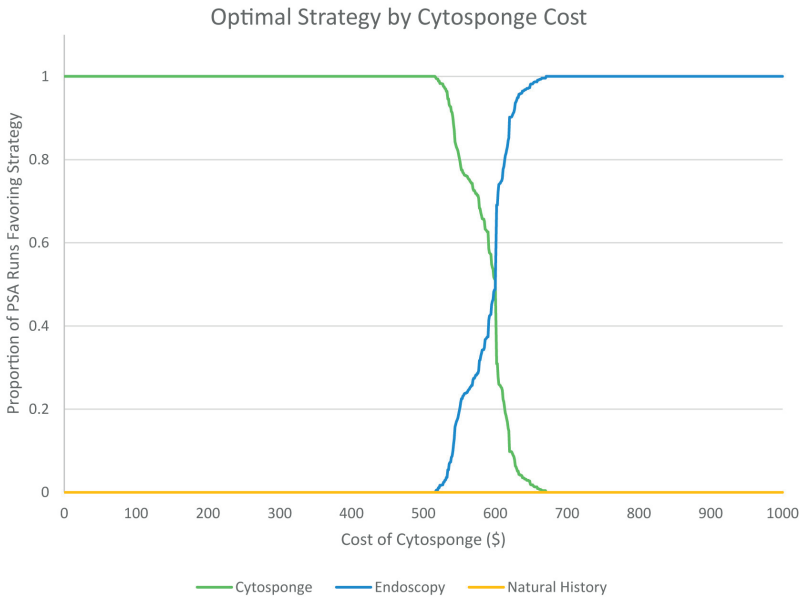
EAC: esophageal adenocarcinoma, CE: Complete eradication, IM: intestinal metaplasia, D: dysplasia, ND: no dysplasia, BE: Barrett's esophagus, LGD: low-grade dysplasia, HGD: high-grade dysplasia

Supplementary Table 3: Results of Sensitivity Analyses – MGH Model

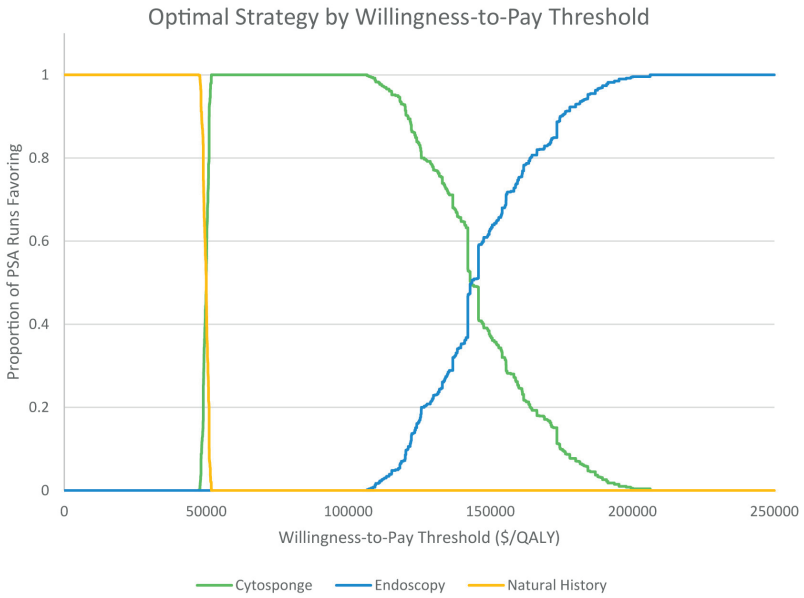
Analysis		Cytosponge vs. Natural History ICER ($)	Endoscopy vs. Natural History ICER ($)	Endoscopy vs. Cytosponge ICER ($)
All Female		89,674	211,332	(dominated)
Cytosponge Performance Characteristics	Upper Bound	32,168	56,391	823,979
	Lower Bound	34,758	56,391	191,076
Radiofrequency Ablation Effectiveness	Upper Bound	31,564	53,720	303,055
	Lower Bound	41,981	70,579	547,718
Recurrence after Radiofrequency Ablation	Upper Bound	34,709	58,480	346,459
	Lower Bound	32,380	54,952	314,574
Start-Age 50		27,561	62,990	298,929
Start-Age 70		45,435	74,279	722,430
Indirect costs		48,749	84,365	507,069

Supplementary Table 4: Results of Sensitivity Analyses – Erasmus/UW Model

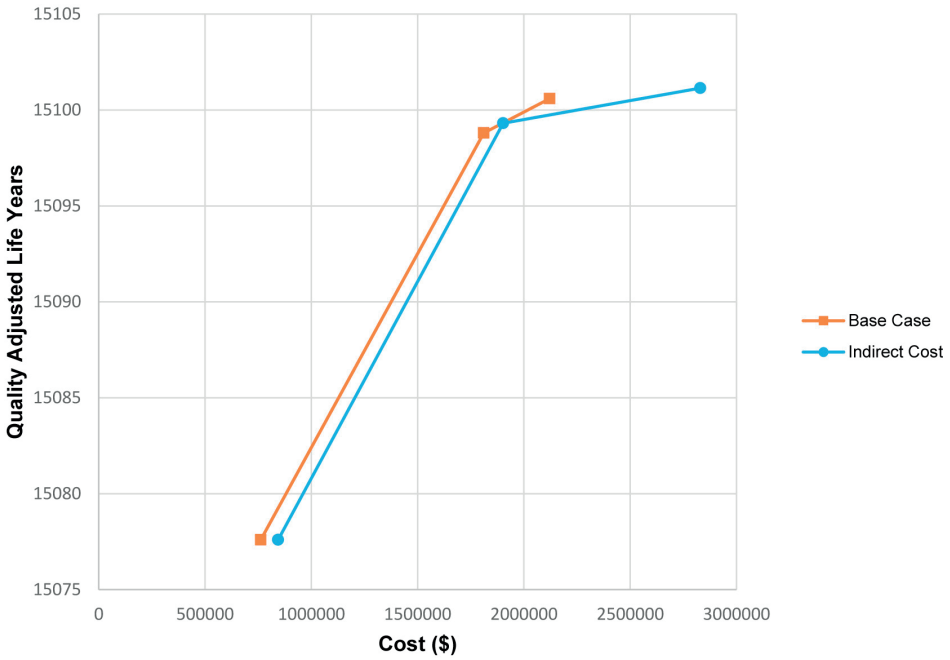
Analysis		Cytosponge vs. Natural History ICER ($)	Endoscopy vs. Natural History ICER ($)	Endoscopy vs. Cytosponge ICER ($)
All Female		86,850	251,354	(dominated)
Cytosponge Performance Characteristics	Upper Bound	24,769	37,630	215,674
	Lower Bound	29,172	37,630	64,031
Radiofrequency Ablation Effectiveness	Upper Bound	23,787	34,320	98,277
	Lower Bound	27,603	39,245	112,499
Recurrence after Radiofrequency Ablation	Upper Bound	27,583	39,056	110,470
	Lower Bound	25,546	35,183	83,686
Start-Age 50		21,664	37,653	127,320
Start-Age 70		39,576	58,548	283,514
Indirect costs		40,934	58,689	168,871



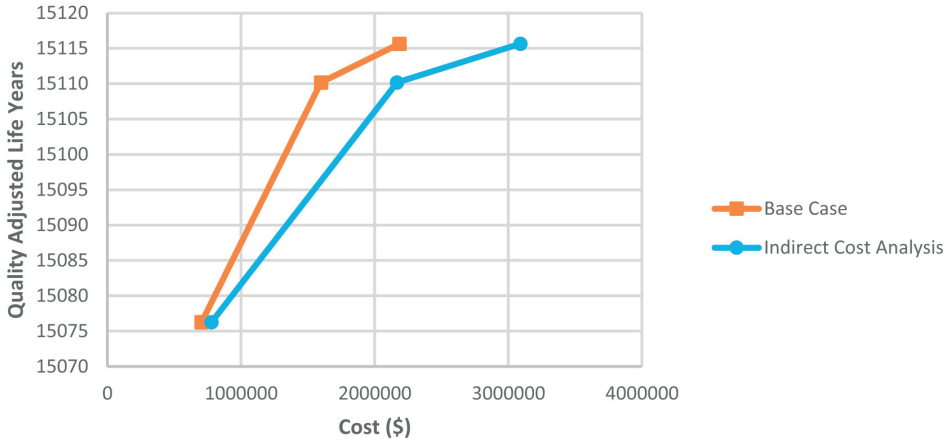
Supplementary Figure 1: Proportion of PSA Runs Favoring Each Strategy by Willingness-to-Pay (MGH Model)



Supplementary Figure 2: Proportion of PSA Runs Favoring Each Strategy by Willingness-to-Pay (MGH Model)



Supplementary Figure 3: Indirect Cost Adjustment and Base Case Results (MGH Model)



Supplementary Figure 4: Indirect Cost Adjustment and Base Case Results (Erasmus/UW Model)

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3

Impact of unrelated health and cost outcomes on the cost-effectiveness of cancer screening; A model exploration

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ABSTRACT

Objectives

In evaluations of cancer prevention strategies, future health outcomes and costs unrelated to the condition of primary interest are often not completely taken into account. This may bias decision making based on cost-effectiveness outcomes. We explored the possible impact of this in the context of colorectal cancer (CRC) and esophageal adenocarcinoma (EAC) screening.

Methods

The Microsimulation Screening Analysis (MISCAN) model was used to simulate a 40-year-old US population undergoing either one of 20 colonoscopy screening strategies varying in start age, stop age, and intervals; and a 60-year-old cohort of US men with gastroesophageal reflux symptoms undergoing once-only screening with endoscopy or cytosponge. Incremental cost-effectiveness analysis with a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY) gained was used to determine optimal strategies with and without adjustments for unrelated health.

Results

For CRC, the analysis without adjustments identified three cost-effective screening strategies. The optimal strategy was the currently recommended colonoscopy every 10 years from age 50 through 75 years, with an incremental cost of $63,200/QALY. For EAC, the incremental costs per QALY for cytosponge and endoscopy screening were $26,400 and $107,600, respectively. For CRC, with adjustments for unrelated health outcomes and costs, only one colonoscopy screening strategy remained cost-effective; the currently recommended strategy was no longer cost-effective. For EAC, cost-effectiveness ratios nearly doubled.

Conclusions

Unrelated health outcomes and costs may substantially impact cost-effectiveness estimates for cancer screening. This underscores their importance, and challenges conventional cost-acceptance thresholds which no longer included these strategies.

INTRODUCTION

Cancer is the leading cause of death in many Western countries.[1] Screening can be effective for preventing disease incidence and mortality, and has been widely recommended for several types of cancer, including breast, colorectal, and cervical cancer.[2-4] Recommendations for screening are generally based primarily on convincing evidence for its effectiveness[5, 6] in acceptable balance to harms and cost.[7] Cost-effectiveness analysis integrates these aspects into a composite metric, such as the cost per QALY gained, and is increasingly used for health services evaluation.

Cost-effectiveness analysis is meaningful only if researchers realistically represent health effects and associated costs, whether related or unrelated to the condition of primary interest.[8] Cancer has many shared risk factors with other conditions,[9] suggesting that patients in whom cancer is prevented may be at increased risk of other conditions. For example, screening for lung cancer in average-risk populations will likely decrease the risk of death from lung cancer.[10] However, those who benefit from lung cancer screening are mostly smokers with a relatively high risk of unrelated conditions, with implications for expected life-years gained (LYG), quality of life, and costs.

A particular challenge in screening evaluation is the lack of data specific to those who benefit from screening. A common assumption is that those who benefit are similar to those invited (i.e. the broader population) in terms of the risk of unrelated conditions, which may misrepresent true risks. On the basis of such assumptions, numerous modeling studies have suggested that screening for various types of cancer may be cost-effective at common willingness-to-pay thresholds.[11-14] However, to our knowledge, few existing models for cancer screening consider potential (excess risk of) unrelated conditions for those in whom screening averts cancer.[15]

In this study, we used an established microsimulation model to investigate the potential impact of accurately representing unrelated health outcomes on the cost-effectiveness of two types of cancer screening: screening for colorectal cancer (CRC) in the general population, and screening for esophageal adenocarcinoma (EAC) in people with gastroesophageal reflux disease (GERD) symptoms.

METHODS

We used the Microsimulation Screening Analysis (MISCAN) model to estimate the cost-effectiveness of a selection of previously evaluated screening strategies for CRC and EAC under a range of assumptions for unrelated health effects on life expectancy, quality of life, and health care utilization. For the purposes of this illustration, costs were expressed in US dollar and considered from a healthcare sector perspective, including all health-related expenses. (***Supplementary Table 1***). All costs All costs were adjusted for year 2015 using the US consumer price index and both costs and effects were discounted at an annual rate of 3%.

Microsimulation modeling

The MISCAN was developed by the Department of Public Health, Erasmus MC University Medical Center Rotterdam, and is being used as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). The model has previously informed cancer screening recommendation by the United States (US) Preventive Services Task Force and the American Cancer Society,[16, 17] and has been described in detail elsewhere.[18-21] MISCAN simulates the relevant life histories for a synthetic population reflective of the US population, or a subset of the population. First, a date of birth and date of death for each individual is simulated based on US life tables.[22] During their lifetime, individuals may develop cancer through a number of diseases states, from healthy, through benign precursor lesions (small, medium, or large adenoma for CRC, and Barrett's esophagus (BE) with no, low-grade, or high-grade dysplasia for EAC), through preclinical cancer, to clinical (symptomatic) cancer (***Figure 1***). A person may die from clinical cancer, or from other causes first. Screening may lead to gains in LY through detection and treatment of cancer in an earlier stage, or through detection and treatment of precancerous lesion.

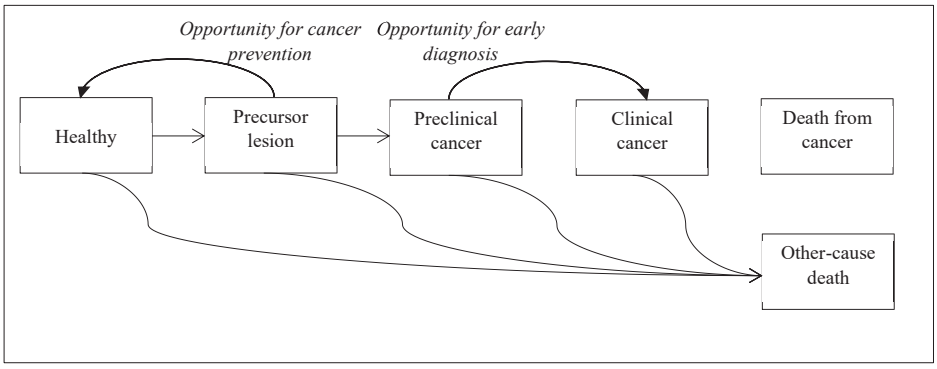


Figure 1. The MISCAN model

Screening strategies

We re-evaluated a number of strategies that were considered before in previous studies.[16, 23] For CRC, we simulated an average-risk US population cohort aged 40 years, without diagnosed cancer. For EAC, we simulated a 60-year-old US male population with GERD symptoms. First, we followed both cohorts without any interventions until death (natural history scenario). Then, for CRC, 20 unique colonoscopy screening strategies were evaluated with varying start ages (45, 55, 65), stopping ages (75, 80, 85), and intervals (5, 10, 15). Patients with detected adenomas received colonoscopy surveillance in 3-5 years depending on risk characteristics, as suggested by US guidelines.[24] For EAC, we evaluated two different screening methods: once-only screening at age 60 years with either endoscopy or cytosponge with endoscopy follow-up of positive cytosponge results.[23] Patients with detected BE entered surveillance or received endoscopic therapy in accordance with guidelines.[25]

Cost-effectiveness definition

Cost-effectiveness was defined as the ratio of incremental costs over incremental QALY gained of one strategy *vs.* another (or no screening). The numerator consists of the incremental costs related and unrelated to cancer, while the denominator (Effect) consists of the LYG minus the net harms (disutilities) related and unrelated to cancer:

$$CER = \frac{C^r + C^u}{LYG - U^r - U^u} \quad \textbf{(1)}$$

The costs and harms related to cancer can be further decomposed into those related to screening ($C^{r,scr}$, $U^{r,scr}$) or therapy ($c^{r,ca}$ and $u^{r,ca}$ per life year in therapy). The costs and disutilities unrelated to cancer can be decomposed into those for life years with ($c^{u,ca}$, $u^{u,ca}$ per LY^{ca}) and without the disease ($c^{u,nc}$, $u^{u,nc}$ per LY^{nc}). Incorporating this, formula (1) becomes:

$$CER = \frac{C^{r,scr} + (c^{r,ca} + c^{u,ca})\,\Delta LY^{ca} + c^{u,nc}\Delta LY^{nc}}{LYG - U^{r,scr} - (u^{r,ca} + u^{u,ca})\,\Delta LY^{ca} - u^{u,nc}\Delta LY^{nc}} \quad \textbf{(2)}$$

Screening can add life years with or without cancer, and convert life years from non-cancer to cancer status or vice versa, due to early diagnosis or removal of preclinical lesions, respectively (***Figure 1***). Considering this, and assuming that $c^u = c^{u,ca} = c^{u,nc}$ and $u^u = u^{u,ca} = u^{u,nc}$ for patients with preclinical lesions, formula (2) can be simplified (**Supplementary Panel 1**) to:

$$CER = \frac{C^{r,scr} + c^{r,ca}\,\Delta LY^{ca} + c^u LYG}{LYG - U^{r,scr} - u^{r,ca}\,\Delta LY^{ca} - u^u LYG} \quad \textbf{(3)}$$

Where LYG includes life years with and without cancer (LYG^{ca}, LYG^{nc}).

Although we do not show further distinctions here in life years with cancer by stage or phase of care, or in screening tests and screening-related complications, these distinctions were made in actual outcome calculations (See assumptions below). Although we did not label LYG as either related or unrelated to cancer above, we allow for possible adjustment of *expected* LYG based on general population data ($E[LYG^{ca}]$, $E[LYG^{nc}]$) by a factor *h* to consider potential excess risk of competing conditions (e.g. $[1- \underline{h}^{nc}]\ E[LYG^{nc}]$).

Unrelated health assumptions

We considered two scenarios for unrelated health outcomes and costs: one with *standard* and one with *adjusted* model assumptions.

Assumptions for the costs and disutilities of screening ($C^{r,scr}$, $U^{r,scr}$) were not varied (***Supplementary Table 2***). For patients with cancer, *standard* assumptions for survival (life expectancy, $E[LYG^{ca}]$) were based on recent Surveillance Epidemiology and End Results program (SEER) data according to age, stage of diagnosis, and anatomic subsite (***Table 1***);[26] assumed disutilities ($u^{r,ca}$) of 4%-70% for receipt of cancer care by stage and phase of care were based on published literature (***Supplementary Table 2***);[27-29] assumed net costs of cancer care ($c^{r,ca}$) by stage and phase of care of $3,100-86,800 were based on SEER-Medicare linked data with average-risk controls (***Supplementary Table 2***).[30] Under *adjusted* assumptions, no changes were assumed in cancer survival, since the source data include deaths from cancer and other causes. However, we considered up to 5% loss in quality of life for unrelated conditions ($u^{u,ca}$), similar to the estimated lack in quality of life associated with stage I CRC.[29, 31] To account for other conditions not included in net cost estimates, we considered $0-17,000 unrelated costs ($c^{u,ca}$).[32] In addition, to account for potential higher baseline expenses in patients with cancer due to potential excess risk of other conditions compared with the general population,[33-35] we decreased the related costs ($c^{r,ca}$) by up to $7,000 (average cancer care cost for stage I CRC) (***Table 1***).

For patients without cancer, under *standard* model assumptions, life expectancy ($E[LYG^{nc}]$) was calculated based on US population life tables,[22] quality of life was assumed to a perfectly healthy patient, and the incremental cost per life year gained was assumed zero (i.e., disutilities and costs were considered only for screening and therapy) (***Table 1***). In the scenario with *adjusted* assumptions for unrelated health, the quantity of life years lived (life expectancy) was decreased by up to 20% (h^{nc}) in both CRC and EAC models to reflect observed excess all-cause mortality for precursor adenoma or BE patients *vs*. the general population[38, 39] Similar as above, we assumed up to 5% disutility for unrelated conditions ($u^{u,nc}$), and up to $17,000 per LYG for unrelated health care costs ($c^{u,nc}$).

Table 1. Model assumptions regarding life expectancy, quality of life, and cost

Component	Assumption		Standard assumptions		Adjusted assumptions	
	.		Value	Source	Value (range)[a]	Source
Screening	Disutility	$U^{r,scr}$	See Supplementary Table 2		Standard	
	Cost	$C^{r,scr}$	See Supplementary Table 2		Standard	
LY with cancer	Quantity	(LY^{ca})	Age, stage and location-specific	SEER[26]	Standard	SEER [26]
	Unit disutility	Related ($u^{r,ca}$)	4-70%	Literature [36, 37]	Standard	Literature [36, 37]
		Unrelated (u^{u})	0%		0-5%[b]	[29]Literature
	Unit cost	Related ($c^{r,ca}$)	Stage and phase specific, $3,100-86,800 per LYG	SEER-Medicare[30]	Standard *minus* $0-7,000[c,d]	SEER-Medicare[30]
		Unrelated (c^{u})	$0		$0 - $17,000[e] per LYG	Literature[30, 32]
LY without cancer	Quantity	(LY^{nc})	Age-specific	US Life table[22]	Standard *minus* 0- 20%[f]	Literature[38, 39]
	Unit disutility	Related	0%	-	Standard	-
		Unrelated (u^{u})	0%	-	0-5%[b]	Literature[29]
	Unit cost	Related	$0	-	Standard	-
		Unrelated (c^{u})	$0	-	$0-17,000 per LYG[e]	Literature[30, 32]

CRC: colorectal cancer; LY: life year; LYG: life year gained; SEER: The Surveillance, Epidemiology, and End Results program of the National Cancer Institute

[a] We have assumed a range of assumptions for adjusted values.
[b] Decrease to level no worse than stage I CRC survivors to reflect possible less-than-average overall health.
[c] $7,000 is the average cancer care cost for stage I CRC across initial, continuous, and final phase of care.
[d] The cancer-attributable costs (c^{r}) in standard assumptions are overestimated because the cost (c^{r}) is computed compared with average-risk controls while the patients with cancer have higher potential baseline expenses due to excess comorbidity.
[e] Increase by up to average health care expenditure per life year in US population ages 45-84 ($10,000) plus average cancer care cost for stage I CRC to reflect expenses for causes other than cancer.
[f] This adjustment is h^{nc} as introduced in the section of *Cost-effectiveness definition*. We assumed that this adjustment effectively only concerns patients with preclinical lesions. Therefore it affects only LYG without cancer.

Analysis

First, we evaluated the outcomes for the currently recommended screening strategies for CRC: colonoscopy every 10 years from age 50 through 75 years and endoscopic screening for EAC at age 60 years, as recommended for GERD patients with multiple risk factors. Outcomes considered were LYG, QALY gained, cost and the average cost-effectiveness ratio (ACER) compared to natural history. Outcomes were evaluated both under standard unrelated health parameters and including the various adjustments described above, both one-by-one and all combined.

Subsequently, we compared the outcomes of all evaluated screening strategies. We assessed incremental cost-effectiveness ratios (ICERs) to determine the recommendable screening strategies under a willingness-to-pay threshold of $100,000 per QALYG.[40] ICERs were assessed only for the efficient options among all evaluated strategies, i.e. strategies on the efficient frontier of QALY gained for a given level of expenses, and were assessed relative to the next less effective strategy on the efficient frontier. Again, we assessed cost-effectiveness both with standard and adjusted assumptions for unrelated health outcomes and costs.

RESULTS

Average cost-effectiveness analysis

For CRC, under standard assumptions for unrelated health, the recommended colonoscopy screening every 10 years between age 50 and 75 years was predicted to result in 74 QALY gained per 1,000 adults, at a net expense of $1.5 million, resulting in an ACER of $20,700 per QALY gained (***Table 2***). Adjustments for the quality of life or quantity of LYs, increased the ACER to maximum $21,900 and $24,700, respectively. ACERs were more sensitive to adjustments for unrelated health care costs. The ACER increased up to $51,700 with higher assumed cost per LY. The joint effect of all considered model adjustments was an increase of the ACER to $63,100 per QALY gained, i.e. a superadditive effect of individual model adjustments. The impact of the considered range of adjustments for unrelated health effects and costs in the CRC model on ACER is presented in ***Figure 2(a)***.

For EAC, under standard assumptions for unrelated health, endoscopy screening was predicted to result in 39 QALY gained per 1,000 patients with GERD symptoms, at a net expense of $1.5 million, yielding an ACER of $37,600 per QALY gained (***Table 2***). Under adjusted assumptions, the ACER increased to $60,900 per QALY gained (***Figure 2(b)***).

Table 2. Results of colorectal cancer (CRC) and esophageal adenocarcinoma (EAC) screening models including and excluding adjustments for unrelated health impacts and associated costs, per 1,000 adults.

	Model results without unrelated health impact and costs adjustments				Model results with 50% of unrelated health impacts and costs adjustments				Model results with maximum unrelated health impacts and costs adjustments			
Strategy [a]	LY gained	QALY gained	Net costs ($mln)	ICER ($/QALY)	LY gained	QALY gained	Net costs ($mln)	ICER ($/QALY)	LY gained	QALY gained	Net costs ($mln)	ICER ($/QALY)
CRC screening strategies												
No screening [b]	22,941	22,919	2.3	N.A.	22,941	22,919	2.3	N.A.	22,941	22,919	2.3	N.A.
COL_55_75_15	65	61	0.9	14,400	59.8	54.9	1.9	33,900	54.9	48.8	2.8	56,600
COL_50_75_15	71	68	1.2	43,300	65.9	61.0	2.3	71,800	60.4	54.1	3.3	105,900 [c]
COL_50_75_10 [d]	77.3	73.6	1.5	63,200	71.4	65.9	2.8	95,000	65.4	58.4	3.9	133,300
COL_45_75_10	83.6	78.5	2.2	135,400	77.0	70.0	3.6	190,500	70.4	61.8	4.8	264,600
COL_45_75_5	90.1	80.6	3.5	640,800	82.8	71.3	5.1	- [e]	75.6	62.4	6.5	- [e]
EAC screening strategies												
No screening [b]	15,081	15,076	0.7	N.A.	15,081	15,076	0.7	N.A.	15,081	15,076	0.7	N.A.
Cytosponge	32.8	33.9	0.9	26,400	30.1	30.5	1.1	37,300	27.4	27.2	1.3	49,100
Endoscopy	40.5	39.4	1.5	107,600	37.1	35.1	1.8	139,400	33.8	31	2.0	180,600

Col: colonoscopy; ICER: incremental cost-effectiveness ratio; LY: Life year; QALY: quality-adjusted life-year.

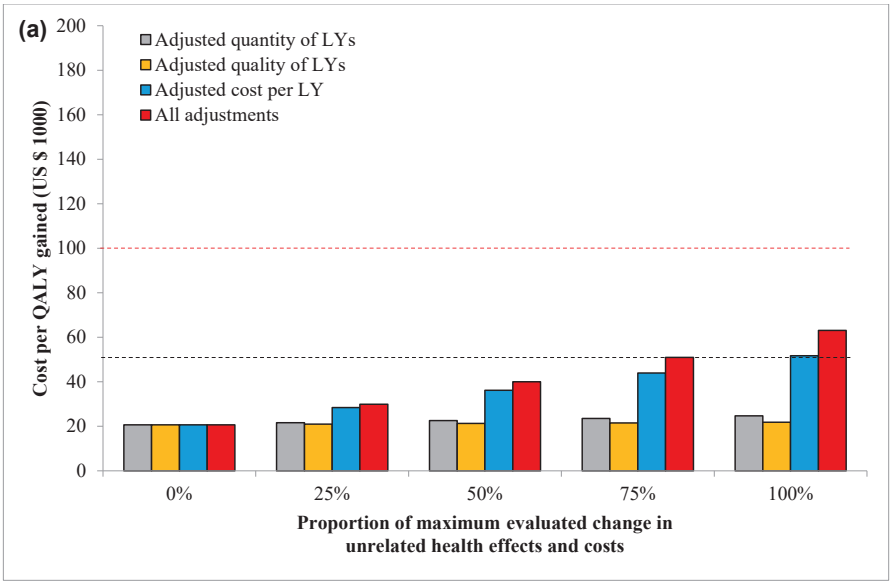
[a] Strategies are characterized as start age-stop age, interval, all in years.

[b] For no screening strategy, the total LYs, QALYs and costs are presented in the table, and the LY and QALY gained and net costs are reported for other strategies.

[c] Red color indicates that a strategy has an incremental cost-effectiveness ratio (R) exceeding the commonly accepted threshold of US $100,000 per quality-adjusted life-year (QALY) gained.

[d] Recommended colonoscopy screening strategy.

[e] Strategy COL_45_75_5 with unrelated health impacts and costs adjustments is dominated by other strategies.



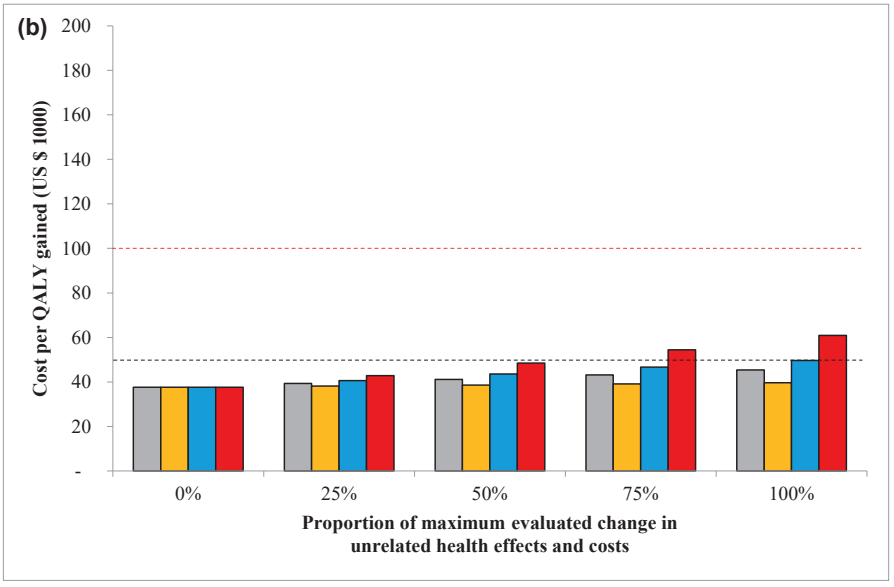


Figure 2. Average cost-effectiveness ratio of the recommended screening strategy for colorectal cancer[b] (a) and esophageal adenocarcinoma[c] (b) vs. no screening, by applied proportion of the maximum considered adjustment in life expectancy, quality of life, and cost for unrelated health (0% is no adjustment, 100% is the maximum adjustment in ***Table 1***).[d]

[a] The scale shows the applied percentage of the maximum adjustments for life expectancy (up to 20% reduction in the quantity of life years (LY)), quality of life of LYs (up to 5% reduction), cost for LY with cancer (up to $17,000 additional cost).

[b] Colonoscopy every 10 years from age 50 through 75 years.

[c] Endoscopy at age 60 in men with gastroesophageal reflux symptoms.

[d] Adjustment for unrelated health effects evaluated are described in ***Table 1***.

Incremental cost-effectiveness analysis

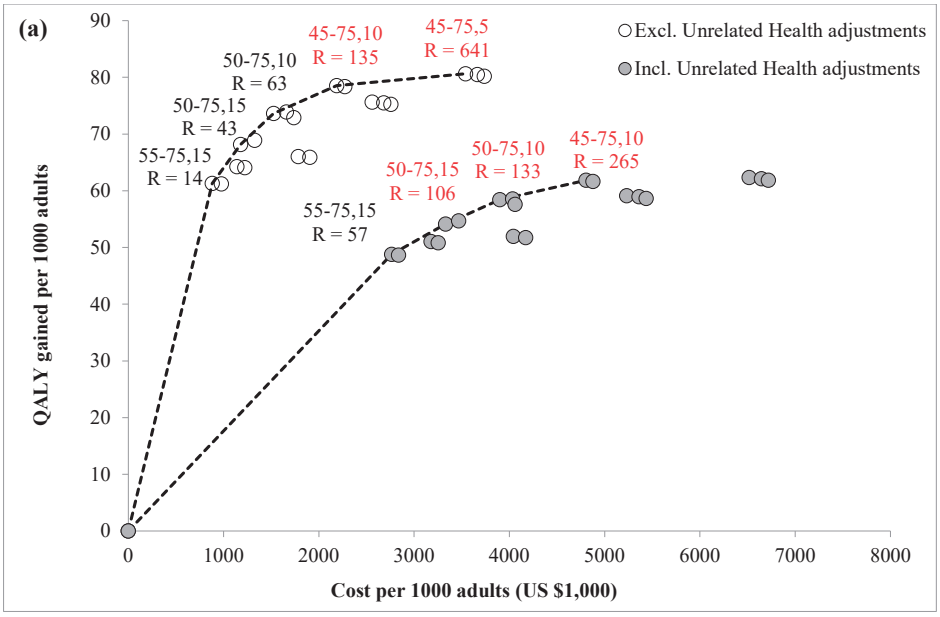
For CRC, when comparing all screening strategies under standard assumptions for unrelated health, there were five colonoscopy screening strategies on the efficient frontier, of which three had an ICER within the accepted threshold of $100,000 per QALY gained (***Table 2***, ***Figure 3a***). The currently recommended colonoscopy screening strategy, colonoscopy every 10 years from age 50 through 75 years, was the optimal (most effective) strategy within the threshold. Under adjusted assumptions, one of the originally efficient strategies was now dominated, and only one strategy maintained an ICER below the willingness-to-pay threshold of $100,000 per QALY gained (colonoscopy every 15 years between age 55 and 75 years). The currently recommended strategy was no longer cost-effective, with an ICER of $133,000.

For EAC, ICERs for cytosponge and endoscopy screening under standard assumptions were $26,400 and $107,600 per QALYG, respectively (***Table 2***, ***Figure 3b***). Under adjusted assumptions, ICERs almost doubled, but cytosponge screening remained cost-effective at $49,100 per QALY gained.

DISCUSSION

In this exploratory study, we estimated the possible impact unrelated health outcomes and associated costs on cost-effectiveness for two cancer prevention strategies, CRC and EAC screening. By contrasting scenarios with standard *vs*. adjusted assumptions in an established decision-analytic simulation model, we showed that ignoring these effects and costs may lead to serious misrepresentation of cost-effectiveness. With only relatively moderate adjustments in life expectancy, quality of life, and cost, we found a joint effect big enough to substantially increase the ICERs of currently recommended strategies. Both EAC endoscopic screening and the currently recommended CRC screening strategies were no longer incrementally cost-effective compared to other less intensive screening strategies.

The relative importance of the specific model adjustments varied to some degree across the two models. For both diseases, ACERs were influenced most by the cost adjustment, and only marginally by quality of life adjustments. Standard model assumptions included no healthcare-related costs for the majority of LYG (only the 15% with cancer, see ***Supplementary Figure 1***), so a relatively large compensatory adjustment of up to $10,000 was considered. However, while the partial relabeling of related costs for patients with cancer as unrelated also had a big impact on outcomes in CRC screening, it was negligible for EAC. This adjustment mainly affected



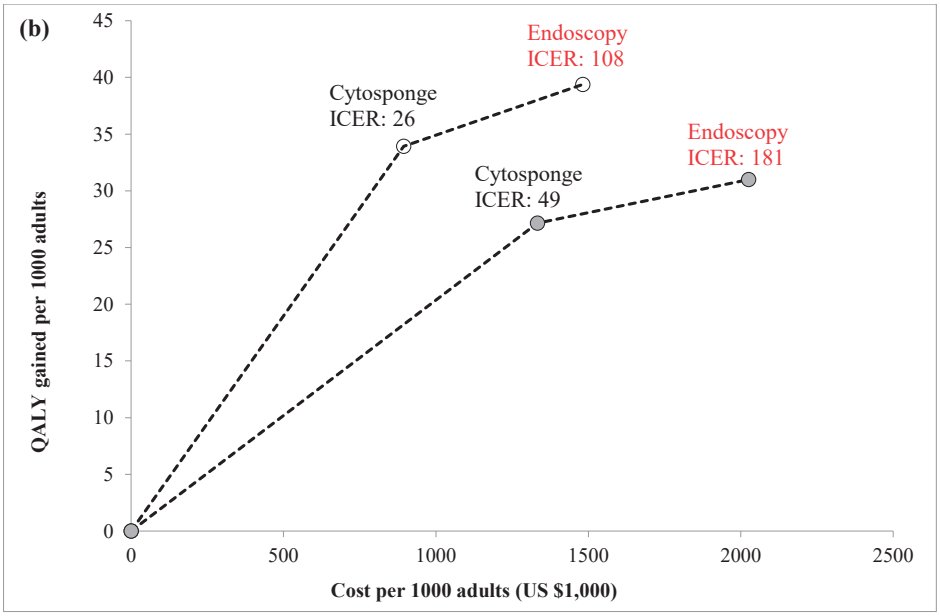


Figure 3. Incremental cost-effectiveness ratios for colorectal cancer (a) and esophageal adenocarcinoma (b) screening, under standard and adjusted assumptions for unrelated health (***Table 1***).[a]

[a] Red color indicates that a strategy has an incremental cost-effectiveness ratio (R) exceeding the commonly accepted threshold of US $100,000 per quality-adjusted life-year (QALY) gained. In figure panel (a), strategies are characterized as start age-stop age, interval, all in years.

simulated individuals in whom cancer was averted. Because the survival rate is lower for EAC than CRC patients, life-years with averted EAC are small in number.[41, 42] Although none of the above factors alone shifted ACERs beyond the willingness-to-pay threshold for the US, all factors combined constituted a considerable impact.

There is uncertainty regarding the magnitude of unrelated health effects in cancer screening. Current cancer models assume no excess cost for unrelated conditions for patients in whom screening is effective, and assume average life expectancy and quality of life. Research is needed to assess appropriate specific assumptions for patients with precursor lesions or cancer, i.e. the ones who may benefit from screening [43]. It is likely that these patients are at increased risk of either alternative cancers,[9, 44-46] or other chronic conditions like cardiovascular disease[33, 47-49] due to common risk factors.

The impact of including future unrelated costs or effects on cost-effectiveness estimates for interventions for different medical conditions has been evaluated in previous studies.[50-52] In a recent published systematic review, authors have evaluated the impact of medical costs and quality of life losses due to other diseases on the cost-effectiveness of US cancer screening.[52] By considering these factors, they have updated the ICER of screening strategies in relevant included studies. They found that considering the costs and effect of the competing risks can substantially change the cost-effectiveness of various screening programs. However, the study considered no elevated risk and loss in life-years due to higher competing risks. In our study, we adjusted life expectancy up to 20%, based on observational data [38, 39], the range reflecting the uncertainty due to the strength of the evidence. There were no data available to directly inform our quality of life and cost assumptions. We also considered a range for quality of life adjustments up to the assumed disutility from cancer in for stage I CRC survivors.[29] Similarly, for patients with precancerous conditions, we assumed an excess costs over the average person in the US of no more than to $7,000, the average net amount spent on stage I CRC patients. The maximum adjustments could well be realistic, considering that these patients may have 20% higher-than-average risks of serious conditions leading to death,[38, 39] and likely even higher risks of less serious conditions.

This study had limitations. First, it was exploratory in its assumed ranges for unrelated health effects, and simplistic in assuming no age dependency in adjustments. Thus, the results cannot be used to directly support any clinical practice reforms. Further, we evaluated the cost-effectiveness outcomes from a healthcare sector perspective only, because unrelated health effects and cost mainly affect the health-

related outcome domain. Other indirect costs (e.g. patient-time or caregiver–time costs) required for a societal perspective are unknown.

Despite these limitations, our study has important implications. First, it indicates that health services researchers should be aware of a potential substantial influence of unrelated health outcomes on cost-effectiveness. In the absence of specific studies on the actual magnitude of unrelated health effects, future cost-effectiveness studies should at least conduct sensitivity analyses to assess the potential influence of unrelated health outcomes. Further, the results from this study challenge current accepted willingness-to-pay thresholds in different countries. Adequate assessment of unrelated health effects may systematically shift cost-effectiveness estimates for cancer prevention strategies, and push ratios for many currently established prevention strategies beyond currently accepted thresholds. To this date, society has been prepared to pay for these strategies, and this is unlikely to change. It should be debated whether thresholds should be shifted along with potential shifts in cost-effectiveness estimates, or whether public health agencies should effectively become more selective in promoting preventive strategies by holding on to the same thresholds.

In conclusion, unrelated health outcomes may be more important for validity of cost-effectiveness estimates in cancer screening than one might expect from the actual attention for them in current research. More widespread awareness is needed among researchers and policy makers.

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Chapter 3 Supplementary Materials

Supplementary Table 1. The impact inventory checklist for cost-effectiveness analysis conducted in this study.

Sector	Type of Impact (list category within each sector with unit of measure if relevant)	Included in This Reference Case Analysis From…Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
	Formal Health Care Sector			
Health	*Health outcomes (effects)*			
	Longevity effects	✓		
	Health-related quality-of-life effects	✓		
	Other health effects (e.g., adverse events and secondary transmissions of infections)	✓		
	Medical costs			
	Paid for by third-party payers	✓		
	Paid for by patients out-of-pocket	✓		
	Future related medical costs (payers and patients)	✓		Unrelated medical costs were explored in this paper
	Future unrelated medical costs (payers and patients)	✓		
	Informal Health Care Sector			
Health	Patient-time costs	NA		
	Unpaid caregiver-time costs	NA		
	Transportation costs	NA		
	Non–Health Care Sectors (with examples of possible items)			
Productivity	Labor market earnings lost	NA		
	Cost of unpaid lost productivity due to illness Cost of uncompensated household production	NA		
		NA		
Consumption	Future consumption unrelated to health	NA		
Social Services	Cost of social services as part of intervention	NA		
Legal or Criminal Justice	Number of crimes related to intervention	NA		
	Cost of crimes related to intervention	NA		
Education	Impact of intervention on educational achievement of population	NA		

Supplementary Table 1. The impact inventory checklist for cost-effectiveness analysis conducted in this study. (*continued*)

Sector	Type of Impact (list category within each sector with unit of measure if relevant)	Included in This Reference Case Analysis From…Perspective?		Notes on Sources of Evidence
		Health Care Sector	Societal	
Housing	Cost of intervention on home improvements (e.g. removing lead paint)	NA		
Environment	Production of toxic waste pollution by intervention	NA		
Other (specify)	Other impacts	NA		

Supplementary Panel 1. Cost-effectiveness formula

Let LYG^{ca} denote life years gained (LYG) with cancer, LYG^{nc} denote LYG without cancer, $LY^{t,ca}$ life years converted to cancer due to earlier cancer diagnosis, and $LY^{t,nc}$ life years with averted cancer due to detection and removal of precursor lesions (***Figure 1***). Then formula (2) becomes:

(i) $$CE = \frac{C^{r,scr} + (c^{r,ca} + c^{u,ca})[LYG^{ca} + LY^{t,ca} - LY^{t,nc}] + c^{u,nc}[LYG^{nc} + LY^{t,nc} - LY^{t,ca}]}{LYG - U^{r,scr} - (u^{r,ca} + u^{u,ca})[LYG^{ca} + LY^{t,ca} - LY^{t,nc}] - u^{u,nc}[LYG^{nc} + LY^{t,nc} - LY^{t,ca}]}$$

Under the assumption that $c^{u} = c^{u,ca} = c^{u,nc}$ and $u^{u} = u^{u,ca} = u^{u,nc}$, this becomes:

(ii) $$CE = \frac{C^{r,scr} + c^{r,ca}(LYG^{ca} + LY^{t,ca} - LY^{t,nc}) + c^{u}(LYG^{ca} + LYG^{nc})}{LYG - U^{r,scr} - u^{r,ca}(LYG^{ca} + LY^{t,ca} - LY^{t,nc}) - u^{u}(LYG^{ca} + LYG^{nc})}$$

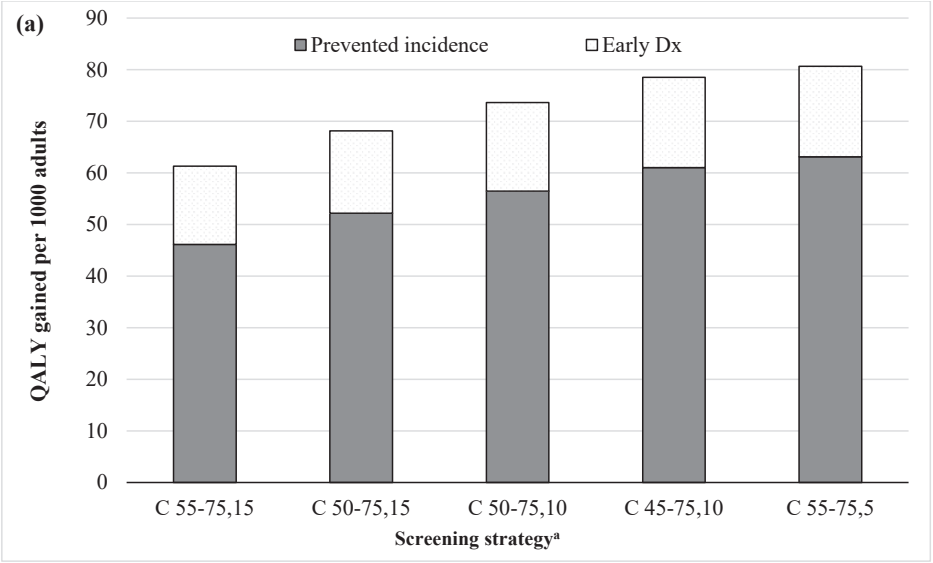
Which can be further simplified to:

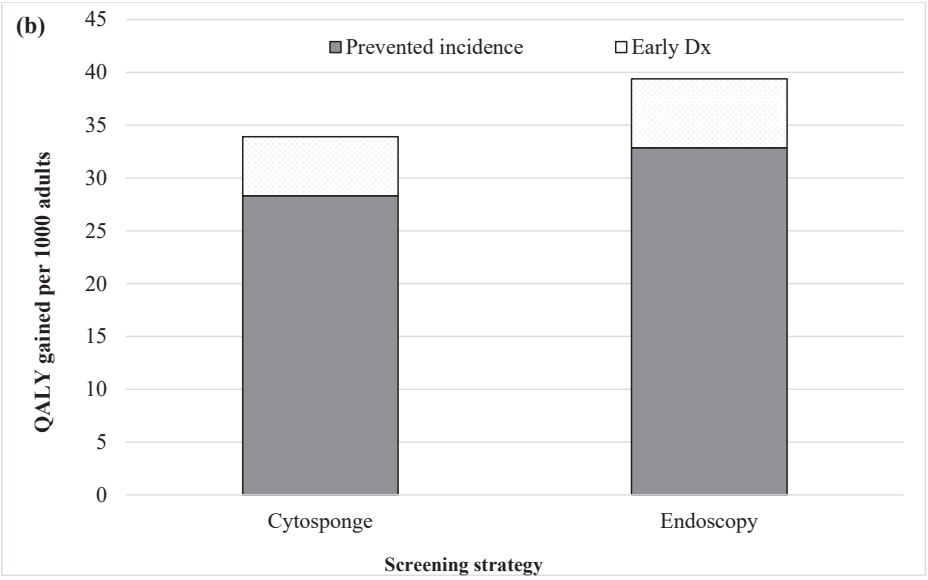
(iii) $$CE = \frac{C^{r,scr} + c^{r,ca}\Delta LY^{ca} + c^{u}LYG}{LYG - U^{r,scr} - u^{r,ca}\Delta LY^{ca} - u^{u}LYG}$$

Supplementary Table 2. Utility losses and cost associated with colorectal cancer (CRC) and esophageal adenocarcinoma (EAC) screening and treatment.

Variable	CRC model	EAC model
Utility loss		
Per screening test		
Colonoscopy with/without polypectomy	2 days, 0.0055	-
Endoscopy	-	1 day, 0.0008
Per treatment	-	
Endoscopic eradication therapy	-	16 days, 0.0131
Radiofrequency ablation touch-up	-	1 week, 0.0057
Per complication		
Stricture	-	1 week, 0.0057
Perforation	2 weeks, 0.0384	8 weeks, 0.0460
Bleeding	2 weeks, 0.0384	1 week, 0.0057
Serosal burn	2 weeks, 0.0384	-
Per life year with cancer care		
Initial care	0.12-0.70[a]	0.16-0.61[a]
Continuing care	0.05-0.70[a]	0.04-0.35[a]
Terminal care, ending in cancer death	0.70	0.04-0.61[a]
Costs, 2015 US $		
Per screening test		
Colonoscopy with/without polypectomy	1,275-1,418	-
Endoscopy	-	745
Cytosponge	-	182
Per treatment		
Endoscopic eradication therapy	-	5,630
Radiofrequency ablation touch-up	-	1,012
Per complication		
Stricture	-	1,012
Perforation	15,495	28,553
Bleeding	1,540-7,342	1,012
Serosal burn	5,818	-
Per life year with cancer care		
Initial care	36,375-76,371[a]	57,169-75,295[a]
Continuing care	3,061-11,952[a]	4,080
Terminal care, ending in cancer death	62,878-86,774[a]	64,704-85,212[a]

[a] Depending on the cancer stage.





Supplementary Figure 1. Quality-adjusted life-years (QALY) gained from prevented cancers or early diagnosed (Dx) cancer by screening strategy for colorectal cancers (a) and for esophageal adenocarcinoma (b).

Dx: diagnosis; QALY: quality-adjusted life-years gained

[a] In figure panel A, strategies are characterized as start age-stop age, interval, all in years.

Part 2

Surveillance of Barrett's esophagus

4

Cost-effectiveness of surveillance for GI cancers

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ABSTRACT

Gastrointestinal (GI) diseases are among the leading causes of death in the world. To reduce the burden of GI diseases, surveillance is recommended for some diseases, including for patients with inflammatory bowel diseases, Barrett's esophagus, precancerous gastric lesions, colorectal adenoma, and pancreatic neoplasms. This review aims to provide an overview of the evidence on cost-effectiveness of surveillance in GI practice, specifically focussing on the aforementioned diseases. We searched the literature and reviewed 21 studies. Despite heterogeneity of studies in terms of setting, study population, surveillance strategies and outcomes, most reviewed studies suggested at least some surveillance of patients with these GI diseases to be cost-effective. For some high-risk conditions frequent surveillance with 3-month intervals was warranted, while for other conditions, surveillance may only be cost-effective every 10 years. Further studies based on more robust effectiveness evidence are needed to inform and optimise surveillance programmes in GI practice.

INTRODUCTION

Gastrointestinal (GI) diseases are responsible for considerable morbidity and mortality worldwide. Causing almost 8 million deaths annually, GI diseases are among the leading causes of death in the world.[1] Not surprisingly, they have a large associated economic burden. In the United States (US), 10% of deaths occur due to GI diseases, and associated costs have been estimated at around $142 billion per year.[2] Alarmingly, the incidence and prevalence of major GI conditions such as gastroesophageal reflux disease, inflammatory bowel diseases (IBD) and GI cancers are increasing, particularly in North-American and European countries.[1, 3]

Many GI diseases are curable if detected in early stages, or even preventable. For instance, diseases like gastric and colorectal cancer have well-detectable and treatable precursor states that allow for disease prevention.[1] Patients with precursor lesions are often at higher risk for recurrent lesions and cancer, which suggests that lesion removal with frequent subsequent examination may prevent disease. Other GI conditions such as IBD and Barrett's esophagus may also increase the risk of other diseases including cancer.[4-6] Therefore, as discussed in the other chapters of the current issue, surveillance is common in current GI practice. It has been recommended by international guidelines for patients with diverse conditions, including Barrett's esophagus, ulcerative colitis (UC), Crohn's disease and pancreatic neoplasms.[7-10]

Surveillance is very similar to screening in that both refer to the early identification of potential unrecognized disease with the aim to prevent poorly treatable disease. Often, the same tests can be used. Similar to screening, surveillance may have both health benefits (e.g. deaths averted) and harms (e.g. false-positive or false-negative test results, complications due to tests, overdiagnosis and overtreatments). The main difference between screening and surveillance is that the former targets healthy populations, while surveillance generally targets patients who are at increased risk of a specific disease. Because of the similarity of the concepts of screening and surveillance, the same approach can be used for their evaluation.

One possible approach to evaluate screening and surveillance programmes is the "balance approach" introduced by Harris et al.[11] In this approach, evaluation of a programme is based on the evidence for the magnitude of health benefit, magnitude of harm, and the required resources.[11] The approach considers the balance between benefits and harms and determines whether the magnitude of net benefits justifies the required use of resources for a specific programme. With rapidly increasing

health care costs in Western countries, efficient allocation of scarce resources is becoming increasingly important criterion for health policy evaluation.

Cost-effectiveness is a popular concept to summarize the relationship between the monetary inputs for implementing a healthcare intervention, its consequent health expenditure effects, and the health outcomes. Cost-effectiveness can be determined using cost-effectiveness analysis (CEA). CEA is a form of decision analysis which enables policy makers to identify the most effective interventions considering the limited available resources and to determine which one provides the highest value for money.[12-14] The advantage of CEA is that it integrates harms, benefits and cost of health care strategies into a single outcome measure. CEA results often take the form of a cost-effectiveness ratio, which estimates the cost of an intervention to attain one unit of a health outcome (e.g. quality-adjusted life years gained).[15] This may be reported either comparing (1) an intervention such as surveillance to the situation without the intervention, or regular care (i.e. the average cost-effectiveness ratio) or (2) comparing each surveillance strategy with the next most effective one (i.e. incremental cost-effectiveness ratio (ICER)). The relative uniformity in outcomes from cost-effectiveness studies allows for comparative analysis both of alternative interventions for a single disease, as well as for different organs and diseases.[15]

This paper aims to provide an overview of the evidence on cost-effectiveness of surveillance in GI practice as measured by ICERs. It will focus on IBD, Barrett's esophagus, gastric precancerous lesions, colorectal polyps and neoplasia in the pancreas.

REVIEW METHODS

To achieve the objective of the review, we searched the following six electronic databases to find the relevant studies which have been published from 2000 to June 2016; Ovid Medline, Ovid Embase, The Cochrane library, The British National health System Economic Evaluation Database (NHS EED), the American Economic Association's electronic database (EconLit) and Cost-Effectiveness Analysis Registry (CEA Registry) (see **Supplementary Materials**, for search algorithm used in Ovid Medline). The search was limited to papers published in English language. We excluded studies without a reference scenario of no surveillance. The database was supplemented by expert suggestions and by reviewing reference lists from all discovered previous literature reviews. All reported costs were converted to US$ ($) using historical conversion rates.

RESULTS

Our search resulted in reviewing 21 studies which evaluated the cost-effectiveness of surveillance strategies in the GI conditions described below. The majority of studies took a third party payer perspective (i.e. incorporating only direct costs) with 3% discount rates for benefits and cost. For studies which adopted a societal perspective or alternative discount rates, this was explicitly noted (***Table 1-5*** footnotes).

Inflammatory Bowel Diseases

Four studies which investigated the cost-effectiveness of surveillance of patients with inflammatory bowel diseases (IBD) were included. All were Markov modelling studies. Study settings included the Netherlands, US and Canada. The studies were heterogeneous with respect to the study population, and the surveillance tests and intervals evaluated. Two studies considered patients with UC, one IBD in general (including both UC and Crohn's disease), and one study included patients with concomitant IBD and Primary Sclerosing Cholangitis (PSC). (***Table 1***).

Both studies which considered UC patients found that surveillance was cost-effective. Rubenstein et al.[16] analysed the cost-effectiveness of different surveillance strategies for men at age of 35 years with a 10-year history of UC. They considered two population subgroups, patients with and without medication of 5-Aminosalicylates (5-ASA) and found surveillance in both to be cost-effective. In patients with 5-ASA, the most effective strategy under a willingness-to-pay threshold of $100,000 was colonoscopy surveillance every 3 years (ICER: $63,387 per quality-adjusted life years (QALY)). Without 5-ASA, the optimal strategy was annual colonoscopy (ICER: $69,105 per QALY). In the other study, Konijeti et al.[17] used chromo-endoscopy and colonoscopy as surveillance tests. Both tests were cost-effective, but the analysis suggested that chromo-endoscopy with targeted biopsies was more effective and less costly than colonoscopy with random biopsies at all intervals.

The Negron et al.[18] study, which considered patients with IBD-PSC, also found that surveillance colonoscopy was cost-effective compared to no surveillance (for 2-yearly surveillance strategy the ICER of $37,522 per QALY was reported). In that study, annual surveillance was not cost-effective (ICER: $174,650 per QALY). Lutgens et al.[19] compared the cost-effectiveness of surveillance strategies of the American Gastroenterological Association (AGA) and the British Society of Gastroenterology (BSG) for patients with IBD. AGA recommends annual surveillance for patients with PSC and biennial surveillance for patients without PSC, while BSG guidelines distinguish three risk groups and recommend annual, biennial and every 5-year surveillance.

Table 1. Overview of cost-effectiveness studies of surveillance in patients with IBD

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (year)¶	Cost ($)	Effectiveness (QALY)	ICER
Rubenstein 2009[16]	US	35-year-old men with chronic UC	Until age 90 or death	QALY	None	-	71,000	20.07	NA
					Colonoscopy	1-10 *	NR	NR	≤ 69,105*
					Colonoscopy plus 5-ASA	1-2	NR	NR	≥147,503
					Colonoscopy plus 5-ASA	3-10 *	NR	NR	≤63,387*
Konijeti 2014[17]	US	Patients with population-based age distribution and ≥8 years history of UC	Until age 90 or death	QALY	None	-	100,200	13.18	NA
					Chromo-endoscopy with targeted biopsies	1-10 ¥	103,100-125,00	13.10-13.36	17,150¥
					Colonoscopy with random biopsies	1-10 #	103,900-128,000	13.06-13,34	Dominated
Negron 2014§[18]	Canada	35-year old patients with 10-year history of well-controlled IBD and recent PSC diagnosis	Life time	QALY	None	-	101,663	9.84	NA
					Colonoscopy	5	104,517	10.03	15,021
						2	107,894	10.12	37,522
						1	114,880	10.16	174,650
Lutgens 2014[19]	Netherlands, US	40-year-old patients with IBD for 10 years	40 years	QALY	BSG	1, 3 or 5¤	NR	24.16	11,130
					AGA	1 or 2 ǂ	NR	24.16	Dominated

AGA: American Gastroenterological Association, ASA: aminosalicylate, BSG: British Society of Gastroenterology, IBD: inflammatory bowel disease, ICER: incremental cost-effectiveness ratio, NR: not reported, NA: not applicable, PSC: primary sclerosing cholangitis, QALY: quality adjusted life year, UC: ulcerative colitis.

¶ The numbers in this column show different intervals of surveillance strategies which have been evaluated in the study, e.g. 1-10 means that intervals of 1 year, 2 years, 3 years etc. up to 10 years were evaluated.

* The optimal strategy with a willingness-to-pay threshold of $100,000 was at intervals of 1 and 3 years for colonoscopy alone and colonoscopy plus 5-ASA, respectively.

¥ The optimal strategy was at an interval of 10 years for chromo-endoscopy with the presented ICER.

Colonoscopy with random biopsies were dominated by the chromo-endoscopy strategy at all intervals.

§ A societal perspective with 5% discount rate for benefit and cost was adopted.

¤ Surveillance interval depended on the risk profile of the patients.

ǂ Annual surveillance for patients with PSC and biennial surveillance for patients without PSC.

Although both strategies were equally effective, the BSG surveillance strategy was more cost-effective due to a lower number of colonoscopies (ICER: $11,130 per QALY).

Barrett's esophagus

We included 8 studies on surveillance in Barrett's esophagus (BE) from the US, Netherlands, United Kingdom (UK) and Australia. All studies were Markov modelling studies evaluating endoscopy with biopsy as the surveillance modality. The studies were heterogeneous in terms of the study population (all BE patients, BE patients without dysplasia (BE-ND), BE patients with low-grade dysplasia (BE-LGD), and high-grade dysplasia (BE-HGD)), health outcomes (QALY, life year (LY), and life expectancy) and surveillance intervals. (***Table 2***) With one exception, all studies suggested surveillance to be cost-effective up to varying level of intensity.

Studies which considered all BE patients reported conflicting results. Sonnenberg et al.[20] estimated that surveillance endoscopy and biopsy every 2 years was cost-effective compared to no surveillance (ICER: $16,965 per LY), while another study representing a UK setting suggested that endoscopic surveillance with 3-year, 1-year and 3-month intervals for patients with BE-ND, BE-LGD and BE-HGD respectively, was not cost-effective compared to no surveillance (dominated).[21]

Four studies assessed the cost-effectiveness of endoscopic surveillance in patients with BE-ND. All studies suggested that surveillance was cost-effective. Kastelein et al [22] evaluated various surveillance strategies with different intervals for a cohort of 55-year-old men with BE-ND, to find that with a willingness-to-pay threshold of €35,000, the optimal strategy was surveillance endoscopy every 5 years, with radio-frequency ablation if BE-ND patients developed HGD (ICER: $6,604 per QALY). Gordon et al. [23] suggested that 2-yearly endoscopic surveillance for NO-BD patients and more intensive surveillance if patients developed dysplasia was also cost-effective according to Australian standards (ICER: $60,858 per QALY), although probabilistic sensitivity analysis suggested that the likelihood of cost-effectiveness was only 16%. Two other studies from the US found for 50-year-old patients that endoscopic surveillance with biopsy every 5 and 3 years, respectively, was cost-effective with ICERs of $22,011 [24] and $86,434 per QALY.[25]

Studies looking specifically at BE-LGD patients also found surveillance to be cost-effective. Kastelein et al.[22] suggested that the optimal cost-effective strategy was surveillance every 3 years, with radio-frequency ablation (RFA) for patients who developed HGD (ICER: $40,664 per QALY). In another study, Inadomi et al.[24] suggested

Table 2. Overview of cost-effectiveness studies of surveillance in patients with Barrett's **esophagus**

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval[¶]	Cost ($)	Effectiveness (QALY/LY/LE)	ICER
Patients with general BE									
Sonnenberg 2002[20]	US	60-year-old patients with long segment BE	NR	LY	None	-	2,061	NR	NA
					Endoscopy plus oesaphogectomy for HGD	2y	6,262	NR	16,965
Somerville 2008[#21]	UK	55-year-old men with BE	20 years	QALY	None	-	5,312	12.03	NA
					Endoscopy	3y for ND, 1y for LGD, 3m for HGD	6,964	11.98	Dominated
Patients with BE-ND									
Kastelein 2015[§22]	The Netherlands	55-year-old men with BE-ND	NR	QALY	None	-	7,119	12.62	NA
					Endoscopy plus RFA for HGD and early EAC	1-5y	8,774-18,842	12.87-12.90	6,604[¥1]
					Endoscopy plus EMR followed by RFA for HGD and early EAC	1-5y	9,059-19,276	12.87-12.90	Dominated
					Endoscopy plus esophagectomy for HGD and EAC	1-5y	17,456-29,607	12.54-12.64	Dominated
Gordon 2014[§23]	Australia	50-year-old patients with BE-ND	Until age 80 years or death	QALY	None	-	5,226	12.04	NA
					Endoscopy	2y for ND, 6m for LGD, treatment of HGD and EAC	14,659	12.190	60,858

Table 2. Overview of cost-effectiveness studies of surveillance in patients with Barrett's esophagus (*continued*)

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval[¶]	Cost ($)	Effectiveness (QALY/LY/LE)	ICER
Inadomi 2009[24]	US	50-year-old patients with BE-ND	Until age 80 years	QALY	None	-	471*	15.2*	NA
					Endoscopy and ablation for dysplasia	1y, 5y after another exam finds ND	10,816*	15.67*	22,011
Das 2009[25]	US	50-year-old patients with BE-ND	Until age 80 years	QALY	None	-	2,894	17.959	NA
					Endoscopy	3y for ND, 1y for LGD, 3m for HGD	13,016	18.076	86,434
Patients with BE-LGD									
Kastelein 2015[§22]	The Netherlands	55-year-old men with BE-LGD	NR	QALY	None	-	27,258	10.95	NA
					Endoscopy plus RFA for HGD and early EAC	1-5y	33,202-52,607	11.91-12.27	40,664[¥2]
					Endoscopy plus EMR followed by RFA for HGD and early EAC	1-5y	35,306-56416	11.91-12.27	Dominated
					Endoscopy plus esophagectomy for HGD and EAC	1-5y	63,636-68,949	11.33-11.34	Dominated
Inadomi 2009[24]	US	50-year-old patients with BE-LGD	Until age 80 years	QALY	None	-	687*	14.7*	NA
					Endoscopy	1y	16,334*	15.38*	23,010
Patients with BE-HGD									

Table 2. Overview of cost-effectiveness studies of surveillance in patients with Barrett's esophagus (*continued*)

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval¶	Cost ($)	Effectiveness (QALY/LY/LE)	ICER
Shaheen 2004[26]	US	50-year-old Caucasian males with BE-HGD	Until death	QALY	None	-	748	13.9	NA
					Endoscopy	3m during first year, 6m during second year if no further HGD detected, 6m and 1y thereafter	34,724	14.96	32,053
Sonnenberg 2003[27]	US	60-year-old patients with BE-HGD	NR	LE	None	-	14,178*	71.59*	NA
					Endoscopy	1y	18,732*	72.26*	6,797
					Endoscopy plus NSAID	1y	21,267*	72.82*	4,526
Inadomi 2009[24]	US	50-year-old patients with BE-HGD	Until age 80 years	QALY	None	-	1,859*	12.4*	NA
					Endoscopy	3m during first year, 1y thereafter if no further HGD	48,084*	14.84*	18,945

BE Barrett's esophagus, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, ICER: incremental cost-effectiveness ratio, LDG: low-grade dysplasia, LY: life year, NA: not applicable, ND: no dysplasia, NR: not reported, NSIAD: nonsteroidal anti-inflammatory drugs, EAC esophageal adenocarcinoma, QALY: quality adjusted life year, LE: life expectancy, RFA: radiofrequency ablation.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study, e.g. 1-5y means that intervals of 1 year, up to 5 years were evaluated.

1.5% discount rate for benefit and 6% for cost were adopted.

§ 5% discount rate was adopted.

¥ The ICER of the optimal strategy with regards to the willingness-to-pay threshold of 35,000 Euro is reported in the table.

1. The optimal strategy was surveillance every 5 years for patients with LGD and treatment of patients who developed HGD or EAC with RFA. According to international standards, 4-yearly surveillance was also cost-effective (ICER: $78,273).

2. The optimal strategy was surveillance every 3 years for patients with LGD and treatment of patients who developed HGD or EAC with RFA. According to international standards, annual surveillance was also cost-effective (ICER: $94,501).

* The values were estimated from graphs.

that annual endoscopic surveillance was cost-effective compared to no surveillance (ICER: $23,010 per QALY).

Finally, three US studies evaluating surveillance in BE-HGD patients also estimated that this was cost-effective. Shaheen et al.[26] estimated that a regressive endoscopic surveillance strategy of 3-month intervals in the first year, 6-month intervals in the second year (if no further HGD were detected) and 1-year subsequent intervals had an ICER of $32,053 per QALY compared to no surveillance. Sonnenberg et al.[27], suggested annual surveillance endoscopy was cost-effective (ICER: $6,797 per LY). Inadomi et al.[24] found that a similar strategy to Shaheen et al. with three-month intervals during the first year and subsequent 1 year intervals would be cost-effective for patients with HGD at baseline (ICER: $18,945 per QALY).

Colorectal adenomas

We found four studies assessing the cost-effectiveness of surveillance programmes in patients with adenomas. All four studies were modelling studies and evaluated colonoscopy for surveillance. Similar to BE, health outcomes and surveillance intervals were different across studies. (***Table 3***)

Three studies simulated cohorts of 50-year-old patients with adenomas. First, Saini et al.[28] evaluated different surveillance intervals for these patients depending on the level of patient's risk to develop new adenomas and colorectal cancer. They found that colonoscopy surveillance every 3 years for high-risk patients and 10 years for low-risk patients (3/10 strategy) was cost-effective compared to 10-yearly surveillance for all patients (ICER: $5,743 per QALY). Although effective, a 3/5 strategy was much more costly (ICER: $296,266 per QALY). In another study, Arguedas et al.[29] considered colonoscopy surveillance every 3 years and if no further adenomas were found, surveillance resumed every 5 years. They estimated that this strategy had an ICER of $27,970 per LY compared to no surveillance. Finally, Shaukat et al.[30] estimated that colonoscopy surveillance every 3 or 5 years depending on whether large adenomas (≥10 mm) were found or not, to be cost-effective (ICER: $20,600 per LY). The fourth study[31] simulated a group of 60-year-old adenoma patients. The study suggested that even a single colonoscopy surveillance after 1 year was cost-effective with an ICER of $66,136 per LY.

Table 3. Overview of cost-effectiveness studies of surveillance in patients with colorectal adenomas

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (year)¶	Cost ($)	Effectiveness (QALY/LY)	ICER
Saini 2010[28]	US	50-year-old patients with adenomas	Until death	QALY	None*	10	1775	17.57	NA
					Colonoscopy	3 for HR patients 10 for LR patients¥	1,831	17.58	5,743
					Colonoscopy	3 for HR patients 5 for LR patients¥	3,170	17.58	296,266
					Colonoscopy	3 for both HR and LR patients¥	4,936	17.58	dominated
Arguedas 2001[29]	US	50 year-old patients with adenomas	10 years	LY	None	-	1014	8.45	NA
					Colonoscopy	3 and 5#	1572	8.48	27,970
					Celecoxib chemoprevention	-	11503	8.49	1,715,199
Shaukat 2009[30]	US	50 year-old patients with adenomas	Until age of 100 years or death	LY	None	-	2,796	18.64	NA
					Colonoscopy	3 for large adenoma (≥10 mm), 5 for small or no adenoma (<10 mm),	4,579	18.72	20,600
Hassan 2009§[31]	Italy	60-year-old patients with adenomas	Lifetime	LY	None	-	NR	NR	NA
					Colonoscopy	Once after 1 year	NR	NR	66,136

ICER: incremental cost-effectiveness ratio, HR: high risk, LY: life year, LR: low risk, NA: not applicable, QALY: quality adjusted life year.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

* This is similar to screening of average-risk patients as recommended in the United States.

¥ HR patients: patients with >2 adenomas or advanced adenomas (adenomas ≥1 cm, villous, or with high-grade dysplasia), LR patients: patients with 1–2 small (<1 cm) tubular adenomas.

If any adenoma was detected in the surveillance colonoscopy, the next colonoscopy was done in 3 years, if no adenomas were detected, the colonoscopy was repeated 5 years later.

§ Not-discounted rate was reported.

Neoplasia in the pancreas

Three studies evaluated the cost-effectiveness of surveillance strategies for neoplasia in the pancreas. All were simulation modelling studies and conducted in the US. Again, studies evaluated varying study populations, health outcomes and surveillance strategies.(***Table 4***)

Two out of three studies focused on familial pancreatic cancer. Rubenstein et al. [32] simulated a cohort of 45-year-old men with chronic pancreatitis who had at least a first-degree relative with pancreatic cancer. Two surveillance strategies including 6-monthly endoscopic ultrasound (EUS) plus fine needle aspiration and EUS alone were both not cost-effective compared to no surveillance. Rulyak et al.[33] considered a cohort of 100 members of familial pancreatic cancer kindreds who underwent EUS at age of 50 years. Any abnormal findings in EUS were followed up using endoscopic retrograde cholangiopancreatography and, if cancer was confirmed, total pancreatectomy. The results suggested this strategy to be cost-effective compared to regular care (ICER: $16,855 per LY).

A third study considered surveillance after curative treatment of pancreatic cancer.[34] The investigators simulated patients who had recent neoadjuvant therapy and pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. They found that clinical evaluation of the patients and CA 19-9 assay every 6 months was cost-effective (ICER: $5,364 per LY). The alternative strategy, clinical evaluation with CA19-9 and routine abdominal/pelvic computed tomography and chest X-ray every 6 months was dominated. More intensive surveillance strategies were not cost-effective.

Gastric precancerous conditions

Surveillance of gastric precancerous conditions was considered in two studies. Again these two studies used simulation modelling to evaluate endoscopic surveillance, and varied in terms of study populations, health outcomes and surveillance strategies. (***Table 5***)

Both studies suggested that endoscopic surveillance was cost-effective for patients with gastric precancerous lesions. One Portuguese study modelled a group of 50-year-old patients with extensive gastric atrophy or intestinal metaplasia who underwent endoscopic surveillance and biopsy every 3, 5 or 10 years.[35] This study found that surveillance every 3 years was cost-effective (ICER: $24,204 per QALY). Endoscopic surveillance strategies with intervals of 5 and 10 years were dominated by a non-surveillance strategy. Another study simulated a population of 60-year-old patients with only gastric intestinal metaplasia, and found that annual surveillance

Table 4. Overview of cost-effectiveness studies of surveillance for pancreatic neoplasia

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (months)¶	Cost ($)	Effectiveness (QALY/LY)	ICER
Rubenstein 2007[32]	US	45-year-old men with chronic pancreatitis and ≥1 FDR with pancreatic cancer	Until age 90 or death	QALY	None	-	2,983	18.57	NA
					EUS and FNA	6	42,521	17.94	Dominated
					EUS	6	186,089	14.54	Dominated
					Prophylactic total pancreatectomy	NA	199,911	14.28	Dominated
Rulyak 2003[33]	US	50-year-old patients with family risk (unspecified)	Life time	LY	None	-	3,271	17.20	NA
					EUS and ERCP (if the EUS result was positive)	once	9,677	17.58	16,855
Tzeng 2013[34]	US	Patients who recently received neoadjuvant therapy and pancreatico-duodenectomy for PDAC	Median follow-up of 26 months	LY	None	-	3,837	2.05	NA
					clinical evaluation and CA19-9 testing	6	7,496	2.73	5,364
					clinical evaluation and CA19-9 testing with routine abdominal/ pelvic CT and CXR	6	10,961	2.73	Dominated
					clinical evaluation and CA19-9 testing	3	18,523	2.81	127,680
					clinical evaluation and CA19-9 testing with routine abdominal/ pelvic CT and CXR	3	24,775	2.84	294,696

CA19-9: carbohydrate antigen 19-9, CT: computed tomography, CXR: chest X-ray, EUS: endoscopic ultrasound, ERCP: endoscopic retrograde cholangiopancreatography, FDR: first-degree relative, FNA: fine needle aspiration, ICER: incremental cost-effectiveness ratio, LY: life year, NA: not applicable, PDAC: Pancreatic ductal adenocarcinoma, QALY: quality adjusted life year.

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

Table 5. Overview of cost-effectiveness studies of surveillance in patients with gastric precancerous conditions

Study ID	Country	Participants	Follow-up	Health outcome	Surveillance strategy	Interval (years)¶	Cost ($)	Effectiveness (QALY/LY)	ICER
Arei 2014*[35]	Portugal	50-year-old patients with extensive gastric atrophy or intestinal metaplasia	25 years	QALY	None	-	172	13.607	NA
					Endoscopy	10	2,400	13.268	Dominated
					Endoscopy	5	1,972	13.565	Dominated
					Endoscopy	3	2,091	13.687	24,204
Hassan 2010[36]	Italy	60-year-old patients with gastric intestinal metaplasia	10 years	LY	None	-	583	NR	NA
					Endoscopy	1	3,552	NR	72,519

ICER: incremental cost-effectiveness ratio, LY: life year, NA: not applicable, NR: not reported, QALY: quality adjusted life year

¶ The numbers in this column, show different intervals of surveillance strategies which have been evaluated in the study.

* A societal perspective was adopted.

endoscopic may be cost-effective with an ICER of $72,519 per LY compared to no surveillance.[36]

DISCUSSION

In this review, we searched the literature on cost-effectiveness of surveillance for a variety of GI diseases, including IBD, BE, gastric precancerous lesions, colorectal adenomas and diverse patients with a high risk of pancreatic neoplasia in the pancreas. We included 21 modelling studies from high income-countries of which more than one-third considered surveillance in BE (8 studies) and few studies considered other GI diseases (2-4 studies per disease each). Although studies differed in terms of settings, study populations, surveillance strategies and health outcomes, most reviewed studies suggested that at least some surveillance of patients with BE, IBD, precancerous gastric lesions, colorectal adenoma, and with increased risk of pancreatic neoplasia may be cost-effective. Cost-effective surveillance strategies generally used endoscopy, except in patients with resected pancreatic cancer, where clinical evaluation and carbohydrate antigen 19-9 testing was used instead. Surveillance intervals varied from 3 months for patients with BE-HGD up to 10 years for patients with ulcerative colitis.

At the disease level, there was considerable heterogeneity in cost-effective surveillance intervals depending on the risk for and fatality of the preventable disease. Apart from one study in UC patients finding only 10-year surveillance cost-effective, for most IBD patients 1-5 year surveillance colonoscopy was found to be cost-effective, with the intervals varying by study and depending on additional risk characteristics. For BE, again with one exception,[21] all studies found endoscopic surveillance with biopsy to be cost-effective, with minimum cost-effective intervals varying from 2-5 years for BE-ND, to 1-3 years for BE-LGD patients, to 3-12 months for BE-HGD patients. Surveillance colonoscopy was generally found to be cost-effective in the studies retrieved for patients with colorectal adenomas with intervals of 3-5 years, however, one study found that 5 year surveillance may not be cost-effective in low-risk patients,[28] and another study suggested that one-time only colonoscopy after 1 year may be cost-effective.[31] For patients with increased risk of pancreatic neoplasia, follow-up clinical evaluation plus CA19-9 essay every 6 months was deemed cost-effective after pancreatic cancer therapy,[34] while the evidence for cost-effectiveness of endoscopic examination for patients with a family history of pancreatic cancer was conflicting. Finally, precancerous gastric lesions seemed to deserve surveillance endoscopy every 1-3 years.[35, 36]

Surveillance of patients with IBD, BE, colorectal adenomas, precancerous gastric lesions and neoplastic pancreatic cysts is generally recommended by current international clinical practice guidelines. Supporting organizations include the AGA, BSG, National Institute for Health and Clinical Excellence (NICE), European Crohn's and Colitis Organisation, European Helicobacter Study Group, European Society of Pathology and European Society of Gastrointestinal Endoscopy.[7, 8, 10, 37-44] None of the above expert groups except NICE considered cost-effectiveness in developing their guidelines. NICE has provided guidelines on management of IBD, BE and colorectal adenomas, [43, 44] and conducted cost-effectiveness analyses for all three conditions. Although the results from these studies were partly consistent with the studies included in this review, there were also some discrepancies. For BE patients, although the NICE analysis suggested that surveillance endoscopy every 2 years for BE-ND, every 6 months for BE-LGD, and every 3 months for BE-HGD patients would improve health outcomes, it was not considered cost-effective at a threshold of £20,000 (ICER £35,277).[43] Therefore, treatment for BE-HGD patients was recommended by NICE, but not surveillance of these patients. In our review, although Somerville et al.[21] found a similar surveillance strategy (3 year intervals for BE-ND, 1 year for BE-LGD, 3 months for BE-HGD patients) not only inefficient but even harmful (***Table 2***), 7 other studies all found BE surveillance to be cost-effective, often even with lower ICERs. In contrast, the NICE evaluation of surveillance in colorectal adenoma patients (colonoscopy every 5, 3 or 1 years depending on adenoma characteristics) suggested this to be cost-effective. However, while several studies in our review also found 3- to 5-year intervals to be cost-effective, the most recent study included by Saini et al. suggested that 5-year intervals may not be cost-effective for low-risk patients as mentioned before.[28, 44] Also, the 1-year interval for high-risk patients was not studied by any of the included studies in this review. Finally, while the NICE analysis for IBD patients was restricted to high-risk patients and suggested that colonoscopy surveillance every year was cost-effective in the UK setting with a acceptance threshold of £20,000 (ICER: £17,557 per QALY),[44] in our review there were no studies included looking specifically at high-risk patients. The partly discrepant results both between studies included in this review and compared to studies used to inform UK guidelines suggest that further research is needed to clarify precisely when surveillance is appropriate.

Although most cost-effectiveness studies are concordant in suggesting that at least some surveillance in GI practice is cost-effective, they share an important caveat. All studies included here assumed that surveillance was effective in reducing disease-specific mortality. The problem with this assumption is that currently for most of the included disease no evidence exists from randomized controlled trials

that this is actually the case. This lack of evidence is also explicitly acknowledged in the guidelines. It is an important limitation given all criteria for screening or surveillance state that effectiveness and net benefits of the programme should be established before considering cost-effectiveness.[11, 45] To the extent possible, where surveillance is already recommended, it should preferably be conducted in research settings to establish the effectiveness retroactively. When issuing new guidelines, policy makers should be aware that this may have ethical implications for the possibility to conduct experimental studies to establish effectiveness.

There were other limitations for the studies included in this review. All the included studies were modelling simulation analyses, the results of which depend on the model structure and assumptions regarding e.g. disease onset and progression. There is uncertainty regarding the true values for many of these parameters, which may influence outcomes substantively. Moreover, the models and assumptions represent high-income countries only. Parameters such as the risk of disease and the cost of care may differ for low- or middle-income countries, such that the results of these analyses should be generalised with caution to other settings.

Further, the coverage of cost-effectiveness studies for some of the conditions in scope for this review was low. Given the evidence across studies was fragmented in terms of study populations, settings, and evaluated strategies, for many patient subgroups cost-effectiveness was either not assessed or assessed by only one study. Most reviewed studies also tended to evaluate only the already recommended surveillance strategies and compare them to a non-surveillance strategy. There were few studies which evaluated a range of different surveillance intervals or strategies. The strategies found to be cost-effective this way may not be optimal. As an illustrative example, for surveillance of BE patients, Das et al.[25], Shaheen et al.[26], and Inadomi et al. [24] all found that endoscopic surveillance with aforementioned intervals (***Table 2***) was cost-effective compared to no-surveillance strategy, however, that it was dominated by other strategies including ablation therapy without surveillance.

In conclusion, although this review suggests that surveillance in GI practice may be cost-effective for all evaluated GI conditions, for most disease the evidence was scant and the effectiveness evidence basis was weak. More research is needed on the effectiveness of surveillance to inform more comprehensive and evidence-based cost-effectiveness studies searching for optimal surveillance strategies beyond currently recommended strategies.

PRACTICE POINTS

- Current practice guidelines partly based on the expert opinion recommend surveillance for a variety of GI diseases.
- Cost-effectiveness studies suggest current surveillance practice may also be cost-effective.
- There is a lack of rigorous evidence for effectiveness and of surveillance optimization studies.

RESEARCH AGENDA

- Evidence is needed on the effectiveness of surveillance for GI diseases.
- Future cost-effectiveness studies should look for optimal surveillance strategies.
- Surveillance should be evaluated for low- and middle-income settings.

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Chapter 4 Supplementary Materials

Supplementary 1. Search strategy for Ovid Medline

1	(Barrett*).tw.
2	((gastric or stomach) and (precancerous or premalignant or precursor) and (lesion* or condition*)).tw.
3	((neoplas* or cancer* or adeno* or carcino* or tumo*) and pancrea*).tw.
4	((colon OR colorect* OR sigmoid* OR bowel OR "large intestine*" OR cecum) and (cancer* OR neoplas* OR tumo* OR carcino* OR adeno* OR polyp* OR lesion*)).tw.
5	(Inflammatory bowel disease? OR IBD? OR crohn* or colitis).tw.
6	"Costs and Cost Analysis"/
7	(costs or cost eff* or cost benef* or cost anal*).tw.
8	surveillance.tw.
9	(case reports or editorial or guideline or letter or news or newspaper or article or practice guideline).pt.
10	1 or 2 or 3 or 4 or 5
11	6 or 7
12	8 and 10 and 11
13	12 not 9
14	limit 13 to English language
15	limit 14 to yr="2000 -Current"
16	limit 15 to human

5

Optimizing management of patients with Barrett's esophagus and low-grade or no dysplasia based on comparative modeling

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ABSTRACT

Background

While endoscopic treatment for patients with Barrett's esophagus (BE) with high-grade dysplasia is recommended by guidelines, clinical management recommendations for BE patients without dysplasia (NDBE) or with low-grade dysplasia (LGD) are inconsistent. This study aimed to identify the optimal management strategies for these patients through a comparative modeling analysis.

Methods

We used three independent population-based models to simulate cohorts of 60-year-old U.S. individuals with BE. We followed each cohort until death without surveillance and treatment (natural history) compared with 78 different strategies of management for NDBE or LGD patients. We determined the optimal strategy using cost-effectiveness analysis at a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY).

Results

The three models' average cumulative EAC incidence in the natural history was 111 cases with costs totaling $5.7 million per 1,000 male BE patients. Surveillance and treatment of BE patients prevented 23-75% of EAC cases, but increased costs to $6.2-17.3 million per 1,000 BE patients. The optimal strategy was surveillance every 3 years for NDBE patients and treatment of LGD after confirmation by repeat endoscopy (incremental cost-effectiveness ratio (ICER: $53,044/QALY). The average results for women were consistent with the results for men for LGD management, but the optimal surveillance intervals for female NDBE patients was 5 years (ICER: $36,045/QALY).

Conclusions

The optimal management strategy for patient with BE and LGD is endoscopic eradication, but only after LGD is confirmed by a repeat endoscopy. The optimal strategy for NDBE patients is endoscopic surveillance using a 3-year interval in men and a 5-year interval in women.

Keywords: cost-effectiveness; surveillance; esophageal adenocarcinoma

INTRODUCTION

Esophageal adenocarcinoma (EAC) is the most common subtype of esophageal cancer in the U.S. and other western countries.[1] The incidence and mortality of EAC have increased dramatically since the 1970's.[2] Barrett's esophagus (BE) is the only known precursor lesion for EAC.[3] Therefore, clinical guidelines recommend endoscopic surveillance and/or treatment of BE patients depending on the presence and grade of dysplasia. There is general consensus among gastrointestinal professional societies regarding management of BE patients with high-grade dysplasia (HGD): endoscopic eradication therapy (EET) using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection to remove endoscopically visible lesions, followed by radiofrequency ablation (RFA) of flat dysplastic and metaplastic epithelium. However, there is uncertainty about the optimal surveillance interval for non-dysplastic BE patients (NDBE) and whether EET or surveillance is the optimal management strategy for patients with low-grade dysplasia (LGD) (***Supplementary Table 1***).

Due to inter-observer variation in diagnosis of dysplasia, particularly LGD, most clinical guidelines recommend that a histologic diagnosis of LGD should be confirmed by a second pathologist with expertise in gastroenterological pathology. The American College of Gastroenterology (ACG) guidelines recommend endoscopic eradication therapy for patients with confirmed low-grade dysplasia, although endoscopic surveillance every 12 months is an acceptable alternative.[4] Of note, the American Gastroenterological Association (AGA) recommends a repeat endoscopy after proton pump inhibitor therapy for 8-12 weeks to reduce inflammatory and regenerative changes that could be misdiagnosed as dysplasia, prior to initiating EET.[5]

Optimal BE management should be guided by the relative benefits and harms of competing strategies. Since clinical trials are of insufficient duration to accurately assess cancer mortality and survival, simulation modeling studies are helpful to compare overall effectiveness and cost-effectiveness of different BE management strategies throughout the lifetime of individual patients and across populations. Population models use aggregates of hypothetical individual event histories associated with key components of a disease process, based on available relevant data, to estimate population-level effects of interventions on outcomes and the comparative effectiveness of a variety of interventions.[6] A number of previous modeling studies, including those conducted by our group, reported inconsistent results on management of LGD and NDBE patients.[7-11] While these studies examined the influence of variations in model parameters on conclusions, the influence of variations in model structural assumptions (e.g. regression of dysplasia or metaplasia) on conclusions

could not be examined because most studies were based on individual models. Moreover, prior studies were not adequately calibrated to current population-based EAC incidence and mortality. Finally, the impact of repeat endoscopy to confirm LGD after high dose acid suppression to reduce false-positive tests was not assessed.[7-9]

In this study we conducted a comparative effectiveness analysis using three independently developed models to determine the most cost-effective management strategy for BE patients with LGD and optimal interval for surveillance of patients with NDBE.

METHODS

We used three independent population-based models which are part of the National Cancer Institute (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) to compare the benefits, harms and costs of different management strategies for BE patients.

CISNET-EAC models

Three models were used for this analysis: (1) MISCAN-EAC: Microsimulation Screening Analysis model from Erasmus University Medical Center (Rotterdam, The Netherlands) and University of Washington (Seattle, WA); (2) EACMo: Esophageal Adeno Carcinoma Model originally developed at the Massachusetts General Hospital (Boston, MA) and currently at the Columbia University Medical Center (New York, NY); (3) MSCE-EAC: Multistage Clonal Expansion for EAC model from the Fred Hutchinson Cancer Research Center (Seattle, WA). See *Model Appendix* for details. Full descriptions of the models are published and available online. [12]

Population simulated

For the main analysis, a hypothetical cohort of U.S. white men diagnosed with BE at age 60 in 2010 was simulated and followed until death or age 100, whichever occurred first, without surveillance and BE treatment (natural history). We separately simulated a cohort of U.S. white women diagnosed with BE at age 60 who underwent the same strategies.

Strategies assessed

We compared 78 different BE management strategies: the large number results from permutations in surveillance intervals and differences in management of LGD. In all strategies HGD patients received EET consisting of EMR of visible lesions followed by RFA. The strategies varied in (a) LGD management: surveillance with different

intervals; or EET, with or without confirmation of LGD by a repeat endoscopy after 2 months of high dose acid suppression; and (b) NDBE management: no surveillance or surveillance with different intervals (1, 2, 3, 4, 5, 10 years). See ***Figure 1*** and ***Appendix Table 2*** for details.

<table>
<tr><th>NDBE patients</th><th colspan="2">LGD patients</th></tr>
<tr><td>No surveillance</td><td rowspan="3">No confirmation endoscopy at 2m</td><td>Surveillance every 6m</td></tr>
<tr><td>surveillance every 1y</td><td>Surveillance every 6m × 2, then every year</td></tr>
<tr><td>surveillance every 2y</td><td>Surveillance every year</td></tr>
<tr><td>surveillance every 3y</td><td rowspan="4">Confirmation endoscopy at 2m</td><td>Surveillance every 1y × 2, then every 2y</td></tr>
<tr><td>surveillance every 4y</td><td>Surveillance every 1y × 2, then every 3y</td></tr>
<tr><td>surveillance every 5y</td><td rowspan="2">Endoscopic eradication therapy</td></tr>
<tr><td>surveillance every 10y</td></tr>
</table>

Figure 1. Differences in simulated strategies
BE: Barrett's esophagus, LGD: low-grade dysplasia, m: month, ND: Non-dysplastic BE, , y: year
The 78 simulated strategies were combinations of different options presented in each column of this figure.

Surveillance and treatment assumptions

Assumptions about the performance of surveillance endoscopy were based on the current literature. We assumed that individuals without BE could be misdiagnosed as NDBE with a probability of 0.075 (false-positive rate) while NDBE patients were missed with a probability of 0.125 (false-negative rate). [13] Other patients were detected but could be misdiagnosed as NDBE, LGD, HGD or EAC with the probabilities specified in the ***Supplementary Table 3***. Misdiagnosis can be due to sampling error, misclassification or disease regression. Only one model (MSCE-EAC model) explicitly simulates all three pathways. Two models (MISCAN-EAC and EACMo) capture all misdiagnosis in misclassification and sampling errors, but do not distinguish these pathways separately. In the MISCAN-EAC model, additional misdiagnosis may occur because of disease regression. However, the contribution to total misdiagnosis is negligible.

All BE patients who received EET entered post-treatment surveillance depending on initial dysplasia status of the patient and the outcome of the EET (***Supplementary Table 4***).[5, 14] Assumptions concerning the efficacy of endoscopic therapy are presented in ***Supplementary Table 5*** based on the pre-treatment dysplasia status of the BE patients.[15] For recurrence of dysplasia or metaplasia after initial EET, patients received RFA touch-ups followed by surveillance (***Supplementary Table 4***). Patients could undergo a maximum of three RFA touch-ups, after which management was limited to surveillance for early diagnosis of cancer. [7] The stop age of surveillance and treatments was assumed to be 80 years.

Duration of initial EET was assumed to be 2 years in all strategies.[7] Fifty-five percent of patients received EMR of mucosal irregularities (nodules, masses or ulcers) prior to RFA.[16] On average, patients received 3.55 sessions of RFA during the initial EET period.[7] Complication rates of EET and endoscopies were estimated based on the literature. See common model inputs in ***Supplementary Table 5***.

Cost and utility

The costs of surveillance endoscopy and EETs were based on Centers for Medicare and Medicaid Services (CMS) reimbursement rates.[17] Costs and utilities of cancer care, perforation due to endoscopy, and complications resulting from stricture were estimated based on the published literature (***Supplementary Table 5***). All costs were adjusted for year 2015 using the US consumer price index.[18]

Outcomes

For each strategy, we computed health outcomes including the incidence of symptomatic and surveillance-detected EAC, EAC mortality, complications of endoscopies and treatments, and life years and quality-adjusted life-years (QALYs) per 1,000 BE patients. In addition, we calculated the number of endoscopies, EETs, RFA touch-ups, complications and cancer care years to estimate the total costs of surveillance and treatment per strategy. The outcomes were analyzed for each model separately, then the average results of the three models were presented per strategy as the base case.[19] Individual model results were presented in the sensitivity analysis.

Analysis

The optimal strategy was identified through an incremental cost-effectiveness analysis from a third-party payer perspective using the average results of the three models.[19] Costs and QALYs were discounted at an annual rate of 3%. We performed an incremental cost-effective analysis using a willingness-to-pay threshold (WTP) of $100,000/QALY to determine the optimal BE management strategy which has been suggested to be consistent with societal willingness to pay for medical interventions.[20]

Sensitivity analyses

We performed seven sensitivity analyses to assess the robustness of our results to our structural and parameter assumptions. First, we considered the results of each model separately. In addition, we conducted a sensitivity analysis using a more intensive post-treatment surveillance of LGD patients consistent with the ACG recommendations[4] with endoscopic surveillance every 6 months in the first year after EET and then annually in the strategies where LGD patients received EET. We also conducted one-way sensitivity analyses applying higher and lower values than

the main analysis for EET efficacy and recurrence rates after complete eradication of intestinal metaplasia after EET (***Supplementary Table 6***). Finally, we performed a probabilistic sensitivity analysis (PSA) where cost and utility values, as well as the rate of complications of endoscopy and EET were varied simultaneously (***Supplementary Table 7***). In the PSA, we also considered lower ($50k) and higher ($150k) thresholds for cost-effectiveness.

RESULTS

Results for Men

Without surveillance or EET, the models predicted an average EAC cumulative incidence and mortality of 111 cases and 77 deaths per 1,000 BE patients, respectively, with a total cost of $5.7 million for the care of incident EAC cases (***Table 1***). Surveillance or EET prevented 23-75% of EAC cases and decreased mortality by 31-88% while increasing costs to $6.2-17.3 million depending on the management strategy (***Supplementary Table 8***).

Table 1. Results of base-case natural history and selected BE management strategies (average of the models) per 1,000 BE male patients

Strategy **Outcome**	Natural history	ND5y LGD^{nc}1y	ND3y LGD^{nc}1y	ND3y LGD^{c}1y	ND3y LGD^{c}EET	ND3y LGD^{nc}EET
EAC incidence	111	59	52	51	32	38
EAC mortality	77	26	21	21	12	15
Endoscopies	-	7,408	9,882	10,234	9,968	9,158
Initial EET	-	187	216	220	635	358
RFA touch-ups	-	84	100	104	337	178
Cost ($1,000)						
Cancer care	5,668	3,709	3,302	3,240	2,162	2,477
Endoscopies	-	4,149	5,593	5,830	5,864	5,327
EET/Touch-ups	-	994	1,146	1,178	3,635	1,994
Total Cost	5,668	8,851	10,041	10,247	11,662	9,799
LY	14,566	14,854	14,878	14,881	14,923	14,909
QALY	14,523	14,825	14,850	14,853	14,888	14,881

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed, EET: endoscopic eradication therapy, m: month, EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, HGD: high-grade dysplasia, LGD: low-grade dysplasia, LY: life-years, m: million, ND: non-dysplastic BE, QALY: quality-adjusted life-years, RFA: radiofrequency ablation, y: year

The average results of selected different BE management strategies are presented in the ***Table 1*** to compare the effect of different BE management strategies. Surveillance with a 5-year interval for NDBE and a 1-year interval for LGD patients without confirmation endoscopy decreased EAC incidence to 59 cases (-47%) and EAC mortality to 26 (-66%) per 1,000 BE patients. The total costs increased to $8.9 million while gaining 302 more QALYs compared to the natural history. Reducing the surveillance interval for NDBE patients to 3 years prevented more EAC cases and achieved greater QALYs, but the total costs increased. (***Table 1***).

EET for patients with LGD increased QALYs and costs, and decreased EAC incidence and mortality compared with surveillance for LGD. The strategy with EET for LGD patients after endoscopic confirmation with every 3-year surveillance for NDBE patients decreased EAC incidence and mortality to 38 cases (-66%) and 15 deaths (-81%) per 1,000 BE patients compared with natural history, respectively. The costs increased to $9.8 million while gaining 358 more QALYs than natural history. EET for LGD without endoscopic confirmation resulted in slightly higher QALYs, compared with EET for LGD with confirmation, but the costs increased by almost $2 million per 1,000 BE patients (***Table 1***).

Cost-effectiveness analysis

Strategies using EET for LGD patients (either with or without confirmation endoscopy) were generally more effective than strategies with surveillance for LGD patients (***Supplementary Table 8***). In men, only strategies limiting EET to patients confirmed to have LGD on endoscopic confirmation after acid suppression were cost-effective (***Table 2A, Figure 2A***). Considering a WTP threshold of $100,000, the optimal BE management strategy for men was EET for endoscopically confirmed LGD after 2 months of acid suppression, and surveillance every 3 years for NDBE patients (ICER of $53,044/QALY).

Results for women

Predicted EAC cases in women were lower than in men (75 and 111 per 1,000 in women and men, respectively). Consequently, QALY gained from BE surveillance and treatment were lower in women than in men and incremental costs per QALY gained for similar BE management strategies were higher. Most cost-effective strategies in women included EET for LGD confirmed by endoscopy after 2 months of acid suppression, similar to results for men (***Table 2B and Figure 2B***). Because of the higher incremental costs per QALY gained in women, the optimal strategy was surveillance every 5 years for NDBE (ICER: $36,045/QALY).

Table 2. The results of cost-effectiveness analysis per 1,000 BE male patients (A), and per 1,000 female patients (B)

A. Per 1,000 BE male patients			
Strategy	**Cost ($1,000)**	**QALY**	**ICER ($/QALY)[1]**
Natural history	5,668	14,523	-
ND0 LGD^{c}EET	6,176	14,728	2,476
ND5y LGD^{c}EET	8,672	14,855	19,779
ND4y LGD^{c}EET	9,148	14,869	32,850
ND3y LGD^{c}EET[2]	9,799	14,881	53,044
ND2y LGD^{c}EET	11,518	14,892	156,313
ND2y LGD^{nc}EET	13,253	14,894	1,105,045
ND1y LGD^{c}EET	15,698	14,896	1,446,520
B. Per 1,000 BE female patients			
Strategy	**Cost ($1,000)**	**QALY**	**ICER ($/QALY)[1]**
Natural history	3,534	16,268	
ND0 LGD^{nc}1y×2, 3y	4,450	16,405	6,716
ND0 LGD^{c}EET	4,553	16,419	7,561
ND5y LGD^{c}EET[3]	7,448	16,499	36,045
ND4y LGD^{c}EET	8,064	16,504	118,233
ND3y LGD^{c}EET	8,839	16,508	202,874
ND3y LGD^{nc}EET	10,869	16,511	700,093

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic BE, QALY: quality-adjusted life-years, y: year, 1y×2, 3y: surveillance every 1 year for 2 years, thereafter every 3 years.

[1]The ICERs were calculated prior to rounding the numbers reported for costs and QALYs in this table.

[2]The optimal strategy was EET after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBE patients. Strategies that were dominated are not displayed in the table.

[3]The optimal strategy was EET after confirmation by repeat endoscopy for LGD patients and surveillance every 5 years for NDBE patients. Strategies that were dominated are not displayed in the table.

Sensitivity analysis

All three models consistently found EET to be the optimal strategy for male BE patients with LGD (***Table 3***). However, because costs per QALY gained were generally lower in the MISCAN-EAC model, the optimal strategy for male NDBE patients varied from surveillance every 2 years (MISCAN-EAC) to surveillance every 3 years (EACMO and MSCE-EAC) (***Supplementary Tables 9-14***).

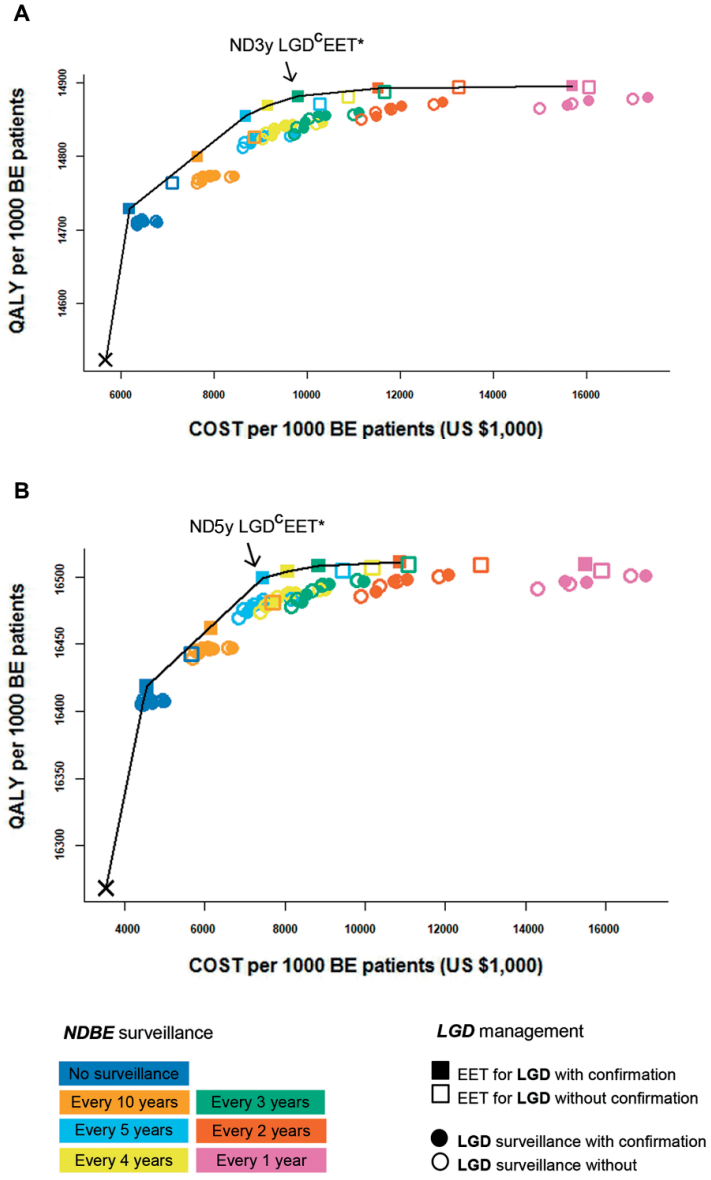

Figure 2. Results of cost-effectiveness analysis for men (A) and women (B)
BE: Barrett's esophagus, ᶜ: confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, LGD: low-grade dysplasia, ND: Non-dysplastic BE, QALY: quality-adjusted life-year, y: year
* The optimal strategy for men was EET after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBE patients with an incremental cost-effectiveness ratio (ICER) of $53,044/ QALY gained, and the optimal strategy for women was EET after confirmation by repeat endoscopy for LGD patients and surveillance every 5 years for NDBE patients with an ICER of $36,045/ QALY gained assuming a willingness-to-pay threshold of $100,000/QALY.

Table 3. Optimal management strategy by analysis for male BE patients

Analysis	NDBE[1]	LGD	EAC prevented[2]	Net cost ($1,000)[2]	QALY gained[2]	ICER ($/QALY)[3]
Base-case[4]	3y	2m[c], EET[4]	66%	4,131	358	53,044
MISCAN-EAC model	2y	2m[c], EET	67%	6,676	452	78,140
EACMo model	3y	2m[c], EET	67%	3,514	365	67,225
MSCE-EAC model	3y	2m[c], EET	67%	3,822	278	84,564
More intensive post-EET surveillance[4]	3y	2m[c], EET	66%	4,785	353	68,199
Higher EET efficacy[4]	3y	2m[c], EET	70%	3,785	364	49,379
Lower EET efficacy[4]	3y	2m[c], EET	62%	4,458	341	59,180
Higher recurrence rate after CE-IM[4]	3y	2m[c], EET	59%	5,007	338	66,501
Lower recurrence rate after CE-IM[4]	3y	2m[c], EET	66%	4,131	358	49,115

BE: Barrett's esophagus, CE-IM: complete eradication of intestinal metaplasia, 2m[c]: confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, LGD: low-grade dysplasia, m: month, NDBE: non-dysplastic BE, QALY: quality-adjusted life-year, y: year.

1. The numbers in the column show the optimal surveillance interval.
2. Per 1,000 BE patients compared with natural history.
3. The ICERs were calculated prior to rounding the numbers reported for costs and QALYs in this table
4. Combined results of the models (mean).
5. Confirmatory endoscopy at 2 months, if LGD is confirmed then EET.

The optimal strategy for men did not change in the one-way sensitivity analyses: applying a more intensive surveillance strategy after treatment of LGD patients, a higher or lower value for EET efficacy, or a higher or lower value for recurrence rate after complete eradiation of metaplasia after receiving EET (***Table 3, Supplementary Tables 15-19***). Results were also robust to wide variations in assumptions on complication rates, cost and utility values. The optimal BE management strategy for men (EET after confirmation by repeat endoscopy after acid suppression for LGD patients and surveillance every 3 years for NDBE patients) was optimal in 100% of runs in probabilistic sensitivity analyses for WTP thresholds of $67,500-137,500/QALY (***Figure 3***).

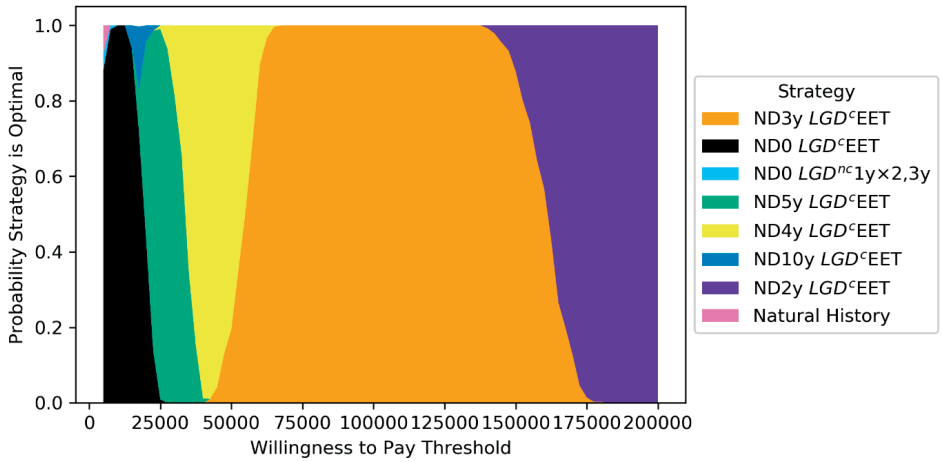

Figure 3. Results of probabilistic sensitivity analysis by willingness-to-pay thresholds ($/QALY) for men

[c]: confirmed by a repeat endoscopy at 2 months, [nc]: not confirmed, EET: endoscopic eradication therapy, LGD: low-grade dysplasia, ND: Non-dysplastic Barrett's esophagus, QALY: quality-adjusted life-year, y: year

DISCUSSION

Our comparative modeling analysis indicates that the most cost-effective strategy for patients with BE and LGD is EET, but only if the LGD is confirmed by a repeat endoscopy after 2 months of high dose acid suppression therapy. Our analysis also finds that the most cost-effective strategy for NDBE patients is surveillance every 3 years in men but every 5 years in women.

We found that none of the strategies using surveillance for LGD patients, or EET without confirmation of LGD, were cost-effective in men. For women, only one out of seven efficient strategies used surveillance for LGD. This finding was consistent between the individual models and the wide variation in assumptions examined in the sensitivity analyses. Despite the potential harms and cost of endoscopic therapy, EET of LGD reduces the number of endoscopies required for surveillance of LGD patients because of prolonged surveillance intervals after successful treatment and generally prevents more EAC cases than strategies using only surveillance for LGD. Consequently, EET strategies are not much more expensive than some surveillance-only strategies, while gaining greater QALYs. Importantly, confirmation of LGD before EET is more cost-effective than EET without confirmation. Confirmatory endoscopy decreases the number of false-positive results of LGD diagnosis. Although one more

endoscopy is required per BE patient, the additional costs are compensated by the reduced number of inappropriate EET (ablation of misdiagnosed NDBE patients).

The three models are less consistent in identifying the optimal strategy for NDBE patients, while two models show that surveillance every 3 years is the optimal strategy for men, the MISCAN-EAC model suggests that surveillance every 2 years is optimal. This discrepancy can be explained by different model assumptions between the three models, e.g. on regression and progression of BE patients.

Prior analyses reported inconsistent findings regarding the management of NDBE patients. A modeling study in Australia reported that surveillance of all NDBE patients was likely not cost-effective,[21] while studies in the Netherlands and US reported that surveillance of NDBE patients could be cost-effective using a 3- or 5-year interval, respectively.[10,22] These studies were limited by the use of a single model/natural history,[8,9] and they examined fewer competing management strategies.

In our analysis, we simulated cohorts of 60-year-old BE patients as the mean/median age of BE patients at diagnosis is greater than 60 years.[23, 24] In all strategies, the stop age of surveillance was assumed to be 80 years. This stopping age was chosen to reflect the balance between benefits and harms of surveillance with increasing age. The USPSTF recommended age 75 for the stopping age of average-risk individuals for colorectal cancer and breast cancer screening.[25, 26] We chose the higher age of 80 because patients with BE, even NDBE, are no longer average risk.

An innovative feature of our analysis is the ability to test different structural assumptions about the natural history of progression from BE to EAC by comparing three independently developed models. Two models (MISCAN-EAC and MSCE-EAC) assume that regression from HGD to LGD, and from LGD to NDBE can occur in the absence of EET, while the third model (EACMo) does not allow regression to occur. MSCE-EAC model is based on the molecular and cellular changes that underlie the progression from normal squamous epithelium to BE and to EAC, whereas the other two models are population-based cohort simulations reflecting the clinically identifiable stages leading to EAC development. All models are independently calibrated to reproduce SEER data and use identical clinical parameter estimates (variable values);[27] however, the manner in which these variables interact differs substantially between models. Despite these differences in model structure, our results are remarkably consistent. A further strength of our study is the ability to present a sensitivity analysis that simultaneously varies the estimated values of variables in three models with unique natural history assumptions about BE and EAC. For these reasons, we believe our

comparative modeling results are more robust than prior studies in which analyses were limited to a single model.

Our study has several limitations. A major concern is the limited amount of published long-term EET outcome data. For this reason, short-term clinical effects were used to inform our models and extrapolated to project long-term effects, and we conducted sensitivity analyses applying higher and lower values for EET efficacy and recurrence rates after complete eradication of metaplasia. Furthermore, there is limited evidence regarding the association of multifocal LGD or LGD with nodularity and progression;[5] and only one of our models (MSCE-EAC) explicitly models mutations throughout the tissue that may lead to multifocal clonal growth. This is an area with less information, requiring more explorative research in the future. In addition, the underlying prevalence of BE driving the overall incidence of EAC is unknown and for this reason, the models differed in the numbers of total EAC (preclinical and clinically detected) estimated over the lifetime of the cohort. Cost estimates used CMS data, which are relevant to individuals 65 years of age and older and may underestimate the costs incurred in individuals 60-64 years of age in this study. Finally, utilities were estimated from limited data and may not accurately represent individuals' preferences for different health states. Therefore, we conducted PSA on cost and utility values to evaluate the impact of our assumptions on our results.

Notwithstanding these limitations, our analysis has important implications for management of BE patients and can inform BE policy development and practice decisions. We focus particularly on BE patients without dysplasia or with LGD, who represent the majority of patients diagnosed with BE. The management of BE, particularly LGD, has received inconsistent recommendations from societies. In addition to informing U.S. guidelines, our findings are applicable in other settings. The analyses in our study were conducted for a U.S. cohort, but we expect similar results for BE populations in other settings with similar BE progression rates and high EAC incidence such as Northern and Western Europe.[28-32]

In summary, our comparative modeling analysis using three independent simulation models finds that the most cost-effective management strategy for BE patients with LGD is EET, if LGD is confirmed by a repeat endoscopy after 2 months of high dose acid suppression therapy. For NDBE patients, our analysis finds the optimal cost-effective strategy is surveillance at 3-year intervals for men and at 5-year intervals for women.

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Chapter 5 supplementary materials

METHODS

We used three independent population-based models which are part of the National Cancer Institute (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) to compare the benefits, harms and costs of different management strategies for BE patients.

CISNET-EAC models

Three models were used for this analysis: (1) MISCAN-EAC: Microsimulation Screening Analysis model from Erasmus University Medical Center (Rotterdam, The Netherlands) and University of Washington (Seattle, WA); (2) EACMo: Esophageal Adeno Carcinoma Model originally developed at the Massachusetts General Hospital (Boston, MA) and currently housed at the Columbia University Medical Center (New York, NY); (3) MSCE-EAC: Multistage Clonal Expansion for EAC model from the Fred Hutchinson Cancer Research Center (Seattle, WA). These models were developed independently, but were calibrated in joint comparative modeling exercises to common calibration targets such as the Surveillance, Epidemiology, and End Results (SEER) EAC incidence data (1975-2013).[1]

The models simulate development of EAC through BE in a hypothetical cohort of the US population from birth (MISCAN-EAC, MSCE-EAC) or from age 20 (EACMo) until death. NDBE may develop in asymptomatic individuals, but the incidence is increased in individuals with symptoms of gastroesophageal reflux disease (GERD). Following the onset of NDBE, patients may develop dysplasia followed by cancer. The following states are simulated in all three models: no BE (with or without GERD symptoms), NDBE, LGD, HGD, preclinical (asymptomatic, undiagnosed) EAC, clinical (symptomatic, diagnosed) EAC, and death. However, each model differs in how transitions between states are conducted.

The MSCE-EAC model is a biologically-based stochastic model of cellular and tissue processes that occur during progression from normal squamous epithelium in the esophagus to BE and to EAC. BE onset is modeled as a tissue-field transition in which a variable length segment of normal squamous esophageal tissue is converted to (or replaced by) BE metaplasia. Following onset of BE, two successive rate-limiting mutations in any of the cells within the BE segment create dysplastic cells that may either go extinct or grow clonally into one or more lesions showing LGD. Further

clonal growth of any of the LGD clones may be followed by a transition to HGD that may continue to undergo stochastic clonal growth. The MSCE-EAC model explicitly simulates the biopsy sampling process, including sampling error where small patches of LGD are not observed on a second biopsy because the lesion is missed. The MISCAN-EAC and EACMo models are state-transition models based on natural history simulations. They model the progression of a population through discrete health states with transition probability from one state to another state depending on the state of the disease. Whereas the EACMo model does not allow for regression between health states, the MISCAN-EAC and MSCE-EAC models allow regression from LGD to NDBE and from HGD to LGD.

Screening and surveillance can detect BE, dysplasia and preclinical cancer, and patients with detected disease may receive periodic endoscopic surveillance or undergo EET. Full descriptions of the models have been published and are also available online.[2-4]

Supplementary Table 1. Recommendation of different guidelines for management of non-dysplastic Barrett's esophagus (NDBE) and low-grade dysplasia (LGD) patients

Guideline	Year	Management recommendations for	
		NDBE	LGD
European Society of Gastrointestinal Endoscopy[5]	2017	< 1 cm: no endoscopic surveillance. 1-3 cm: surveillance every 5 years. 3-10cm: surveillance every 3 years. ≥ 10 cm: refer to a BE expert center.	Confirmation by a second expert GI pathologist. ->>Surveillance endoscopy after 6 months: - If no dysplasia->> surveillance every year for 2 years, if no dysplasia persists, surveillance as NDBE patients, thereafter. - If LGD ->> endoscopic ablation therapy should be offered.
Dutch Gastroenterology Association[6]	2017	3 cm: surveillance every 5 years. 3-10 cm: surveillance every 3 years. ≥ 10 cm: refer to a BE expert center.	Confirmation by a second expert GI pathologist. ->>Surveillance endoscopy after 6 months: - If no dysplasia->> surveillance every year for 2 years, if no dysplasia persists, surveillance as NDBE patients, thereafter. - If LGD->> surveillance every year. If LGD persists under surveillance, endoscopic therapy can be considered for long-segment LGD.
British Society of Gastroenterology[7, 8]	2014, 2017	IM at the cardia or an irregular Z-line: no endoscopic surveillance. < 3 cm, without intestinal metaplasia (IM) or dysplasia: repeat endoscopy, if it confirms the diagnosis, no endoscopic surveillance. < 3 cm, with IM: Surveillance every 3-5 years ≥ 3 cm, with IM: Surveillance every 2-3 years.	Confirmation by a second expert GI pathologist. ->>Surveillance endoscopy after 6 months: - If LGD ->> endoscopic ablation therapy should be offered. If ablation is not performed, surveillance endoscopy every 6 months.

Supplementary Table 1. Recommendation of different guidelines for management of non-dysplastic Barrett's esophagus (NDBE) and low-grade dysplasia (LGD) patients (*continued*)

Guideline	Year	Management recommendations for	
		NDBE	LGD
American College of Gastroenterology[9]	2016	Endoscopic surveillance every 3 to 5 year.	Confirmation by a second expert GI pathologist. ->>A repeat endoscopy after optimization of acid suppressant therapy. -If LGD: The preferred modality: endoscopic therapy. Acceptable alternative: endoscopic surveillance every year.
American Society for Gastrointestinal Endoscopy[10, 11]	2012, 2018	Endoscopic surveillance every 3–5 years.	Confirmation by a second expert GI pathologist. ->> endoscopic eradication therapy. - Alternative option for patients avoiding the adverse effects of endoscopic therapy: surveillance in 6 months and every year thereafter.
American Gastroenterological Association[12, 13]	2011, 2016	Endoscopic surveillance every 3–5 years.	Confirmation by a second expert GI pathologist. ->>Surveillance endoscopy after 8-12 weeks. - if LGD is confirmed: endoscopic eradication therapy. - In the absence of the endoscopic therapy: surveillance every 6 months for one years, then annually.
Australian guideline[14]	2015	< 1 cm without IM: No surveillance < 3 cm with IM: Surveillance every 3-5 years < 3 cm with IM: surveillance after 3-5 years, if no IM, no surveillance is needed. ≥ 3 cm: Surveillance every 2-3 years	Confirmation by a second expert GI pathologist. ->>Surveillance endoscopy every 6 months. If two consecutive 6 monthly endoscopies show NDBE->> less frequent follow up schedule. Endoscopic ablation should be considered where LGD is definite, multifocal, and present on more than one occasion.

Supplementary Table 2. The list of simulated strategies

*Strategy name**	Surveillance interval/ treatment				*Strategy name**	Surveillance interval/ treatment		
	ND	LGD				ND	LGD	
ND0 LGD^{c}6m	None	2m×1	6m	6m	ND0 LGD^{nc}6m	None	6m	6m
ND0 LGD^{c}6m×2,1y	None	2m×1	6m×2	1y	ND0 LGD^{nc}6m×2,1y	None	6m×2	1y
ND0 LGD^{c}1y	None	2m×1	1y	1y	ND0 LGD^{nc}1y	None	1y	1y
ND0 LGD^{c}1y×2,2y	None	2m×1	1y×2	2y	ND0 LGD^{nc}1y×2,2y	None	1y×2	2y
ND0 LGD^{c}1y×2,3y	None	2m×1	1y×2	3y	ND0 LGD^{nc}1y×2,3y	None	1y×2	3y
ND10y LGD^{c}6m	10y	2m×1	6m	6m	ND10y LGD^{nc}6m	10y	6m	6m
ND10y LGD^{c}6m×2,1y	10y	2m×1	6m×2	1y	ND10y LGD^{nc}6m×2,1y	10y	6m×2	1y
ND10y LGD^{c}1y	10y	2m×1	1y	1y	ND10y LGD^{nc}1y	10y	1y	1y
ND10y LGD^{c}1y×2,2y	10y	2m×1	1y×2	2y	ND10y LGD^{nc}1y×2,2y	10y	1y×2	2y
ND10y LGD^{c}1y×2,3y*	10y	2m×1	1y×2	3y	ND10y LGD^{nc}1y×2,3y	10y	1y×2	3y
ND5y LGD^{c}6m	5y	2m×1	6m	6m	ND5y LGD^{nc}6m	5y	6m	6m
ND5y LGD^{c}6m×2,1y	5y	2m×1	6m×2	1y	ND5y LGD^{nc}6m×2,1y	5y	6m×2	1y
ND5y LGD^{c}1y	5y	2m×1	1y	1y	ND5y LGD^{nc}1y	5y	1y	1y
ND5y LGD^{c}1y×2,2y	5y	2m×1	1y×2	2y	ND5y LGD^{nc}1y×2,2y	5y	1y×2	2y
ND5y LGD^{c}1y×2,3y	5y	2m×1	1y×2	3y	ND5y LGD^{nc}1y×2,3y	5y	1y×2	3y
ND4y LGD^{c}6m	4y	2m×1	6m	6m	ND4y LGD^{nc}6m	4y	6m	6m
ND4y LGD^{c}6m×2,1y	4y	2m×1	6m×2	1y	ND4y LGD^{nc}6m×2,1y	4y	6m×2	1y
ND4y LGD^{c}1y	4y	2m×1	1y	1y	ND4y LGD^{nc}1y	4y	1y	1y
ND4y LGD^{c}1y×2,2y	4y	2m×1	1y×2	2y	ND4y LGD^{nc}1y×2,2y	4y	1y×2	2y
ND4y LGD^{c}1y×2,3y	4y	2m×1	1y×2	3y	ND4y LGD^{nc}1y×2,3y	4y	1y×2	3y
ND3y LGD^{c}6m	3y	2m×1	6m	6m	ND3y LGD^{nc}6m	3y	6m	6m
ND3y LGD^{c}6m×2,1y	3y	2m×1	6m×2	1y	ND3y LGD^{nc}6m×2,1y	3y	6m×2	1y
ND3y LGD^{c}1y	3y	2m×1	1y	1y	ND3y LGD^{nc}1y	3y	1y	1y
ND3y LGD^{c}1y×2,2y	3y	2m×1	1y×2	2y	ND3y LGD^{nc}1y×2,2y	3y	1y×2	2y
ND3y LGD^{c}1y×2,3y	3y	2m×1	1y×2	3y	ND3y LGD^{nc}1y×2,3y	3y	1y×2	3y
ND2y LGD^{c}6m	2y	2m×1	6m	6m	ND2y LGD^{nc}6m	2y	6m	6m
ND2y LGD^{c}6m×2,1y	2y	2m×1	6m×2	1y	ND2y LGD^{nc}6m×2,1y	2y	6m×2	1y
ND2y LGD^{c}1y	2y	2m×1	1y	1y	ND2y LGD^{nc}1y	2y	1y	1y
ND2y LGD^{c}1y×2,2y	2y	2m×1	1y×2	2y	ND2y LGD^{nc}1y×2,2y	2y	1y×2	2y
ND1y LGD^{c}6m	1y	2m×1	6m	6m	ND1y LGD^{nc}6m	1y	6m	6m
ND1y LGD^{c}6m×2,1y	1y	2m×1	6m×2	1y	ND1y LGD^{nc}6m×2,1y	1y	6m×2	1y
ND1y LGD^{c}1y	1y	2m×1	1y	1y	ND1y LGD^{nc}1y	1y	1y	1y
ND0 LGD^{c}EET	None	2m×1	EET		ND0 LGD^{nc}EET*	None	EET	
ND10y LGD^{c}EET	10y	2m×1	EET		ND10y LGD^{nc}EET	10y	EET	
ND5y LGD^{c}EET	5y	2m×1	EET		ND5y LGD^{nc}EET	5y	EET	
ND4y LGD^{c}EET	4y	2m×1	EET		ND4y LGD^{nc}EET	4y	EET	

Supplementary Table 2. The list of simulated strategies (*continued*)

*Strategy name**	Surveillance interval/ treatment			*Strategy name**	Surveillance interval/ treatment	
	ND	LGD			ND	LGD
ND3y LGD^{c}EET	3y	2m×1	EET	ND3y LGD^{nc}EET	3y	EET
ND2y LGD^{c}EET	2y	2m×1	EET	ND2y LGD^{nc}EET	2y	EET
ND1y LGD^{c}EET	1y	2m×1	EET	ND1y LGD^{nc}EET	1y	EET

^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed, EET: endoscopic eradication therapy, m: month, ND: non-dysplastic Barret's esophagus, LGD: low-grade dysplasia, y: year

* Strategy name of "ND10y LGD^{c}1y×2,3y" means "surveillance every 10 years for NDBE patients, and confirmation endoscopy at 2 months for LGD patients, if LGD is confirmed surveillance every year for 2 times and every 3 years, thereafter".
"ND0 LGD^{nc}EET" means "no surveillance for NDBE patients, and LGD patients, while LGD patients receive EET without any confirmation endoscopy at 2 months"

Supplementary Table 3. Probability of misdiagnosis of patients with Barrett's esophagus and esophageal adenocarcinoma [15-20]

		True State			
		NDBE	LGD	HGD	EAC
Diagnosed state	NDBE	83.5%	17.5%	0.0%	0.0%
	LGD	14.5%	69.2%	11.5%	5.0%
	HGD	1.0%	8.3%	77.5%	17.5%
	EAC	1.0%	5.0%	11.0%	77.5%

EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, NDBE: non-dysplastic Barrett's esophagus

Supplementary Table 4. Post-treatment (EET or touch-up RFA) surveillance strategies

Patients characteristics and treatment outcome	Strategy
Recurrent NDBE patient (Initial LGD)	
After CE-IM (state=normal)	Surveillance at 6, 12, 24 and 36 months, then every 3 years
After non-CE-IM (state=ND)	
Recurrent NDBE patient (Initial HGD)	
After CE-IM (state=normal)	Surveillance at 3, 6, 9, 12, 18 and 24 months, then every 1 year
After non-CE-IM (state=ND)	
Initial or recurrent LGD patients	
After CE-IM (state=normal)	Surveillance at 12 and 24 months, then every 3 years
After CE-D, non-CE-IM (state=ND)	Surveillance at 6, 12, 24 and 36 months, then every 3 years
After non-CE-D, non-CE-IM (state=LGD)	Surveillance at 6 and 12 months, then every 1 year
Initial or recurrent HGD patients	
After CE-IM (state=normal),	Surveillance at 3, 6, 9, 12, 18 and 24 months, then every 1 year
After CE-D, non-CE-IM (state=ND),	
After non-CE-D, non-CE-IM (state=LGD/HGD)	Surveillance every 3 months

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EET: endoscopic eradication therapy, HGD: high-grade dysplasia, IM: intestinal metaplasia, LGD: low-grade dysplasia, ND: No dysplasia, RFA: radiofrequency ablation.

Supplementary Table 5. Model inputs

Parameter/Definition	Value	Source
Maximum number of touch-ups RFA	3	[21]
Duration of initial EET	2 years	[21]
Number of endoscopies during initial EET	4	[21]
Number of RFA sessions during initial EET	3.55	[21]
Proportion of patients receiving EMR treatments before RFA	0.55	[22]
Complication rates		
Perforation due to surveillance endoscopy	0.00025	[23-27]
Bleeding due to surveillance endoscopy	0.00026	[23-26]
Perforation due to EET (per procedure)	0.002#	[28]
Bleeding due to EET (per procedure)	0.004#	[28, 29]
Stricture rate due to EET (per procedure)	0.019#	[28, 29]
Perforation rate resulting from stricture treatment	0.0009	[30]
Bleeding rate resulting from stricture treatment	0.0009	[30]
Success probabilities of EET¥		
In HGD patients		
CE-IM and CE-D	88.9%	[31]
Non-CE-IM, CE-D	3.7%	[31]
Non-CE-IM and non-CE-D	7.4%	[31]

Supplementary Table 5. Model inputs (*continued*)

Parameter/Definition		Value	Source
In LGD patients			
CE-IM and CE-D		98.1%	[31]
Non-CE-IM, CE-D		0	[31]
Non-CE-IM and non-CE-D		1.9%	[31]
Recurrence rates by baseline histologic grade and grade of recurrence			
Annual recurrence rates after CE-IM			
Pre-treatment misdiagnosed NDBE[¥]		7%	[32, 33]
Pre-treatment IND/LGD		8.3%	[31]
Pre-treatment HGD		13.5%	[31]
Recurrent histology of misdiagnosed NDBE[¥] after CE-IM			
NDBE		92%	[32, 33]
IND/LGD		6%	[32, 33]
HGD		2%	[32, 33]
EAC		0%	[32, 33]
Recurrent histology of IND/LGD after CE-IM			
NDBE		50%	[31]
IND/LGD		25%	[31]
HGD		25%	[31]
EAC		0	[31]
Recurrent histology of HGD after CE-IM			
NDBE		50%	[31-33]
IND/LGD		15%	[31]
HGD		25%	[31]
EAC		10%	[31]
Costs			
Endoscopy		$745	[34]
Initial EET treatment (EMR & RFA)		$5,630	[34]
RFA Touch-Up		$1,012	[34]
Complications	Stricture	$1,012	[34]
	Bleeding	$11,815	[35]
	Perforation	$28,533	[36]
Localized EAC initial care		$58,997	[37]
Localized EAC Terminal care		$64,704	[37]
Regional EAC initial care		$75,295	[37]
Regional EAC terminal care		$77,742	[37]
Distant EAC initial care		$57,169	[37]
Distant EAC terminal care		$85,212	[37]
Unstaged[§] EAC initial care		$63,820	[37]
Unstaged[§] EAC terminal care		$75,886	[37]
EAC continuous care		$4,080	[37]
Utility			

Supplementary Table 5. Model inputs (*continued*)

Parameter/Definition	Value	Source
Short term		
Endoscopy with or without EET (1 day)	0.70	[38]
After EET Treatment (1 week) *	0.70	[21]
After RFA Touch-Up (1 week)	0.70	[21]
Stricture (4 week)	0.70	[21], expert opinion
Perforation (4 weeks)	0.70	[21], expert opinion
Bleeding (1 week)	0.70	[21]
Long term (until death)		
Localized EAC initial care (yearly)	0.84	[39, 40]
Localized EAC continuous and terminal care (yearly)	0.96	[39, 40]
Regional EAC care (yearly)	0.65	[39, 40]
Distant EAC care (yearly)	0.40	[39, 40]
Unstaged[§] EAC care (yearly)	0.63	[39, 40]

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, IM: intestinal metaplasia, IND: indefinite dysplasia, ND: non-dysplastic, LGD: low-grade dysplasia, RFA: radiofrequency ablation.

The complication rate per patient was divided per average RFA sessions to compute the complication rate per procedure.[29]
[¥] Recurrent NDBE patients or NDBE patients who are misdiagnosed as LGD/HGD receive EET as well. For NDBE, we assumed the same EET success probability rate that we assumed for LGD patients, but we assumed a different recurrence rate after CE-IM as described in the table.
[§] Unknown
* During initial EET, patients were assumed to receive an average of 3.55 RFA sessions and 0.55 EMR treatments, therefore (3.55+0.55=) 4.1 weeks with utility of 0.7 was assumed per initial 2-year EET.

Supplementary Table 6. Sensitivity analyses parameters

	Base values	Lower values	Higher values
Success probability of EET in HGD patients			
CE-IM and CE-D	88.9%	80.5%	97.3%
Non-CE-IM, CE-D	3.7%	5.1%	2.3%
Non-CE-IM and non-CE-D	7.4%	14.4%	0.4%
Success probability of EET in LGD patients			
CE-IM and CE-D	98.1%	94.3%	100%
Non-CE-IM, CE-D	0%	0%	0%
Non-CE-IM and non-CE-D	1.9%	5.7%	0%
Annual recurrence rates after CE-IM			
Pre-treatment misdiagnosed NDBE	7%	3.5%	14%
Pre- treatment LGD	8.3%	4.15%	16.6%
Pre- treatment HGD	13.5%	6.75%	27%

CE: complete eradication, D: dysplasia, EET: endoscopic eradication therapy, HGD: high-grade dysplasia, IM: intestinal metaplasia, LGD: low-grade dysplasia

PROBABILISTIC SENSITIVITY ANALYSIS

Although the models differ in their natural histories, they share values for costs, test performance characteristics, and utility adjustments. To assess the strength of our findings with respect to a subset of these shared variables, we conducted a probabilistic sensitivity analysis (PSA). Where possible, parameter distributions were estimated with literature; otherwise, expert opinion was consulted. To avoid low probability parameter sets, we generated sets using a Metropolis-Hastings algorithm.[41, 42] The distributions used in the PSA are listed in ***Supplementary Table 5***. Distributions are specified as Beta (alpha, beta) or Normal (mean, standard deviation). Cost-effectiveness calculations were performed for each run, at various willingness-to-pay thresholds.

Supplementary Table 7. Probability sensitivity analysis parameters and distributions

Parameter		Distribution
Complications		
Perforation due to surveillance endoscopy		Beta (94, 383011)
Bleeding due to surveillance endoscopy		Beta (88, 344702)
Perforation due to EET (per procedure)		Beta (54, 8995)
Bleeding due to EET (per procedure)		Beta (15, 3668)
Stricture rate due to EET (per procedure)		Beta (70, 3613)
Perforation rate resulting from stricture		Beta (1, 1119)
Bleeding rate resulting from stricture		Beta (1, 1119)
Costs		Value
Endoscopy		Normal (745.36, 25)
Initial EET treatment (EMR & RFA)		Normal (5630, 25)
RFA Touch-Up		Normal (1012, 25)
	Stricture	Normal (1012, 25)
Complications	Bleeding	Normal (11815, 47595)
	Perforation	Normal (11815, 47595)
Localized EAC initial care		Normal (58997, 2806.1224)
Localized EAC Terminal care		Normal (64704, 3207.1428)
Regional EAC initial care		Normal (75295, 3835.7)
Regional EAC terminal care		Normal (77742, 2534.1836)
Distant EAC initial care		Normal (57169, 5572.9591)
Distant EAC terminal care		Normal(85212, 2826.0204)
Unstaged EAC initial care		Average of Local/Regional/ Distant
Unstaged EAC terminal care		
EAC continuous care		Normal (4080, 416.84)

Supplementary Table 7. Probability sensitivity analysis parameters and distributions (*continued*)

Parameter	Distribution
Utility	
Short terms	
Endoscopy with or without EET (1 day)	Beta (16, 19444)
After EET Treatment (1 week) *	Beta (132, 22750)
After RFA Touch-Up (1 week)	Beta (132, 22750)
Stricture (4 week)	Beta (427, 18130)
Perforation (4 weeks)	Beta (427, 18130)
Bleeding (1 week)	Beta (132, 22750)
Long terms (until death)	
Localized EAC initial care (yearly)	Beta (46, 9)
Localized EAC continuous and terminal care (yearly)	Beta (15, 1)
Regional EAC care (yearly)	Beta (59, 31)
Distant EAC care (yearly)	Beta (38, 59)
Unstaged[§] EAC care (yearly)	Beta (59, 35)

EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, RFA: Radiofrequency ablation

Supplementary Table 8. Results of all strategies by model for 1,000 BE male patients

	Average			MISCAN-EAC model			EACMo model			MSCE-EAC model		
Strategies	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY
Natural history	111	5,668	14,523	116	6,582	14,172	116	5,651	14,627	100	4,770	14,770
ND0 LGD^{c}6m	84	6,787	14,709	97	7,643	14,344	93	5,945	14,798	61	6,772	14,986
ND0 LGD^{c}6m×2,1y	84	6,506	14,710	97	7,645	14,346	93	5,945	14,800	62	5,928	14,984
ND0 LGD^{c}1y	84	6,474	14,712	97	7,646	14,348	92	5,939	14,803	63	5,836	14,985
ND0 LGD^{c}1y×2,2y	85	6,371	14,708	97	7,639	14,348	93	5,962	14,803	65	5,512	14,974
ND0 LGD^{c}1y×2,3y	86	6,356	14,705	97	7,651	14,346	93	5,984	14,802	67	5,433	14,969
ND10y LGD^{c}6m	70	8,438	14,772	76	9,350	14,433	88	7,691	14,870	46	8,273	15,013
ND10y LGD^{c}6m×2,1y	70	8,023	14,774	76	9,327	14,435	87	7,619	14,871	48	7,122	15,016
ND10y LGD^{c}1y	70	7,895	14,774	76	9,258	14,436	86	7,485	14,872	48	6,944	15,014
ND10y LGD^{c}1y×2,2y	72	7,770	14,771	77	9,238	14,434	88	7,584	14,872	52	6,487	15,007
ND10y LGD^{c}1y×2,3y*	74	7,742	14,766	77	9,244	14,431	89	7,614	14,869	54	6,370	14,997
ND5y LGD^{c}6m	56	9,760	14,829	60	10,897	14,520	67	8,434	14,939	40	9,950	15,027
ND5y LGD^{c}6m×2,1y	57	9,184	14,828	61	10,847	14,521	68	8,397	14,938	43	8,307	15,027
ND5y LGD^{c}1y	58	9,028	14,828	62	10,754	14,518	68	8,238	14,936	44	8,093	15,029
ND5y LGD^{c}1y×2,2y	60	8,832	14,823	63	10,709	14,514	71	8,362	14,932	48	7,427	15,023
ND5y LGD^{c}1y×2,3y	63	8,795	14,817	64	10,700	14,508	73	8,418	14,927	51	7,266	15,015
ND4y LGD^{c}6m	52	10,333	14,845	56	11,530	14,544	60	8,815	14,955	39	10,654	15,036
ND4y LGD^{c}6m×2,1y	53	9,690	14,843	57	11,464	14,543	61	8,781	14,953	42	8,824	15,032
ND4y LGD^{c}1y	54	9,514	14,840	58	11,357	14,540	63	8,611	14,951	43	8,574	15,030
ND4y LGD^{c}1y×2,2y	57	9,312	14,835	59	11,308	14,535	66	8,772	14,945	47	7,855	15,026
ND4y LGD^{c}1y×2,3y	60	9,254	14,827	61	11,292	14,528	69	8,824	14,939	50	7,645	15,014
ND3y LGD^{c}6m	48	11,122	14,859	52	12,324	14,570	53	9,422	14,971	39	11,619	15,036

Supplementary Table 8. Results of all strategies by model for 1,000 BE male patients (*continued*)

	Average			MISCAN-EAC model			EACMo model			MSCE-EAC model		
Strategies	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY
ND3y LGD^{c}6m×2,1y	50	10,399	14,855	53	12,249	14,567	55	9,410	14,967	42	9,538	15,032
ND3y LGD^{c}1y	51	10,247	14,853	54	12,148	14,563	57	9,333	14,964	42	9,262	15,032
ND3y LGD^{c}1y×2,2y	54	9,970	14,846	55	12,074	14,555	61	9,434	14,957	47	8,402	15,026
ND3y LGD^{c}1y×2,3y	57	9,929	14,838	57	12,063	14,548	65	9,514	14,948	50	8,210	15,018
ND2y LGD^{c}6m	43	12,911	14,873	46	14,099	14,598	44	11,159	14,984	38	13,477	15,038
ND2y LGD^{c}6m×2,1y	46	12,033	14,868	47	14,012	14,594	49	11,139	14,978	41	10,948	15,033
ND2y LGD^{c}1y	47	11,783	14,864	49	13,844	14,587	51	10,856	14,975	42	10,649	15,031
ND2y LGD^{c}1y×2,2y	51	11,483	14,854	51	13,791	14,577	57	11,025	14,963	47	9,632	15,022
ND1y LGD^{c}6m	38	17,317	14,880	40	18,640	14,617	37	15,966	14,991	38	17,346	15,032
ND1y LGD^{c}6m×2,1y	42	16,052	14,876	42	18,497	14,612	43	15,624	14,983	41	14,034	15,032
ND1y LGD^{c}1y	44	15,587	14,869	44	18,254	14,601	45	14,856	14,979	42	13,652	15,028
ND0 LGD^{c}EET	80	6,176	14,728	89	7,595	14,389	83	5,784	14,835	68	5,151	14,962
ND10y LGD^{c}EET	60	7,638	14,799	63	9,207	14,485	70	7,307	14,908	47	6,399	15,005
ND5y LGD^{c}EET	45	8,672	14,855	49	10,468	14,565	50	8,085	14,968	37	7,464	15,031
ND4y LGD^{c}EET	41	9,148	14,869	45	10,977	14,586	44	8,510	14,981	35	7,957	15,041
ND3y LGD^{c}EET	38	9,799	14,881	43	11,638	14,604	39	9,165	14,992	33	8,592	15,048
ND2y LGD^{c}EET	33	11,518	14,892	38	13,257	14,625	31	10,974	15,003	31	10,323	15,049
ND1y LGD^{c}EET	29	15,698	14,896	35	17,132	14,634	25	15,537	15,009	28	14,423	15,044
ND0 LGD^{nc}6m	83	6,761	14,711	97	7,646	14,347	92	5,941	14,800	61	6,696	14,986
ND0 LGD^{nc}6m×2,1y	84	6,474	14,711	97	7,644	14,349	92	5,939	14,803	63	5,838	14,980
ND0 LGD^{nc}1y	84	6,449	14,714	96	7,640	14,354	92	5,944	14,807	63	5,763	14,980
ND0 LGD^{nc}1y×2,2y	85	6,350	14,710	96	7,650	14,353	92	5,972	14,808	66	5,429	14,970

Supplementary Table 8. Results of all strategies by model for 1,000 BE male patients (*continued*)

	Average			MISCAN-EAC model			EACMo model			MSCE-EAC model		
Strategies	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY
ND0 LGD^{nc}1y×2,3y	86	6,344	14,707	97	7,661	14,349	93	6,011	14,806	68	5,361	14,964
ND10y LGD^{nc}6m	70	8,350	14,772	77	9,263	14,433	88	7,667	14,872	46	8,120	15,010
ND10y LGD^{nc}6m×2,1y	70	7,921	14,772	76	9,229	14,436	86	7,586	14,874	49	6,948	15,007
ND10y LGD^{nc}1y	71	7,767	14,771	77	9,108	14,436	86	7,411	14,874	50	6,781	15,004
ND10y LGD^{nc}1y×2,2y	73	7,662	14,768	78	9,099	14,433	88	7,541	14,874	53	6,345	14,996
ND10y LGD^{nc}1y×2,3y	75	7,632	14,763	79	9,101	14,428	89	7,585	14,871	56	6,209	14,991
ND5y LGD^{nc}6m	56	9,643	14,828	61	10,779	14,519	66	8,404	14,940	41	9,745	15,024
ND5y LGD^{nc}6m×2,1y	58	9,051	14,828	62	10,703	14,518	67	8,361	14,939	44	8,089	15,027
ND5y LGD^{nc}1y	59	8,851	14,825	63	10,489	14,516	68	8,181	14,935	45	7,885	15,024
ND5y LGD^{nc}1y×2,2y	62	8,655	14,818	64	10,426	14,510	71	8,324	14,932	49	7,215	15,014
ND5y LGD^{nc}1y×2,3y	64	8,622	14,811	66	10,414	14,501	74	8,396	14,926	52	7,055	15,007
ND4y LGD^{nc}6m	52	10,193	14,843	57	11,369	14,543	59	8,788	14,956	40	10,423	15,029
ND4y LGD^{nc}6m×2,1y	54	9,537	14,842	58	11,275	14,541	61	8,755	14,954	43	8,582	15,030
ND4y LGD^{nc}1y	55	9,308	14,837	59	11,017	14,537	63	8,565	14,950	44	8,341	15,024
ND4y LGD^{nc}1y×2,2y	59	9,113	14,832	61	10,970	14,529	67	8,743	14,944	48	7,625	15,023
ND4y LGD^{nc}1y×2,3y	61	9,055	14,822	63	10,937	14,518	70	8,812	14,937	52	7,415	15,013
ND3y LGD^{nc}6m	48	10,997	14,857	52	12,198	14,568	52	9,398	14,970	39	11,395	15,032
ND3y LGD^{nc}6m×2,1y	50	10,243	14,853	54	12,086	14,564	55	9,389	14,966	42	9,254	15,030
ND3y LGD^{nc}1y	52	10,041	14,850	55	11,831	14,558	57	9,296	14,963	43	8,996	15,031
ND3y LGD^{nc}1y×2,2y	56	9,771	14,839	57	11,754	14,548	62	9,413	14,954	48	8,145	15,016
ND3y LGD^{nc}1y×2,3y	59	9,727	14,830	59	11,720	14,536	67	9,498	14,944	51	7,962	15,009
ND2y LGD^{nc}6m	43	12,719	14,870	47	13,827	14,595	45	11,138	14,984	39	13,192	15,031

Supplementary Table 8. Results of all strategies by model for 1,000 BE male patients (*continued*)

	Average			MISCAN-EAC model			EACMo model			MSCE-EAC model		
Strategies	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY	EAC	Cost ($1000)	QALY
ND2y LGD^{nc}6m×2,1y	46	11,813	14,864	48	13,678	14,589	49	11,119	14,977	42	10,642	15,026
ND2y LGD^{nc}1y	48	11,472	14,859	51	13,269	14,579	51	10,810	14,972	43	10,337	15,025
ND2y LGD^{nc}1y×2,2y	53	11,170	14,850	54	13,186	14,566	58	10,983	14,960	48	9,342	15,023
ND1y LGD^{nc}6m	39	16,999	14,877	41	18,057	14,613	37	15,940	14,990	38	17,001	15,028
ND1y LGD^{nc}6m×2,1y	43	15,695	14,871	44	17,862	14,603	43	15,556	14,982	42	13,669	15,028
ND1y LGD^{nc}1y	45	15,000	14,865	47	16,969	14,591	46	14,751	14,977	42	13,278	15,026
ND0 LGD^{nc}EET*	70	7,095	14,764	80	8,941	14,433	72	6,753	14,872	56	5,590	14,986
ND10y LGD^{nc}EET	50	8,858	14,826	55	10,871	14,520	56	8,590	14,938	38	7,114	15,021
ND5y LGD^{nc}EET	37	10,271	14,871	43	12,512	14,588	38	9,883	14,986	31	8,418	15,040
ND4y LGD^{nc}EET	35	10,876	14,881	41	13,169	14,602	33	10,476	14,995	30	8,982	15,044
ND3y LGD^{nc}EET	32	11,662	14,888	39	14,016	14,614	29	11,290	15,003	28	9,678	15,046
ND2y LGD^{nc}EET	29	13,253	14,894	37	15,548	14,626	24	12,910	15,008	27	11,301	15,048
ND1y LGD^{nc}EET	27	16,055	14,894	36	18,058	14,629	21	15,479	15,009	26	14,628	15,045

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed, EET: endoscopic eradication therapy, m: month, ND: non-dysplastic Barret's esophagus, LGD: low-grade dysplasia, y: year, QALY: quality-adjusted life-years, y: year

* **Strategy** name of "ND10y LGD^{c}1y×2,3y" means "surveillance every 10 years for NDBE patients, and confirmation endoscopy at 2 months for LGD patients, if LGD is confirmed surveillance every year for 2 times and every 3 years, thereafter".
"ND0 LGD^{nc}EET" means "no surveillance for NDBE patients, and LGD patients, while LGD patients receive EET without any confirmation endoscopy at 2 months"

COST-EFFECTIVENESS ANALYSIS RESULTS

The separate results of cost-effectiveness analysis per 1,000 male and female patients for each model are reported in the following tables. All the reported costs and QALYs are rounded, but ICERs were calculated prior to rounding these numbers.

Supplementary Table 9. The results of cost-effectiveness analysis per 1,000 BE male patients in MISCAN-EAC model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	6,582	14,172	
ND0 LGD^{c}EET	7,595	14,389	4,677
ND5y LGD^{c}EET	10,468	14,565	16,332
ND4y LGD^{c}EET	10,977	14,586	24,537
ND3y LGD^{c}EET	11,638	14,604	35,987
ND2y LGD^{c}EET*	13,257	14,625	78,140
ND1y LGD^{c}EET	17,132	14,634	407,072

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year

* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 2 years for NDBE patients.

Supplementary Table 10. The results of cost-effectiveness analysis per 1,000 BE male patients in EACMo model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,651	14,627	0
ND0 LGD^{c}EET	5,784	14,835	638
ND5y LGD^{c}EET	8,085	14,968	17,336
ND4y LGD^{c}EET	8,510	14,981	31,300
ND3y LGD^{c}EET*	9,165	14,992	60,009
ND2y LGD^{c}EET	10,974	15,003	160,687
ND2y LGD^{ncEET}	12,910	15,008	402,671
ND1y LGD^{nc}EET	15,479	15,009	1,886,888

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year

* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBE patients.

Supplementary Table 11. The results of cost-effectiveness analysis per 1,000 male BE patients in MSCE-EAC model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	4,770	14,770	
ND0 LGD^{c}EET	5,151	14,962	1,982
ND0 LGD^{nc}EET	5,590	14,986	17,776
ND5y LGD^{c}EET	7,464	15,031	41,463
ND4y LGD^{c}EET	7,957	15,041	54,106
ND3y LGD^{c}EET*	8,592	15,048	84,564
ND2y LGD^{nc}EET	10,323	15,049	1,706,731

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 4 years for NDBE patients.

Supplementary Table 12. The results of cost-effectiveness analysis per 1,000 BE female patients in MISCAN-EAC model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	4,366	15,901	
ND0 LGD^{nc} 1y×2,2y	5,805	16,070	8,500
ND0 LGD^{c}EET	6,058	16,097	9,450
ND10 LGD^{c}EET	7,706	16,158	26,757
ND5y LGD^{c}EET	9,268	16,200	37,433
ND4y LGD^{c}EET*	9,918	16,207	88,428
ND3y LGD^{c}EET	10,701	16,214	120,563
ND2y LGD^{c}EET	12,717	16,218	452,025
ND1y LGD^{c}EET	17,138	16,219	17,685,407

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, m: month, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year, 1y×2,3y: surveillance every year for 2 years and thereafter every 3 years
* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 4 years for NDBE patients.

Supplementary Table 13. The results of cost-effectiveness analysis per 1,000 BE female patients in EACMo model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	2,695	16,465	
ND0 LGD^{nc}1y×2, 2y	3,676	16,560	10,254
ND0 LGD^{c}EET	3,872	16,577	12,091
ND10 LGD^{c}EET	5,741	16,607	62,265
ND5y LGD^{c}EET*	7,080	16,627	67,225
ND4y LGD^{c}EET	7,734	16,629	234,011
ND3y LGD^{c}EET	8,575	16,632	315,052
ND2y LGD^{c}EET	10,773	16,633	4,199,337

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic BE, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 5 years for NDBE patients.

Supplementary Table 14. The results of cost-effectiveness analysis per 1,000 BE female patients in MSCE-EAC model

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	3,541	16,440	
ND0 LGD^{c}EET	3,747	16,582	1,455
ND0 LGD^{nc}EET	4,152	16,614	12,540
ND5y LGD^{c}EET	6,021	16,670	33,796
ND4y LGD^{c}EET*	6,567	16,675	99,702
ND4y LGD^{nc}EET	7,058	16,678	151,984
ND3y LGD^{nc}EET	8,413	16,684	251,051

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment for LGD patients without confirmation endoscopy at 2 months and surveillance every 4 years for NDBE patients.

Supplementary Table 15. Sensitivity analysis applying a more intensive post-EET surveillance, the results of cost-effectiveness analysis per 1,000 BE male patients (average of the models)

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,668	14,523	
ND0 LGD^{nc}1y×2, 2y	6,378	14,712	3,766
ND0 LGD^{c}EET	6,443	14,725	4,750
ND5y LGD^{c}EET	9,177	14,851	21,775
ND4y LGD^{c}EET	9,715	14,865	37,026
ND3y LGD^{c}EET*	10,453	14,876	68,199
ND2y LGD^{c}EET	12,299	14,887	171,088
ND1y LGD^{c}EET	16,775	14,893	799,337

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic BE, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBE patients.

Supplementary Table 16. Sensitivity analysis applying a higher EET efficacy rate, the results of cost-effectiveness analysis per 1,000 BE male patients (average of the models)

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,668	14,523	
ND0 LGD^{c}EET	6,009	14,729	1,658
ND5 LGD^{c}EET	8,353	14,860	17,939
ND4y LGD^{c}EET	8,810	14,874	32,237
ND3y LGD^{c}EET*	9,452	14,887	49,379
ND2y LGD^{c}EET	11,157	14,897	176,629
ND1y LGD^{c}EET	15,319	14,903	680,130

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment for LGD patients without confirmation endoscopy at 2 months and surveillance every 3 years for NDBE patients.

Supplementary Table 17. Sensitivity analysis applying a lower EET efficacy rate, the results of cost-effectiveness analysis per 1,000 BE male patients (average of the models

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,668	14,523	
ND0 LGD^{c}EET	6,328	14,719	3,367
ND5 LGD^{c}EET	8,967	14,840	21,802
ND4y LGD^{c}EET	9,455	14,853	38,181
ND3y LGD^{c}EET*	10,125	14,864	59,180
ND2y LGD^{c}EET	11,855	14,875	168,210
ND1y LGD^{c}EET	13,582	14,879	383,938

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic BE, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment after confirmation by repeat endoscopy for LGD patients and surveillance every 3 years for NDBE patients.

Supplementary Table 18. Sensitivity analysis applying a higher recurrence rate after complete eradication of intestinal metaplasia, the results of cost-effectiveness analysis per 1,000 BE male patients (average of the models)

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,668	14,523	
ND0 LGD^{c}EET	6,594	14,715	4,830
ND5 LGD^{c}EET	9,439	14,836	23,491
ND4y LGD^{c}EET	9,966	14,850	37,460
ND3y LGD^{c}EET*	10,675	14,861	66,501
ND2y LGD^{c}EET	12,485	14,870	192,722
ND1y LGD^{c}EET	16,816	14,875	958,178

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year
* The optimal strategy was treatment for LGD patients without confirmation endoscopy at 2 months and surveillance every 3 years for NDBE patients.

Supplementary Table 19. Sensitivity analysis applying a lower recurrence rate after complete eradication of intestinal metaplasia, the results of cost-effectiveness analysis per 1,000 BE male patients (average of the models)

Strategy	Cost ($1,000)	QALY	ICER ($/QALY)
Natural history	5,668	14,523	
ND0 LGD^{c}EET	5,838	14,730	826
ND5y LGD^{c}EET	8,075	14,861	17,077
ND4y LGD^{c}EET	8,517	14,875	29,986
ND3y LGD^{c}EET*	9,131	14,888	49,115
ND2y LGD^{c}EET	10,784	14,899	147,459
ND2y LGD^{nc}EET	12,260	14,904	303,745
ND1y LGD^{c}EET	14,864	14,905	3,381,830

BE: Barrett's esophagus, ^{c}: confirmed by a repeat endoscopy at 2 months, ^{nc}: not-confirmed by a repeat endoscopy at 2 months, EET: endoscopic eradication therapy, ICER: incremental cost-effectiveness ratio, LGD: low-grade dysplasia, ND: non-dysplastic, QALY: quality-adjusted life-years, y: year

* The optimal strategy was treatment for LGD patients without confirmation endoscopy at 2 months and surveillance every 3 years for NDBE patients.

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The optimal age to stop endoscopic surveillance of Barrett's esophagus patients based on gender and comorbidity: a comparative cost-effectiveness analysis

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ABSTRACT

Introduction

Current guidelines recommend surveillance for non-dysplastic Barrett's esophagus (NDBE) patients but do not include a recommended age for discontinuing surveillance. This study aimed to determine the optimal age for last surveillance of NDBE patients by level of comorbidity.

Methods

We used three independently developed models to simulate patients previously diagnosed with NDBE, varying in age (each of 66 to 90 years), gender, and comorbidity level (no, mild, moderate, severe). All patients had received regular surveillance until their current age. We calculated incremental costs and quality-adjusted life-years (QALYs) gained from one additional endoscopic surveillance at the current age versus not performing surveillance at that age. We determined the optimal age to end surveillance as the age at which incremental cost-effectiveness ratio (ICER) of one more surveillance was just below the willingness-to-pay threshold of $100,000/QALY.

Results

The benefit of having one more surveillance endoscopy strongly depended on age, gender and comorbidity, while costs were relatively stable. For male NDBE patients without comorbidity, one additional surveillance at age 80 years provided 14 more QALYs per 1,000 BE patients at an additional cost of $1,2 million, while for women with severe comorbidity the benefit at that age was only 7 QALYs at a cost of $1.3 million per 1,000 BE patients. The optimal age to stop surveillance varied accordingly. For men with no, mild, moderate and severe comorbidity, the optimal ages of last surveillance were 81, 80, 77 and 73 years, respectively. For women, these ages were lower: 75, 73, 73 and 69 years, respectively.

Conclusions

Our comparative modeling analysis finds that in addition to chronological age, the comorbidity status and gender of NDBE patients are important factors to inform the decision to discontinue surveillance.

INTRODUCTION

Barrett's esophagus (BE) is the only known precursor lesion for esophageal adenocarcinoma (EAC).[1] BE patients have a 10 to 55 times higher risk of developing EAC than the general population. Fortunately, BE surveillance and early detection and treatment of dysplasia may avert EAC development.[2] Generally, guidelines in the United States (US) recommend endoscopic eradication therapy (EET) for high-risk patients, i.e. patients with low-grade dysplasia (LGD) or high-grade dysplasia (HGD). Furthermore, they recommend endoscopic surveillance every 3-5 years for non-dysplastic BE (NDBE) patients, who are at a lower risk of developing EAC than those with dysplasia. However, there is no recommendation for when to discontinue surveillance.[3-6]

The expected benefits of surveillance diminish with advancing age and greater comorbidity due to lower life expectancy. For example, US men without comorbidities at age 68 have a life expectancy of 14.7 years, while US men with severe comorbidities at age 80 have a life expectancy of 5.3 years (***Table 1***).[7, 8] Therefore, the harms of endoscopic surveillance (e.g. complications, false-positive results and overtreatment) might outweigh the benefits (e.g. deaths averted) for some patient populations. NDBE patients constitute about 90% of the total BE population.[9] Additional surveillance endoscopies, particularly for this population, increase the cost of the surveillance program considerably, and continuation at older ages may therefore not be cost-effective.

To the best of our knowledge, no prior studies on BE surveillance have investigated the optimal age to discontinue surveillance of NDBE patients with regards to the comorbidity level of patients. Evaluating the harms and benefits of many different stop ages in a clinical study would both be very costly and very time consuming. Therefore, modeling studies are required to estimate the effectiveness and cost-effectiveness of different stop ages.

In this study, we aimed to determine the optimal age of last surveillance for NDBE patients by level of comorbidity using a comparative modeling approach.

METHODS

We used three independently developed simulation models of EAC screening and surveillance that are part of the National Cancer Institute Cancer Intervention and Surveillance Modeling Network (CISNET).

CISNET-EAC models

We used the following models: 1) Microsimulation Screening Analysis model for esophageal adenocarcinoma (MISCAN-EAC) from the Erasmus MC University Medical Center Rotterdam and the University of Washington; 2) Esophageal AdenoCarcinoma Model (EACMo) from the Columbia University Medical Center and Massachusetts General Hospital; and 3) Multistage Clonal Expansion for EAC model from the Fred Hutchinson Cancer Research Center (MSCE-EAC). Each model was independently calibrated to common calibration targets based on US Surveillance, Epidemiology, and End Results (SEER) cancer registry data until 2014.[10]

In all three models, it was assumed that EAC only develops in patients with BE. Healthy (asymptomatic) individuals and individuals with symptomatic gastro-esophageal reflux disease (GERD) may develop NDBE, which can progress to LGD and then HGD. BE patients with HGD may develop preclinical EAC, which can then progress to clinical EAC as symptoms develop. Individuals with clinical EAC may die of the disease with probabilities dependent on age and stage. More details on the structure and quantifications of the models have been published and are available online.[9, 11, 12]

Simulated population and intervention

For the base case, we simulated 200 cohorts of US patients varying in age (66 to 90 years), gender, and comorbidity level (no, mild, moderate, severe) (***Table 1***), and followed them until death. We used the cancer-free age, sex and comorbidity-specific life tables from Lansdorp-Vogelaar, et al[8] and adjusted them to additionally include age and sex-specific mortality due to all cancers except esophageal cancers from CDC Wonder.[13] Surveillance for NDBE patients occurred every 3 years after the initial diagnosis, which was assumed to occur between 60-62 years of age.

For each cohort, we simulated an additional surveillance at the current age, or no further surveillance. For example, a 70-year-old NDBE patient with a mild comorbidity level either did or did not receive one more surveillance at age 70.

Table 1. Overview of comorbidity levels, associated conditions, and life expectancies at selected ages 68, 74 and 80 years in men

Comorbidity level	Conditions included	Life expectancy, years		
		at age 68	at age 74	at age 80
No	None of the conditions listed for mild, moderate or severe	14.7	11.5	8.5
Mild	History of myocardial infarction, ulcer or rheumatologic disease	13.7	11.0	8.0
Moderate	Peripheral vascular disease, cerebrovascular disease, paralysis, diabetes, or combinations of mild conditions	12.8	9.8	6.9
Severe	AIDS, chronic obstructive pulmonary disease, cirrhosis, chronic hepatitis, chronic renal failure, dementia, congestive heart failure, or combinations of at least one moderate condition (except diabetes) with any mild or moderate condition	9.7	7.3	5.3

Patients who were diagnosed with LGD received a repeat endoscopy with biopsies after 2 months of treatment with high-dose proton pump inhibitor to confirm LGD.[14, 15] Patients with HGD or confirmed LGD received EET followed by surveillance until death. In case of recurrence, patients received radiofrequency ablation (RFA) touch-ups followed by surveillance. The post-treatment surveillance strategies were simulated according to the outcome of initial EET or RFA touch-ups (***Supplementary Table 1***). Patients with treatment failure or recurrences more than 3 times, did not receive additional RFA touch-ups and underwent surveillance until death. Treatment and surveillance assumptions are presented in detail in ***Supplementary Table 2***.

Costs and utilities

The costs of endoscopies and EETs were estimated using the 2015 reimbursement rates from Centers for Medicare and Medicaid Services (CMS).[16] The costs and utilities of cancer care by stage at diagnosis and those of complications due to endoscopy and EET were estimated using published literature (***Supplementary Table 2***).[17-23] All costs and utilities were discounted at an annual rate of 3%.[24]

Outcomes and analysis

Using the average results of the three models for every cohort, we calculated the number of EAC cases, EAC deaths, life years (LYs) and quality-adjusted life years (QALYs) with and without one more surveillance. To estimate the total costs, we calculated the cost of cancer care, surveillance endoscopies, EETs, RFA touch-ups and treatment of complications (i.e., bleeding, perforation and stricture).

Subsequently, we calculated incremental costs and QALYs gained from one additional endoscopic surveillance at the current age versus not performing surveillance at that age, using the average results. The incremental cost-effectiveness ratio (ICER) of performing a last surveillance was calculated for all 25 potential stopping ages (66 to 90 years), and the age with the highest ICER just below the willingness-to-pay (WTP) threshold of $100,000 per QALY gained, was considered the optimal age of last surveillance.

Sensitivity analysis

Separate results of each model function as an independent sensitivity analysis of underlying assumptions for the natural history of EAC. In addition, we simulated cohorts of patients diagnosed with NDBE at ages 50, 51, and 52 or 70, 71, and 72 years in addition to 60, 61 and 62 to evaluate the robustness of our findings. Furthermore, we considered EAC survival probabilities, endoscopy and EET complication rates, and disutility scores depending on the comorbidity level of patients. For patients without comorbidity, we considered 50% lower complication rates and disutilities, and 10% higher EAC survival than base case, while for patients with mild comorbidity, we considered the same values assumed in the base case. For patients with moderate or severe comorbidity, we considered 50% or 100% higher complication rates and disutilities, and 10% or 20% lower EAC survival than base case, respectively.

RESULTS

Results for men

Table 2 presents lifetime net benefits and costs of one additional endoscopic surveillance at selected stopping ages of 68, 74, 80, and 86 years. One more surveillance at age 68 in 1,000 NDBE patients without comorbidity prevented 11 more EAC cases than not performing surveillance at that age. Overall, 56 more QALYs were gained at an incremental cost of more than $1 million, resulting in an ICER of $23,600 per QALY, which was well below the WTP threshold. The same comparison for NDBE patients with comorbidities showed that one additional surveillance at age 68 years prevented fewer EAC cases and deaths, which led to higher net costs and lower QALYs. Nonetheless, the ICERs remained below the WTP threshold, and surveillance at age 68 was considered cost effective for NDBE patients of all comorbidity levels.

By increasing the age of the NDBE patients, the net benefits of one additional surveillance decreased, and the ICERs increased accordingly. The ICERs of one additional surveillance versus not performing surveillance at ages 74, 80 or 86 years

were higher than at age 68 years irrespective of comorbidity level (***Table 2***). An additional surveillance at age 74 for NDBE patients with severe comorbidities was not cost-effective, with an ICER higher than $100,000/QALY. Similarly, an additional surveillance at age 80 was not cost-effective for NDBE patients with moderate, or severe comorbidities. At age 86, one more surveillance was not cost effective for any level of comorbidity.

For male NDBE patients without comorbidity, one additional surveillance at age 82 years in comparison with not performing surveillance at that age resulted in an ICER of $116,300 per QALY, while the same comparison at age 81 years resulted in an ICER of $99,000 per QALY. Therefore, 81 years was considered the optimal age of last surveillance for individuals without comorbidity. For individuals with mild, moderate and severe comorbidity, the optimal ages of last surveillance using the average results of the three models were 80, 77 and 73 years, respectively (***Figure 1A***).

Table 2. Lifetime net benefits and costs of one additional endoscopic surveillance at selected ages 68, 74, 80 and 86 versus not performing surveillance at that age per 1000 NDBE male patients

Age	Comorbidity level[1]	EAC prevented	EAC death prevented	QALYs gained	Endoscopies	EET and touch-ups	Net cost ($)	ICER
68	No	10	11	56	1,952	81	1,328,609	23,620
	mild	9	10	49	1,910	79	1,343,689	27,183
	Moderate	8	9	44	1,875	78	1,360,570	30,927
	Severe	5	7	28	1,732	73	1,393,730	49,673
74	No	6	8	31	1,670	70	1,269,878	41,302
	mild	6	7	28	1,650	70	1,275,048	45,230
	Moderate	5	6	22	1,591	68	1,290,369	59,030
	Severe	3	4	13	1,465	64	1,296,268	101,966
80	No	3	5	14	1,401	62	1,192,137	83,986
	mild	3	4	12	1,381	61	1,195,159	96,407
	Moderate	2	3	8	1,322	60	1,195,875	143,993
	Severe	1	2	4	1,220	57	1,175,899	269,344
86	No	1	2	4	1,128	55	1,083,739	254,074
	mild	1	2	4	1,112	54	1,081,072	295,144
	Moderate	1	2	2	1,068	53	1,072,173	482,703
	Severe	0	1	0	981	51	1,033,270	2,352,232

EAC: esophageal adenocarcinoma; EET: endoscopic eradication therapy; ICER: incremental cost-effectiveness ratio

[1] Overview of comorbidity levels and associated conditions can be found in Table 1.

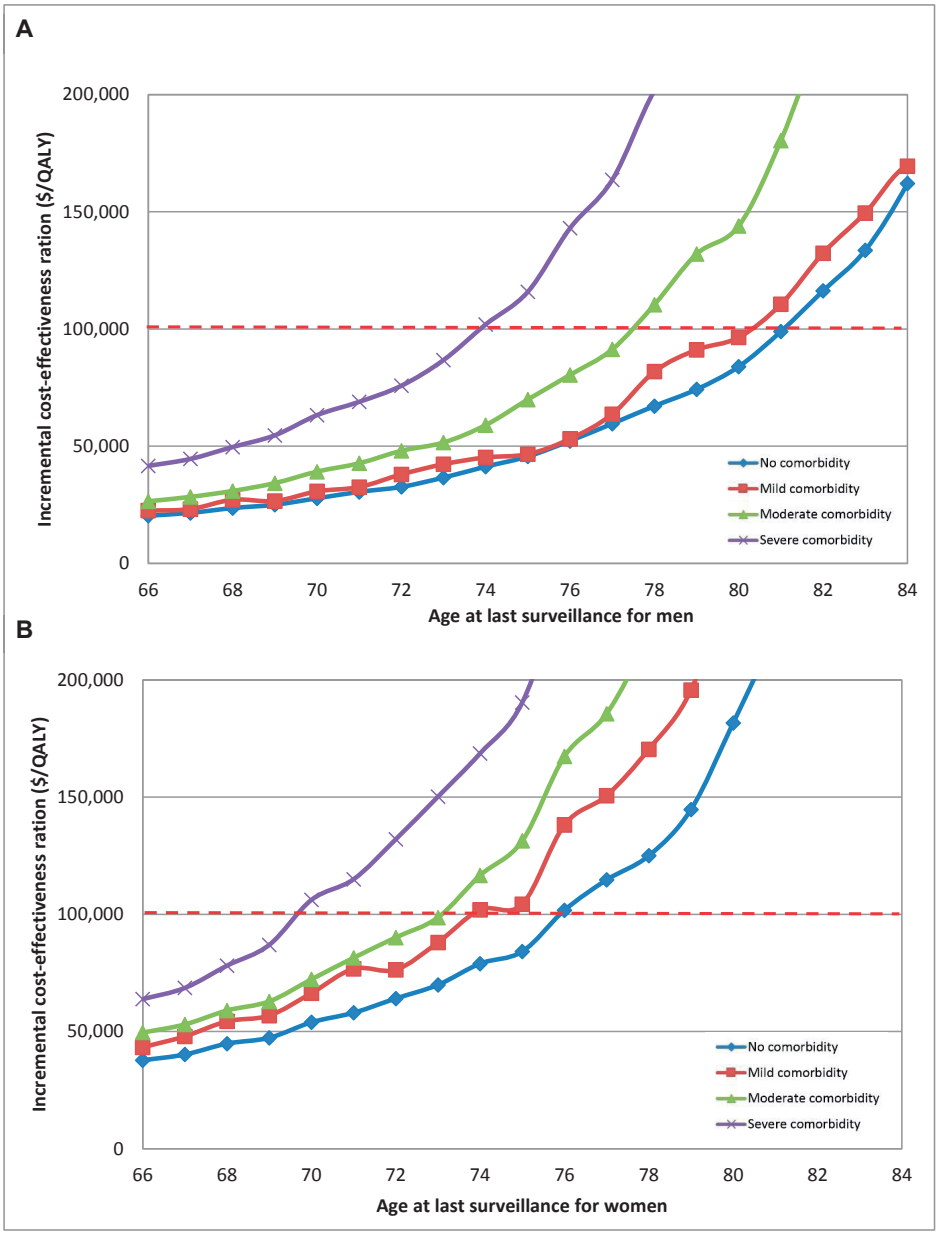

Figure 1. Incremental cost-effectiveness ratio of surveillance of non-dysplastic Barrett's esophagus *male* (*A*) and *female* (*B*) patients at different ages by level of comorbidity

Results for women

Similar to men, the net benefits of one additional surveillance of female NDBE patients decreased with increasing age and comorbidity. However, the ICERs of one more surveillance in women were generally higher than those for men of similar age and comorbidity status (***Supplementary Table 3***). For example, surveillance of female patients aged >75 years was not cost effective (ICERs>$101,800/QALY) for any level of comorbidity.

Consequently, the optimal ages of last surveillance were lower in women than in men. For female patients without comorbidity, 75 years was the optimal age of last surveillance with an ICER of $84,200/QALY. Surveillance of patients with higher comorbidity levels resulted in higher ICERs and lower optimal stopping ages. For females with mild and moderate comorbidity, the optimal age of last surveillance was the same: 73 years; however, the ICERs were different ($88,000 vs. $98,700 per QALY respectively). For female patients with severe comorbidity, the optimal stopping age was 69 years **(*Figure 1*B)**.

Sensitivity analysis

The separate results of each model consistently showed that women had lower optimal ages for last surveillance than men. All three models also showed lower optimal stopping ages for patients with higher comorbidity levels. However, the results from EACMo model suggested earlier optimal ages for last surveillance compared with other models, particularly for female NDBE patients (***Table 3***).

Our results were also robust to different diagnosis ages as well as variation in the assumed complication rates, EAC survival probabilities and utility values by comorbidity level. Only small changes in the optimal age of last surveillance of NDBE patients by these sensitivity analyses were observed (***Table 3, Figure 2***).

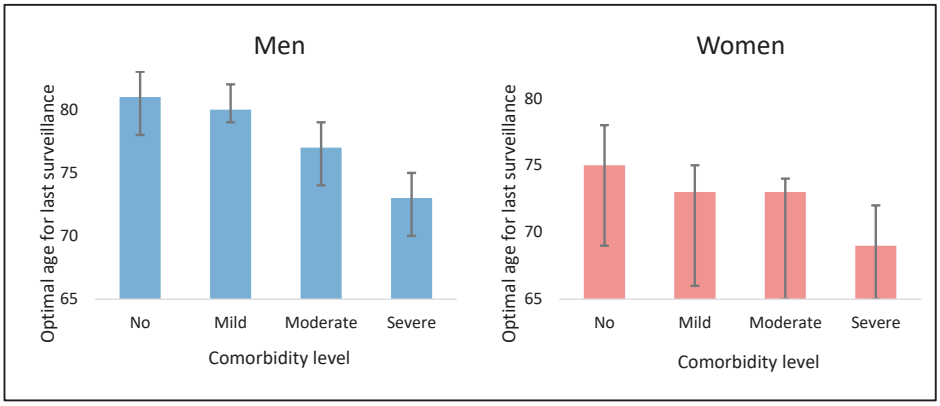

Figure 2. The optimal age of last surveillance for men (A) and women (B) with non-dysplastic Barrett's esophagus
*The error bars present the ranges of surveillance stopping ages resulting from sensitivity analyses.

Table 3. The optimal age of last surveillance by sensitivity analysis and comorbidity level

	Men				Women			
Comorbidity/ Analysis	**No**	**Mild**	**Moderate**	**Severe**	**No**	**Mild**	**Moderate**	**Severe**
Base Case	81	80	77	73	75	73	73	69
MISCAN-EAC model	83	82	79	75	77	74	74	71
EACMo model	78	77	74	70	69	66	≤65	≤65
MSCE-EAC model	81	80	77	75	78	75	74	72
NDBE diagnosis at age 50/51/52	81	80	77	74	76	74	73	70
NDBE diagnosis at age 70/71/72	80	79	77	75	75	75	74	≤70
Complication[1] rate	81	80	77	73	76	73	72	69
Utility values[1]	81	80	77	73	76	73	72	69
EAC survival[1]	80	79	77	74	75	73	73	69

[1] For patients without comorbidity, we considered 50% less complications and disutilities, and 10% less EAC mortality than base case. For patients with moderate comorbidity, we considered the same as what we assumed in the base case. For patients with moderate or severe comorbidity, we assumed 50% or 100% higher complication rate and disutilities, and 10% or 20% higher EAC mortality rate than base case, respectively.

DISCUSSION

Our comparative modeling analysis indicates that the optimal age for last surveillance of NDBE patients depends on the gender and the comorbidity level of patients. We found that for male NDBE patients without comorbidity, the optimal age for last surveillance is 81 years, while it may be up to 8 years earlier for those with comorbidity. For women, we found that without comorbidity, the optimal age for

last surveillance of NDBE patients is 75 years, but can be up to 6 years earlier if patients have comorbidities.

Generally, by increasing the age and level of comorbidity of patients, the life expectancy is decreased and consequently, the benefit of surveillance is decreased. Therefore, above a certain age surveillance of NDBE patients is no longer cost effective. Despite having a longer life expectancy, women have a lower optimal age for last surveillance due to a lower lifetime risk of EAC in females versus males. The separate results of each model showed the same patterns. However, the EACMo model suggests earlier ages to discontinue surveillance in men and women compared to other models. This discrepancy can be explained by different natural history assumptions between the models. EAC incidence varies by age across the models. At older ages, the cumulative incidence of EAC in the EACMo model is lower than the other two models. Therefore, NDBE patients in the EACMo model are more likely to die of other causes before progression to EAC occurs. This is the reason that surveillance of NDBE patients at later ages in the EACMo model was not cost-effective, unlike in the other two models.

None of the previous analyses examining the cost-effectiveness of surveillance of NDBE patients evaluated the optimal age to discontinue surveillance. [15, 25, 26] However, we can compare our findings to a previous study evaluating the age of colorectal, prostate and breast cancer screening cessation based on comorbidity level. This study found that people with higher comorbidity level gained less benefits from cancer screening and suggested to discontinue screening earlier.[8] A prior cost-effectiveness analysis also showed that the comorbidity status of individuals undergoing colorectal cancer screening had a large impact on the effectiveness of the screening program. Screening was therefore cost effective up to a lower age for people with comorbidities compared to those without.[27]

In our base case analysis, we simulated cohorts of NDBE patients diagnosed at age 60 years, as the mean age of BE patients at diagnosis has been reported to be greater than 60 years.[28-30] However, in sensitivity analyses, we assumed lower and higher ages of diagnosis and varied utility values, complication and EAC survival probabilities based on the comorbidity status of patients. Our results were quite robust for these external model parameters. However, they depended quite heavily on the model used, i.e. on structural model assumptions. The main differences between the models are the time it takes to progress from NDBE to EAC and when BE develops in a patient, i.e. how long a patient has lived with BE when she is diagnosed with it. As these pattern are still unknown, future linkage studies with long-term follow-

up might help to address these issues. Nevertheless, all three models in our study show that surveillance should not continue indefinitely, even in patients without any comorbidity.

Our study has some limitations. We are unaware of life tables for patients under age 66 years with different comorbidity levels and therefore we could not determine the optimal age of last surveillance if it was below 66 years (for the EACmo model, this was the case for women with moderate or severe comorbidity). However, this limitation did not affect our combined results. In addition, due to the limited data, we could not apply the impact of patient comorbidity level on the prognosis of cancer. Furthermore, the utility values used in our analysis are derived from limited available literature that may not accurately represent the value or quality of patients' lives.

Despite these limitations, our findings have considerable merits. The three independent models were developed under the auspices of the NCI CISNET modeling consortium over the past ten years with regular meetings lending support to the credibility and prior validation of the models and the comparative modeling process. The largest limitation in simulation modeling is the uncertainty in both model parameter estimates and structure. Our analysis utilized three models, which may provide some reassurance as opposed to the use of one model.

In addition, our results have important clinical implications for personalized management of NDBE patients, as none of the gastroenterology scientific societies recommend any stopping age for BE surveillance. For example, our results suggest that performing one more surveillance might not be appropriate from a cost-effectiveness perspective for a 76-year-old man with NDBE and a severe comorbidity such as congestive heart failure. However, a 76-year-old man without comorbidity may be considered for one more surveillance at that age. It is worth mentioning that in addition to monetary costs, surveillance itself can become harmful and preclude increases in QALYs. For example, surveillance of an 85-year-old woman with NDBE and a severe comorbidity can result in QALY loss. Empiric evidence has demonstrated that advancing age and more severe comorbidity have very little effect on the decision of whether to perform surveillance endoscopy in Medicare patients with Barrett's esophagus.[31]

Our study was conducted in the US setting, but our findings can be applied to other settings with similarly high incidences of BE and EAC such as countries in Northern

and Western Europe, and Oceania, and can inform international GI guidelines on the optimal age for last surveillance of NDBE patients.

In conclusion, our comparative modeling approach shows that in addition to chronological age, gender and the comorbidity status of NDBE patients are important factors to inform the decision when to discontinue surveillance. Our analysis finds that the optimal age for last surveillance of NDBE patients without comorbidity for women is 75 years and for men is 81 years. However, it may be up to 6 years earlier for women and up to 8 years earlier for men if patients have severe comorbidities.

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Chapter 6 Supplementary Materials

Supplementary Table 1. Post-treatment (EET or touch-up RFA) surveillance strategies

Patients characteristics and treatment outcome	Strategy
Recurrent NDBE patient (Initial LGD)	
After CE-IM (state=normal)	Surveillance at 6, 12, 24 and 36 months, then every 3 years
After non-CE-IM (state=ND)	
Recurrent NDBE patient (Initial HGD)	
After CE-IM (state=normal)	Surveillance at 3, 6, 9, 12, 18 and 24 months, then every 1 year
After non-CE-IM (state=ND)	
Initial or recurrent LGD patients	
After CE-IM (state=normal)	Surveillance at 12 and 24 months, then every 3 years
After CE-D, non-CE-IM (state=ND)	Surveillance at 6, 12, 24 and 36 months, then every 3 years
After non-CE-D, non-CE-IM (state=LGD)	Surveillance at 6 and 12 months, then every 1 year
Initial or recurrent HGD patients	
After CE-IM (state=normal),	Surveillance at 3, 6, 9, 12, 18 and 24 months, then every 1 year
After CE-D, non-CE-IM (state=ND),	
After non-CE-D, non-CE-IM (state=LGD/HGD)	Surveillance every 3 months

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EET: endoscopic eradication therapy, HGD: high-grade dysplasia, IM: intestinal metaplasia, LGD: low-grade dysplasia, ND: No dysplasia, RFA: radiofrequency ablation.

Supplementary Table 2. Model inputs

Parameter/Definition	Value	Source
Maximum number of touch-ups RFA	3	[1]
Duration of initial EET	2 years	[1]
Number of endoscopies during initial EET	4	[1]
Number of RFA sessions during initial EET	3.55	[1]
Proportion of patients receiving EMR treatments before RFA	0.55	[2]
Complication rates		
Perforation due to surveillance endoscopy	0.00025	[3-7]
Bleeding due to surveillance endoscopy	0.00026	[3-6]
Perforation due to EET (per procedure)	0.002#	[8]
Bleeding due to EET (per procedure)	0.004#	[8,9]
Stricture rate due to EET (per procedure)	0.019#	[8,9]
Perforation rate resulting from stricture treatment	0.0009	[10]
Bleeding rate resulting from stricture treatment	0.0009	[10]
Success probabilities of EET¥		
In HGD patients		
CE-IM and CE-D	88.9%	[11]
Non-CE-IM, CE-D	3.7%	[11]
Non-CE-IM and non-CE-D	7.4%	[11]
In LGD patients		
CE-IM and CE-D	98.1%	[11]
Non-CE-IM, CE-D	0	[11]
Non-CE-IM and non-CE-D	1.9%	[11]
Recurrence rates by baseline histologic grade and grade of recurrence		
Annual recurrence rates after CE-IM		
Pre-treatment misdiagnosed NDBE¥	7%	[12,13]
Pre-treatment IND/LGD	8.3%	[11]
Pre-treatment HGD	13.5%	[11]
Recurrent histology of misdiagnosed NDBE¥ after CE-IM		
NDBE	92%	[12,13]
IND/LGD	6%	[12,13]
HGD	2%	[12,13]
EAC	0%	[12,13]
Recurrent histology of IND/LGD after CE-IM		
NDBE	50%	[11]
IND/LGD	25%	[11]
HGD	25%	[11]
EAC	0	[11]
Recurrent histology of HGD after CE-IM		
NDBE	50%	[11-13]
IND/LGD	15%	[11]
HGD	25%	[11]

Supplementary Table 2. Model inputs (*continued*)

Parameter/Definition		Value	Source
EAC		10%	[11]
Costs			
Endoscopy		$745	[14]
Initial EET treatment (EMR & RFA)		$5,630	[14]
RFA Touch-Up		$1,012	[14]
	Stricture	$1,012	[14]
Complications	Bleeding	$11,815	[15]
	Perforation	$28,533	[16]
Localized EAC initial care		$58,997	[17]
Localized EAC Terminal care		$64,704	[17]
Regional EAC initial care		$75,295	[17]
Regional EAC terminal care		$77,742	[17]
Distant EAC initial care		$57,169	[17]
Distant EAC terminal care		$85,212	[17]
Unstaged[§] EAC initial care		$63,820	[17]
Unstaged[§] EAC terminal care		$75,886	[17]
EAC continuous care		$4,080	[17]
Utility			
Short term			
Endoscopy with or without EET (1 day)		0.70	[18]
After EET Treatment (1 week) *		0.70	[1]
After RFA Touch-Up (1 week)		0.70	[1]
Stricture (4 week)		0.70	[1, expert opinion]
Perforation (4 weeks)		0.70	[1, expert opinion]
Bleeding (1 week)		0.70	[1]
Long term (until death)			
Localized EAC initial care (yearly)		0.84	[19,20]
Localized EAC continuous and terminal care (yearly)		0.96	[19,20]
Regional EAC care (yearly)		0.65	[19,20]
Distant EAC care (yearly)		0.40	[19,20]
Unstaged[§] EAC care (yearly)		0.63	[19,20]

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, IM: intestinal metaplasia, IND: indefinite dysplasia, ND: non-dysplastic, LGD: low-grade dysplasia, RFA: radiofrequency ablation.

The complication rate per patient due to RFA, was adjusted to average RFA sessions to compute the complication rate per procedure.[9]

[¥] Recurrent NDBE patients or NDBE patients who are misdiagnosed as LGD/HGD receive EET as well. For NDBE, we assumed the same EET success probability rate that we assumed for LGD patients, but we assumed a different recurrence rate after CE-IM as described in the table.

[§] Unknown

* Patients were assumed to receive an average of 3.55 RFA sessions and 0.55 EMR treatments in the first 2 years after initial EET, therefore (3.55+0.55=) 4.1 weeks with utility of 0.7.

Supplementary Table 3. Life-time net benefits and costs of one additional endoscopic surveillance at ages 68, 74, 80 and 86 versus not performing surveillance at that age per 1000 NDBE female patients diagnosed at age 60

Age	Comorbidity level[1]	EAC prevented	EAC death prevented	QALYs gained	Net Endoscopies	Net EET and touch-ups	Net cost ($)	ICER
68	No	5	7	34	1,956	75	1,510,218	44,873
	Mild	5	6	28	1,885	73	1,502,862	54,376
	Moderate	4	6	25	1,861	72	1,498,669	59,010
	Severe	3	4	19	1,753	68	1,468,876	78,148
74	No	3	5	18	1,699	66	1,387,573	79,020
	Mild	3	4	13	1,631	64	1,371,970	102,016
	Moderate	2	3	12	1,603	63	1,365,868	116,662
	Severe	2	3	8	1,500	60	1,325,333	168,689
80	No	2	3	7	1,447	58	1,265,942	181,671
	Mild	1	2	5	1,399	56	1,248,497	248,183
	Moderate	1	2	4	1,356	55	1,235,250	336,392
	Severe	1	1	2	1,265	53	1,196,610	737,790
86	No	1	1	1	1,202	52	1,131,114	778,692
	Mild	1	1	1	1,180	52	1,123,488	1,171,891
	Moderate	0	1	0	1,134	51	1,102,231	5,010,660
	Severe	0	1	-1	1,049	49	1,054,641	Dominated

EAC: esophageal adenocarcinoma; EET: endoscopic eradication therapy; ICER: incremental cost-effectiveness ratio

[1] Overview of comorbidity levels and associated conditions can be found in Table 1 of the main text.

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7

The impact of the policy-practice gap on costs and benefits of Barrett's esophagus management

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ABSTRACT

Introduction

Clinical guidelines recommend surveillance of Barrett's esophagus (BE) patients. However, the surveillance intervals in practice are shorter than policy recommendations. We aimed to determine how this policy-practice gap affects the costs and benefits of BE surveillance.

Methods

We used The Netherlands as an exemplary Western country and simulated a cohort of 60-year-old BE patients using the MISCAN-EAC microsimulation model. We evaluated surveillance according to the Dutch guideline, as well as more intensive surveillance of non-dysplastic BE (NDBE) and low-grade dysplasia (LGD) patients. For each strategy, we computed the quality-adjusted life years (QALYs) gained and costs compared with no surveillance. We also performed a budget impact analysis to estimate the increased costs of BE management in The Netherlands for 2017.

Results

Compared with no surveillance, the Dutch guideline incurred an additional €4.7 ($5.3) million per 1,000 BE patients for surveillance and treatment, while 59 esophageal adenocarcinoma (EAC) cases (>T1a) were prevented. With intensive and very intensive surveillance strategies for both NDBE and LGD, the net costs increased by another €2.3-6.0 ($2.6-6.8) million, while preventing 10-17 more EAC cases and gaining 29-48 more QALYs. On a population level, this amounted to €19-50 ($22-57) million (+29-77%) higher healthcare costs in 2017.

Conclusions

The policy-practice gap in BE surveillance intervals results in 49-128% higher net costs for BE management for only 9-14% increase in QALYs gained, depending on actual intensity of surveillance. Incentives to eliminate this policy-practice gap should be developed to reduce the burden of BE management on patients and healthcare resources.

INTRODUCTION

Barrett's esophagus (BE) is a prevalent condition, with gastro-esophageal reflux disease (GERD) as its most prominent risk factor.[1] It is a precursor lesion of esophageal adenocarcinoma (EAC). The global disease burden because of EAC is growing. In the last three decades, the overall incidence of EAC has increased by six-fold in the western world.[2] The path towards the malignant stage is supposed to proceed by low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Survival rates in patients with symptom-detected EAC are low, which is mainly attributable to the presence of regional or distant metastases at the time of diagnosis.[3] In order to detect neoplastic progression in an earlier stage, surveillance by upper endoscopy with random biopsies is carried out in patients with BE.[4, 5] In case of neoplastic progression towards HGD or early EAC, endoscopic eradication therapy (EET), such as endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA), is available as a minimally invasive treatment strategy.

Due to timely detection of neoplastic progression by surveillance and effective treatment of BE, the burden of EAC on the healthcare system may be reduced. Although BE surveillance also implies an exponential increase of endoscopies, cost-effectiveness analyses have indicated that a strategy of surveillance and EET is beneficial.[6] Recommendations concerning surveillance of BE and EET have been formulated in national and international guidelines.[4, 5, 7]

However, there is a discrepancy between follow-up according to the guidelines and daily practice. Clinicians do not completely adhere to the guidelines. Surveillance intervals are shorter than recommended,[8] and biopsies are not taken according to the Seattle protocol.[9] It is unclear what the influence of this discrepancy between policy and practice is on the burden of BE management.

Therefore, the aim of this study was to determine how current practice in surveillance of patients with BE affects the costs and benefits of the BE management program, compared to practice as recommended by guidelines for BE. We used The Netherlands as an exemplary Western country to evaluate the impact of this policy-practice gap.

METHODS

We used the Microsimulation Screening Analysis model of EAC (MISCAN-EAC) from Erasmus MC University Medical Center (Rotterdam, The Netherlands) to simulate a cohort of patients with BE in The Netherlands. Separate model runs were used to determine the costs and benefits of full adherence with the current Dutch guideline, and of non-adherent scenarios with more intensive surveillance as reported in the literature.[10, 11]

Dutch MISCAN-EAC model

The Dutch MISCAN-EAC model simulates the life histories of a population of individuals from birth to death. In this population, EAC develops through BE and the risk of developing BE and EAC in people with GERD symptoms is higher than in those without GERD symptoms.[12] In the model, BE starts in a state with no dysplasia (ND), but may progress to LGD and HGD. However, patients may also regress from LGD to ND and from HGD to LGD (**Model Appendix**). From HGD, malignant cells can arise and transform to a state of T1a EAC. Subsequently, more advanced stages of EAC can develop. The sequence of BE to EAC can be interrupted by surveillance, which can detect BE with or without dysplasia. Patients with NDBE or LGD enter a surveillance program and patients with persistent LGD, HGD, and early-detected EAC receive treatment, which can change their life histories (e.g. an HGD patient who received EET might not develop EAC anymore). The harms and benefits of surveillance and treatment were incorporated in the model. Comparing all life histories with surveillance and treatment with those without any intervention defines the benefits, harms, and costs of the surveillance and treatment intervention.

The model was calibrated to observed incidence rates of EAC in The Netherlands from 2012-2017.[13] We also used data of an observational multicenter prospective cohort study (ProBar) with currently a median follow-up of 8 years[14] to calibrate the BE progression rates in our model. Additional details on the model structure, assumptions, and calibration are provided in **Model Appendix**.

Population and BE management strategies

We simulated a Dutch cohort of 60-year-old patients with BE, as other studies have shown that the mean/median age of BE patients at diagnosis is higher than 60 years.[15-17] We followed these patients until death and compared four different management strategies (***Figure 1***): (1) no surveillance, (2) the Dutch guideline strategy, and strategies where we assumed (3) intensive or (4) very intensive surveillance, in

accordance with intervals observed in practice.[10, 11, 18] Strategies differed with respect to the intensity of surveillance for NDBE and LGD patients.

In all strategies, patients with HGD/EAC T1a were treated with EET. In the strategies with surveillance, patients with persisting long-segment LGD in the last three endoscopic surveillance exams, also received EET. Except for strategy 1 without surveillance, surveillance after EET was modeled according to the US guidelines and expert opinion (***Supplementary Table 1***).[5, 19] Any recurrences after EET were followed by touch-up RFA and more intensive surveillance. A maximum number of three touch-up RFAs was assumed for each patient. Patients with persistent or recurrent NDBE or LGD after the maximum number of touch-ups underwent surveillance, and those with persistent or recurrent HGD/EAC T1a underwent esophagectomy.

Strategy	Surveillance interval		
	non-dysplastic short segment BE	non-dysplastic long segment BE	low-grade dysplasia BE[1]
1. No surveillance	not applicable	not applicable	not applicable
2. Dutch guideline	5 years	3 years	6 months & 1 year
3. Intensive NDBE & LGD	3.5 years	2 years	3 months & 6 months
3a. Intensive NDBE	3.5 years	2 years	6 months & 1 year
3b. Intensive LGD	5 years	3 years	3 months & 6 months
4. Very intensive NDBE & LGD	2 years	1 years	3 months & 6 months
4a. Very intensive NDBE	2 years	1 years	6 months & 1 year

Recommendation by Dutch guideline
Intensive surveillance intervals
Very intensive surveillance intervals

Figure 1. Simulated Barrett's esophagus management strategies
BE: Barrett's esophagus; LGD: low-grade dysplasia; NDBE: non-dysplastic BE
1 The first interval in this column indicates the first interval for surveillance after diagnosis, and the second interval indicates the interval for following surveillance endoscopies thereafter.

Surveillance and treatment assumptions

In the main analysis, we assumed that all patients attended all surveillance endoscopies and treatment sessions. We assumed that surveillance stopped at the age of 80 years. To consider the high interobserver variability in histological diagnosis of BE patients, we used the results of the ProBar study.[14, 20] In the ProBar study, after the first histological diagnosis of BE, a second BE expert pathologist assessed the histological diagnosis. In case of disagreement, another BE expert pathologist evaluated the result to reach consensus. We compared the results of the first and last assessment of the patients in the ProBar study to estimate the validity of the endoscopic surveillance test to grade dysplasia or detect EAC. ***Table 1*** provides the assumed distribution of diagnosed states for patients with a particular true state in the model. We assumed that initial EET took two years and that patients during this two-year period of EET, received an average of 3.55 RFA sessions and four endosco-

pies (***Table 2***).[21] The proportion of patients receiving EMR treatments before RFA was assumed to be 55%.[22] The EET success and recurrence rates were assumed based on the initial state of the patients (NDBE, LGD, HGD/EAC T1a).[23]

Table 1. The validity of endoscopic surveillance test to grade dysplasia and detect EAC

		True state			
		NDBE	LGD	HGD/EAC T1a	EAC
Diagnosed state*	NDBE	94.7%	34.0%	2.7%	0.0%
	LGD	5.3%	63.2%	15.8%	2.5%
	HGD/EAC T1a	0.0%	2.9%	72.9%	20.5%
	EAC	0.0%	0.0%	8.6%	77.0%

EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, LY: life years, NDBE: non-dysplastic Barrett's esophagus

* 94.7% of NDBE patients, 63.2% of LGD patients, 72.9% of HGD/EAC T1a patients and 77.0% of EAC patients are assumed to be correctly diagnosed by endoscopic surveillance.

Costs and utilities

Based on a retrospective chart review at Erasmus MC University Medical Center, we estimated the average utilization of a BE or EAC patient of specific healthcare products, as defined within the Diagnosis and Treatment Combinations (DTC) system in The Netherlands. This was multiplied by the average price of all hospitals in The Netherlands for these services based on the reimbursement (***Table 2***).[37] A more detailed description of the derivation of cost estimates can be found in ***Supplementary 1***.

Disutilities of initial, continuous, and terminal care of EAC patients as well as endoscopy, EET, esophagectomy, and the complications due to surveillance or treatment were estimated from the literature or based on expert opinion (***Table 2***).

Outcomes

The health outcomes estimated for each strategy included: number of EAC cases (>T1a), mortality due to EAC, treatment complications (*i.e.* perforation, stricture, and bleeding), life years gained, and quality-adjusted life years (QALYs) gained. For each strategy, we also estimated the total costs, including the costs of endoscopy, EET treatment, EET touch-ups, esophagectomy, complications, and cancer care.

Analyses

We compared the results of the more intensive strategies with the Dutch guideline strategy. We calculated incremental costs and benefits, to assess the efficiency of the more intensive surveillance strategies. We also computed the incremental costs per

Table 2. Model inputs and sources

Parameter/Definition	Value	Source
EET and touch-ups assumptions		
Maximum number of EET touch-ups	3	[21]
Duration of initial EET (years)	2	[21]
Number of endoscopies during initial EET	4	[21]
Number of treatments during initial EET	3.55	[21]
Proportion of patients receiving EMR treatments before RFA	0.55	[22]
Complication rates		
Perforation due to surveillance endoscopy	0.00024	[24-27]
Bleeding due to surveillance endoscopy	0.00026	[24-26, 28]
Perforation due to EET (per procedure)	0.002	[29]
Bleeding due to EET (per procedure)	0.004	[23, 29]
Stricture rate due to EET (per procedure)	0.019	[23, 29]
Perforation rate resulting from stricture	0.0009	[30]
Bleeding rate resulting from stricture	0.0009	[30]
Success probabilities of treatment		
Success of therapy in pre-treatment HGD /EAC T1a patients		
CE-IM and CE-D	68%	[23]
Non-CE-IM, CE-D	17%	[23]
Non-CE-IM and Non-CE-D	15%	[23]
Success of therapy in pre-treatment LGD patients		
CE-IM and CE-D	72%	[23]
Non-CE-IM, CE-D	19%	[23]
Non-CE-IM and Non-CE-D	8%	[23]
Success of therapy in pre-treatment NDBE patients		
CE-IM	81%	[23]
Non-CE-IM	19%	[23]
Recurrence rates by baseline histologic grade and grade of recurrence		
Annual recurrence rates after CE-IM		
Pre-treatment NDBE	7%	[31-33]
Pre-treatment LGD	8%	[31-33]
Pre-treatment HGD	14%	[31-33]
Recurrence histology distribution pre-treatment NDBE		
NDBE	92%	[31-33]
LGD	6%	[31-33]
HGD/EAC T1a	2%	[31-33]
EAC	0%	[31-33]
Recurrence histology distribution pre-treatment LGD		
NDBE	82%	[31-33]
LGD	14%	[31-33]
HGD/EAC T1a	2%	[31-33]
EAC	2%	[31-33]

Table 2. Model inputs and sources (*continued*)

Parameter/Definition		Value	Source
Recurrence histology distribution pre-treatment HGD			
NDBE		69%	[31-33]
IND/LGD		15%	[31-33]
HGD/ EAC T1a		10%	[31-33]
EAC		6%	[31-33]
Dutch costs			
Endoscopy		€ 807 ($922)	Supplementary 1
Initial EET treatment (EMR & RFA)		€ 11,662 ($13,326)	Supplementary 1
RFA Touch-Up		€ 2462 ($2,813)	Supplementary 1
EET complication	Stricture	€ 5,863 ($6,699)	Supplementary 1
	Bleeding	€ 2,345 ($2,680)	Supplementary 1
	Perforation	€ 2,345 ($2,680)	Supplementary 1
Esophagectomy		€ 29,280 ($33,457)	Supplementary 1
Annual outpatient visit after esophagectomy		€ 190 ($217)	Supplementary 1
EAC stage 1 care		€ 31,602 ($36,110)	Supplementary 1
EAC stage 2 care		€ 42,806 ($48,913)	Supplementary 1
EAC stage 3 care		€ 43,127 ($49,280)	Supplementary 1
EAC stage 4 care		€ 9,332 ($10,663)	Supplementary 1
Utilities			
Short terms			
Endoscopy with or without EET (1 day)		0.70	[34]
After EET Treatment (1 week)*		0.70	[21]
After RFA Touch-Up (1 week)		0.70	[21]
Stricture (1 week)		0.70	[21]
Perforation (1 week)		0.70	Expert opinion
Bleeding (1 week)		0.70	[21]
After esophagectomy (4 weeks)		0.86	[14]
Long terms (until death)			
Esophagectomy (yearly)		0.90	[14]
EAC stage 1 care (initial year)		0.84	[35, 36]
EAC stage 1 care (yearly after the first year)		0.96	[35, 36]
EAC stage 2 and 3 care (yearly)		0.65	[35, 36]
EAC stage 4 care (yearly)		0.40	[35, 36]

BE: Barrett's esophagus, CE: complete eradication, D: dysplasia, EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, HGD: high-grade dysplasia, IM: intestinal metaplasia, IND: indefinite dysplasia, NDBE: non-dysplastic Barrett's esophagus, LGD: low-grade dysplasia, RFA: radiofrequency ablation.

* During initial EET, patients were assumed to receive on average 3.55 RFA sessions and 0.55 EMR treatments, therefore 28.7 days utility of 0.7 was assumed per initial two-year EET.

QALY gained for the more intensive strategies compared with the Dutch guideline strategy. We used the common Dutch willingness-to-pay (WTP) threshold of €20,000 ($22,853) per QALY gained to determine if these more intensive strategies are cost-effective.[38] Both costs and QALYs were discounted by 3% annually, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine.[39]

Budget impact analysis

We performed a budget impact analysis to estimate the costs for management of BE patients in The Netherlands for 2017. We replicated the Dutch BE population aged 20-80 in 2017. We estimated total annual costs, the numbers of endoscopies, endoscopic therapies, and esophagectomies for the Dutch guideline strategy, and the intensive and very intensive surveillance strategies (strategies 2, 3 and 4).

Sensitivity analyses

We performed the following one-way sensitivity analyses to test the robustness of our results.

- We simulated cohorts of 50-year-old, 55-year-old and 70-year-old BE patients;
- We assumed 20% lower and higher progression rate of BE to EAC;
- We assumed lower patients participation rates for surveillance (80%) and EET (95%);
- We applied discounting rates of 1.5% for effects and 4% for costs to all the strategies, according to the Dutch guideline for economic evaluations in healthcare; [40]
- We used the costs in the US setting for surveillance, EET, treatment of complications, and cancer care (***Supplementary Table 2***).

RESULTS

Main analysis

Without surveillance (strategy 1), 121 EAC cases (>T1a) were diagnosed per 1,000 60-year-old BE patients during lifetime follow-up. The Dutch surveillance guideline (strategy 2) prevented 59 of these EAC cases and gained 345 additional QALYs, while the costs increased by €4.7 ($5.3) million (***Figure 2, Supplementary Table 3***).

Intensive and very intensive surveillance practice in The Netherlands for NDBE and LGD patients (strategy 3 and 4), resulted in 49-128% higher net costs (+€2.3-6.0 million, $2.6-6.8) compared to the Dutch guideline, while 10-17 more EAC cases (+17-29%) were prevented and 29-48 more QALYs (+9-14%) were gained, respectively. In other words, intensive and very intensive surveillance of both NDBE and LGD

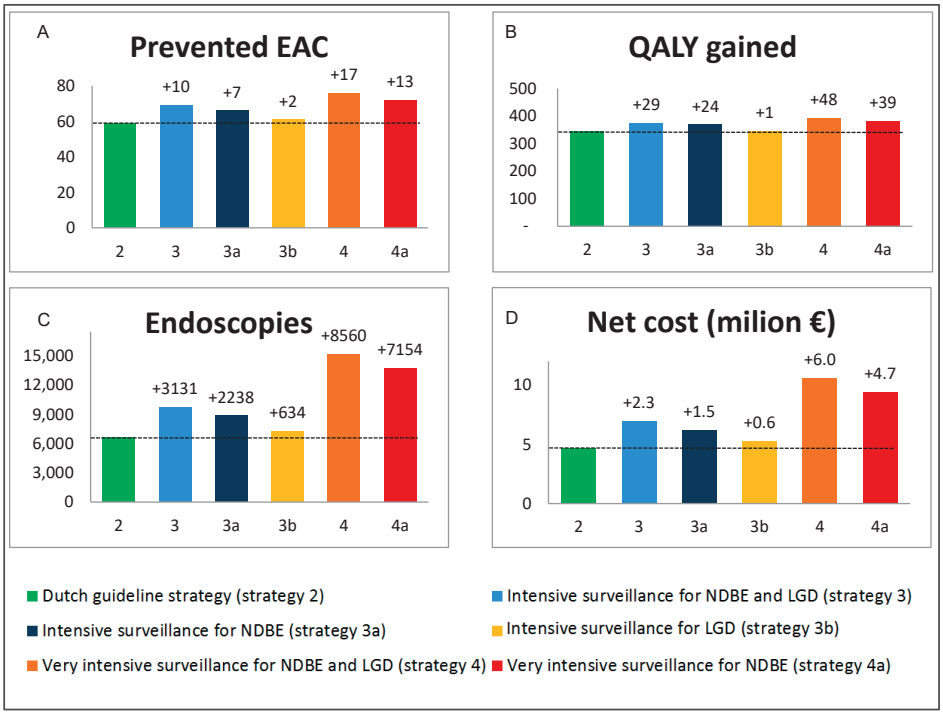

Figure 2. Impact of more intensive surveillance of Barrett's esophagus on (A) prevented EAC cases, (B) QALYs gained, (C) number of endoscopies, and (D) net costs per 1,000 BE patients
EAC: esophageal adenocarcinoma; NDBE: non-dysplastic Barrett's esophagus; LGD: low-grade dysplasia; QALY: quality-adjusted life year

patients led to an incremental cost of more than €78,100 ($89,300) per QALY gained which was more than the commonly accepted Dutch WTP threshold of €20,000 ($22,853) per QALY gained.[38] The incremental cost per QALY gained was worst (€418,830, $478,581) for intensifying surveillance in LGD patients (strategy 3a).

Budget impact analysis

On a national level, management of BE patients with full adherence to the Dutch guideline, required an estimated 51,430 endoscopies, 1,193 initial EETs, 1,081 EET touch-ups, and 140 esophagectomies in 2017. The costs of the program were estimated to be €64.3 ($73.5) million. Intensive surveillance of both NDBE and LGD patients (strategy 3) resulted in an estimated 20,643 more endoscopies, 337 more initial EETs, 299 more EET touch-ups, and 5 more esophagectomies in 2017 (***Table 3***). Very intensive surveillance strategy for NDBE and LGD (strategy 4) was estimated to require even more endoscopies and treatments. The non-adherence to the Dutch guideline increased the costs of BE management in The Netherlands by €19-50 ($22-57) million (+29-77%) in 2017.

Table 3. The impact of the policy-practice gap in management of Barrett's esophagus in The Netherlands in 2017

Strategy	Dutch guideline	Intensive for NDBE and LGD		Very intensive for NDBE and LGD	
Endoscopies	51,430	72,072	+20,643 (40%)	108,135	+56,706 (110%)
Initial EET	1,193	1,530	+337 (28%)	1,776	+583 (49%)
EET touch-ups	1,081	1,380	+299 (28%)	1,604	+523 (48%)
Esophagectomies	140	145	+5 (3%)	150	+10 (7%)
Costs (million €)	64.3	83.3	+19.0 (29%)	114.1	+ 49.7 (77%)
(million $)	73.5	95.2	+21.7	130.4	+56.9

EET: endoscopic eradication therapy, NDBE: non-dysplastic Barrett's esophagus, LGD: low-grade dysplasia, RFA: radiofrequency ablation

Sensitivity analyses

Our results were robust for assumptions regarding the age of the simulated BE cohort, progression rate to BE, and lower participation rates of patients for surveillance or EET with similar increases in costs and QALYs as in main analysis, and incremental costs per QALY gained were around or above €35,000 for all strategies (***Table 4*** and ***Supplementary Table 4***). Assuming US costs resulted in an incremental costs per QALY gained below $90,000 for most scenarios which is considered cost-effective in a US setting (***Supplementary Table 5***).

DISCUSSION

Our findings indicate that more intensive surveillance for BE patients leads to 49-128% higher costs for an almost 9-14% increase in QALYs gained compared to the Dutch guideline, depending on actual intensity of surveillance. Shorter surveillance intervals than recommended can increase the likelihood of preventing EAC diagnosis or EAC death, therefore more QALYs might be gained. However, with a slight increase in QALYs gained versus the considerable increase in costs, we found that more intensive surveillance of BE patients than recommended is unlikely to be cost effective using the WTP threshold of €20,000 ($22,853) per QALY gained in The Netherlands. The policy-practice gap in surveillance of BE patients increased the annual costs of the surveillance program by €19-50 ($22-57) million at a national level in The Netherlands in 2017, as more endoscopic and treatment procedures were required.

Table 4. Results of the main analysis and sensitivity analyses of more intensive strategies versus Dutch guideline per 1,000 Barrett's esophagus patients

Strategy	Intensive for NDBE and LGD (Strategy 3)[1]			Intensive for NDBE (Strategy 3a)[1]			Intensive for LGD (Strategy 3b)[1]			Very intensive for NDBE and LGD (Strategy 4)[1]			Very intensive for NDBE (Strategy 4a)[1]		
Analysis	QALY gained[2]	Net costs[2] (€ m)	Incremental costs (€) per QALY[2]	QALY gained[2]	Net costs[2] (€ m)	Incremental cost (€) per QALY[2]	QALY gained[2]	Net costs[2] (€ m)	Incremental cost (€) per QALY[2]	QALY gained[2]	Net costs[2] (€ m)	Incremental cost (€) per QALY[2]	QALY gained[2]	Net costs[2] (€ m)	Incremental cost (€) per QALY[2]
Main analysis	29.4	2.3	78,113	24.4	1.5	60,994	1.4	0.6	418,830	48.1	6.0	124,080	38.9	4.7	121,862
Cohort of 50-year-old	49.1	2.9	59,413	40.0	1.9	48,643	3.5	0.7	205,760	80.0	7.6	94,998	64.4	6.1	95,328
Cohort of 55-year-old	39.4	2.7	67,500	32.5	1.7	53,860	2.8	0.7	236,099	64.1	6.9	107,146	52.2	5.5	105,177
Cohort of 70-year-old	13.8	1.4	100,605	12.1	0.9	71,548	0.0	0.4	23,736,152	23.6	3.7	154,911	20.0	2.8	141,311
Higher progression rate	46.0	2.2	47,360	39.6	1.4	35,121	5.3	0.5	87,317	73.5	5.8	79,156	61.7	4.6	74,532
Lower progression rate	21.4	2.3	107,433	17.7	1.5	84,104	1.1	0.6	566,097	34.1	6.0	175,634	27.2	4.8	175,182
Lower participation rate	23.8	2.0	83,174	20.7	1.3	62,007	0.1	0.5	4,648,332	43.8	4.6	103,983	37.1	3.6	96,158
Different discount rates[3]	40.4	2.1	51,772	33.0	1.4	41,048	2.5	0.5	217,508	66.4	5.5	82,434	53.1	4.3	81,863
US cost setting[4]	29.5	1.3	43,275	24.5	0.9	34,937	1.4	0.3	218,054	48.1	4.0	83,621	38.9	3.4	86,191

BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, LGD: low-grade dysplasia, LY: life years, m:million, NDBE: non-dysplastic Barrett's esophagus, QALY: quality-adjusted life year

1. Difference of the results of these strategies and Dutch guideline strategy are presented.
2. Costs and QALYs were discounted at an annual rate of 3%, unless specified otherwise.
3. Costs discounted by 4% annually and QALYs by 1.5% annually.
4. US costs are presented in $US. Other costs presented in € in this table are presented in $US in ***Supplementary Tables 3 and 4*** as well.

Interestingly, we found that the impact of more intensive surveillance for both NDBE and LGD patients is larger than the combined impact of intensified surveillance for each of these patient groups separately. In our model, NDBE patients can progress to LGD, and LGD patients can regress to NDBE. Therefore, in a more intensive strategy for both NDBE and LGD, BE patients would have more intensified surveillance in case of progression or regression, while in a more intensive strategy for either NDBE or LGD, in case of progression or regression, these patients would not have intensified surveillance. Furthermore, in an intensified surveillance strategy for both NDBE and LGD patients, NDBE patients undergo surveillance more frequently and we detect more LGD patients who would also undergo surveillance more frequently. Consequently, the number of endoscopies, costs and benefits increase more when there is concurrent intensified surveillance for both NDBE and LGD patients compared to the combined impact of separate intensified surveillance.

Results were quite sensitive to the Dutch cost setting. Using US costs, cost-effectiveness ratios were slightly more favorable because of the higher savings from prevented EAC treatment in that setting. Estimated costs per QALY gained of very intensive surveillance ($83,621) would still not be considered cost-effective using Dutch WTP thresholds, but would be when assuming the commonly used US-based WTP threshold of $100,000 per QALY gained. Furthermore, it is worth mentioning that we have performed a conservative analysis. If we had considered indirect costs, such as patient-time and transportation costs, the increase in costs would have been even larger. In addition, the policy-practice gap in BE management is probably larger, due to low adherence of clinicians to the biopsy protocol, which can result in a lower detection rate of dysplasia.[41] Therefore, the beneficial effect of intensified surveillance may be even lower than what we have estimated.

This is the first study that used budget impact analysis to evaluate the impact of the policy-practice gap in management of BE patients in The Netherlands. In addition, We used a precise method to calculate all BE management program related costs in The Netherlands by estimating the average utilization of a BE or EAC patient of specific healthcare products and the average price of these products in all hospitals in The Netherlands (**Supplementary 1**). Other strong points of our study are that our model fits the Dutch EAC incidence data and we have used the outcomes of an observational multicenter prospective cohort (ProBar) study in The Netherlands to calibrate our model.[14] The baseline characteristics and the incidence rate of HGD/EAC of ProBar study have been shown to be comparable to other international cohorts.[42, 43] Therefore, the findings of this study are generalizable to other Western populations.

Our study also has some limitations. First, for the effectiveness of EET, only short-term outcomes were available from the literature.[23] We therefore extrapolated those outcomes to estimate the long-term effectiveness of EET. Second, the exact progression rate from BE to EAC is unknown. However, we optimized the progression parameters using ProBar data, and we conducted sensitivity analyses with higher and lower progression rates to evaluate the robustness of our findings. Finally, the Dutch guidelines do not provide any recommendations for surveillance after EET. Therefore, we used other guidelines and expert opinion to define the post-treatment strategies.

In spite of these limitations, our results provide strong evidence for clinicians that non-adherence to the guidelines substantially increases the costs of BE management while the benefits are small. The Results seem to suggest that at least some of the more intensive strategies are cost-effective compared to current guidelines in countries like US with higher common accepted WTP threshold than the Netherlands. However, the number of BE patients that will actually benefit from this intensification is very small and harms of intensified surveillance may outweigh its health benefits. We recommend rather than more intensive surveillance for all BE patients to target those at highest risk.

Current guidelines mainly distinguish risk of patients by dysplasia status, but our model results in **Model Appendix** suggest substantial differences in EAC risk by gender and BE length. Using gender, BE length and potentially biomarkers such as P53 to identify those BE patients at the highest risk for developing EAC and target those for more intensive surveillance, could very well be a cost-effective strategy. Such a stratification could also reassure clinicians that they can safely extend the interval in other low-risk patients. In such a setting, risk-stratified management of BE patients based on the risk of progression of BE towards HGD/EAC would reduce the burden of unnecessary surveillance endoscopies and treatments and decreases healthcare cost at a national level, while at the same time maintaining benefits.

In conclusion, our findings indicate that the policy-practice gap in BE surveillance intervals results in more than 100% higher costs for only up to 14% more QALYs gained. It is important to develop incentives to eliminate this policy-practice gap so that the burden of BE management on patients and healthcare resources can be reduced.

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Chapter 7 supplementary materials

SUPPLEMENTARY 1: COST FOR DUTCH MISCAN-EAC MODEL

In this study we calculated the costs of surveillance and treatment of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) by using Diagnosis Treatment Combinations (DTC), healthcare products, and single procedures (***Figure 1***).

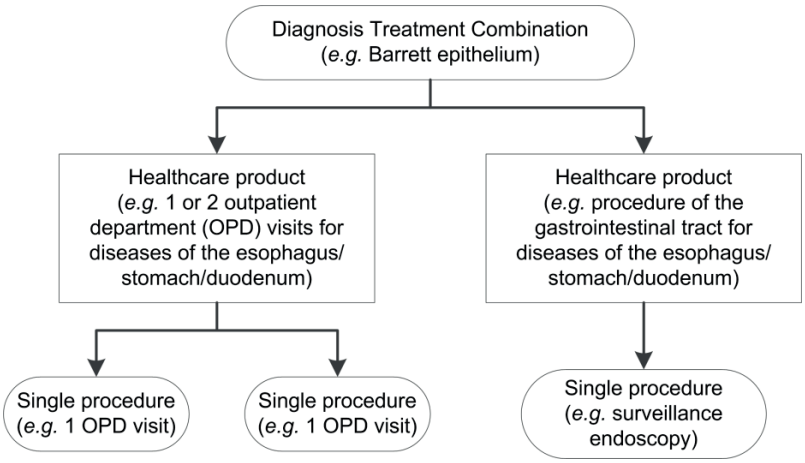

Figure 1. Diagnosis Treatment Combinations, healthcare products, and single procedures

In the Netherlands, patients are assigned a *DTC* by the clinician at presentation to be able to declare healthcare costs at the insurance company. In such a DTC all costs are covered that are related to a patient's diagnosis [1]. A nationwide definition is available for each individual DTC of what exact healthcare costs are included. Although patients with the same DTC have the same diagnosis, the total costs can differ for each individual, since the use of diagnostics and treatment is not always exactly the same.

Therefore, *healthcare products* as consumed per patient are assigned to and declared within a DTC. The costs of these products in the care of patients with BE and EAC may differ between hospitals. The mean declared costs of these products of all hospitals in The Netherlands to insurance companies are made freely available by the Dutch healthcare authority [2].

Healthcare products consist of a predefined number of *single procedures*. For example, if a patient with BE has been assigned the DTC 'Barrett epithelium', this patient could have the corresponding healthcare products '1 or 2 outpatient department (OPD) visits for disease of the esophagus/stomach/duodenum' and 'procedure of the gastrointestinal tract for diseases of the esophagus/stomach/duodenum' to declare for his surveillance endoscopy. These may include the single procedures of either one or two OPD visits and one upper endoscopy with biopsies. Consequently, the same costs are declared for the patient with one as the patient with two OPD visits. Therefore, the number of healthcare products used will define the costs, not the number of single procedures.

Every department has its own DTCs. Consequently, if a patient is treated for EAC and multiple departments are involved (*e.g.* DTC 'esophagus | cardia malignancy' in the department of gastroenterology and DTC 'malignancy esophagus/cardia' for the department of oncology), this patient will be assigned more than 1 DTC for the same condition. The available healthcare products in the system that can be assigned to these DTCs are the same for every department.

Costs per BE and EAC patient

Based on the structure concerning the states as used in our simulation model, 7 treatment groups of BE and EAC patients were defined to calculate the costs per individual (***Table 1***): (1) a BE patient having surveillance, (2) a BE patient having endoscopic treatment with a DTC for BE, (3) a BE patient having endoscopic treatment with a DTC for EAC, (4) an EAC patient treated according to the CROSS regimen, (5) an EAC patient treated with definitive chemoradiation therapy, (6) an EAC patient treated with induction chemotherapy and if indicated esophagectomy afterwards, and (7) an EAC patient who was treated with palliative therapy. Groups 1 up to 3 were considered to contain patients in the premalignant stage, groups 4 up to 7 in the malignant stage.

To calculate the costs per treatment group, first the number of healthcare products per patient per treatment group should be collected, and secondly the costs per healthcare product.

The mean number of healthcare products as consumed per representative patient for each group was calculated, based on data from our own institution. Data concerning these patients were retracted from our electronic patient files by using BusinessObjects (SAP AG, Germany). The following consecutive steps were followed in order to collect these data. First, for each group a representative single procedure

was selected, that was highly likely to be used by every patient in this group (*e.g.* an upper endoscopy for every BE patient having surveillance). All patients at our institution who had this procedure in a certain time period were identified, *e.g.* July 2013 up to June 2017 for BE patients having surveillance. The allocated time period varied between patient types, to be able to exclude periods in which study protocols of clinical trials at our institution may have influenced clinical practice and, consequently, the declaration of healthcare products. Next, only the patients in whom this procedure was linked to the relevant DTC were selected (*e.g.* only the patients with the DTC Barrett epithelium who have had an upper endoscopy). Within the electronic patient files all selected patients were reviewed to confirm their eligibility for that specific treatment group. Finally, all the healthcare products as used within this DTC for these patients were collected.

Table 1. Search strategy as used by business intelligence to convert single procedures to healthcare products.

Group	Procedure code*	DTC code**	1st year filter
1. Surveillance	339141L NOT 334390G	303	July 2013, 2014, 2015, 2016, June 2017
2. Endoscopic treatment	334390G	303	July 2013, 2014, June 2015
3. Endoscopic treament	334390G	307, 904, 102, 319	July 2013, 2014, June 2015
4. EAC CROSS regimen	390791 (23x) 339966A (5x)	307, 904, 102, 319	July 2011, 2012, June 2013
5. EAC definitive chemoradiation	390791 (28x) 339966A (6x)	307, 904, 102, 319	July 2011, 2012, June 2013
6. EAC induction chemotherapy	339966A NOT 390791	307, 904, 102, 319	July 2011, 2012, June 2013
7. EAC palliative phase	339966B	307, 904, 102, 319	July 2011, 2012, June 2013

*339141L surveillance endoscopy, 334390G RFA, 339966A chemotherapy for malignancy without metastasis, 339966B chemotherapy for malignancy with metastasis, 390791 radiotherapy
**303 Barrett epithelium (gastroenterology), 307 esophagus | cardia malignancy (gastroenterology), 904 malignancy esophagus/cardia (oncology), 102 gastroenterological tumors (radiotherapy), 319 malignant neoplasms esophagus | cardia (surgery)

Once patients were identified, we collected all their healthcare products as assigned to their DTC without restriction in time period. The completeness of these healthcare products was checked in the electronic patient file for each patient included. Consequently, all healthcare products within a certain DTC of all patients of a certain group at our institution were collected.

These healthcare products were then multiplied by their most recently reported (mostly 2017) mean costs per healthcare product as made available by the Dutch healthcare authority. This strategy provided the mean costs per patient per treatment group. If the mean costs of a healthcare product were not reported, we derived them from the costs of other healthcare products that were available. Per treatment group, some additional assumptions had to be made to get to final estimates (***Table 2***). For example, for all patients included in group 2, who were treated according to the CROSS regimen, we assumed 49% had recurrence at a certain point in time. For this proportion the costs of group 7 (EAC palliative phase) were added to the costs of a patient of group 4.

For treatment group 7, EAC palliative phase, an additional dataset was used to increase the number of patients the mean costs could be based on. They could not all be identified by using the strategy as reported in ***Table 1***, since they had not all had palliative chemotherapy. All patients with EAC in the palliative phase who received a stent in a certain year were identified by a specialist nurse during clinical practice for another clinical study.

Also, for admission to the intensive care unit (ICU) it was necessary to include extra costs, since healthcare products do not cover the costs of admission to the ICU. Therefore, we used the costs per day of admission to the ICU of 2017 as provided by the financial department of our institution for all treatment groups that included esophagectomy, since in most hospitals a short admission to the ICU post-surgery standard of care. These costs were estimated to be € 2,442 per day.

Touch-ups, complications of endoscopic eradication therapy (EET), esophagectomy

Apart from the main treatment groups, we isolated three additional subgroups: touch-up, complications of EET, and esophagectomy. The costs of these options were derived from the previously collected costs, and the type and number of healthcare products used were based on the literature and expert opinion. The rates of these subgroups are also based on expert opinion and the literature, and they were checked for the individual patients as selected by our search strategy. It was not possible to use the same strategy as for the main treatment groups, because of the expected small amount of touch-ups, complications, and single surgeries occurring in our reviewed patients in the selected time period.

For touch-ups after the initial two-year treatment period of EET, the costs of the healthcare products were used that belonged to a single RFA, together with the costs

of group 1 to account for an upper endoscopy after the touch-up and a potential OPD visit.

Complications of EET included in the model are perforation, bleeding, and stricture. The costs of the healthcare product of a complicated upper endoscopy of the esophagus and gastroduodenal tract with a maximum of two days of admission to the ward were used. For both perforation and bleeding we assumed only a single set of these procedures to be necessary, for a stricture we assumed this set of procedures occurred on average 2.5 per stricture [3-5].

Besides the previously defined treatment groups, some patients received only esophagectomy. Two groups of patients may have used this treatment: persistent HGD after EET, and a proportion of patients with T1b EAC. The costs of two years after the esophagectomy of patients from treatment group 4 'EAC CROSS regimen' were used. The patients having persistent HGD after EET are modelled separately, the proportion of patients with T1b EAC who are treated with only esophagectomy instead of also with chemoradiation according to the CROSS regimen are included in the calculation of the costs per stage, as explained in the next paragraph.

This strategy provided the costs per treatment group as declared by the hospitals to insurance companies in the Netherlands (***Figure 2***).

Malignant stage

Since in our model EAC diagnosis was implemented per stage and not per treatment group, an extra transformation was performed to the costs as retrieved by the previously mentioned methods. To be able to calculate the proportion of each treatment group per EAC stage, data concerning the proportions of treatment groups with EAC stage from 2015 from the Dutch cancer registry (Integraal Kankercentrum Nederland (IKNL)) were used. For each stage 1, 2, 3, and 4 patients, the proportion of treatment groups were calculated (***Table 3***). By combining costs per treatment group and the proportions of treatment groups per stage, the costs per stage were calculated as used in the model.

We have also used these data to calculate the proportion of patients of group 7 who had palliative therapy (***Figure 2***). In case they had a combination, the proportion of what therapy was used could be obtained.

Limitations of the search strategy

Although patients with EAC have diagnostic work-ups, those costs were not included separately in the calculation. In the dataset as composed according to our search strategy the number of healthcare products of an individual patient with and without diagnostic procedures were compared. There were no differences. Therefore, these costs are likely to be incorporated in these healthcare products.

Out of the data concerning stage and treatment from the Dutch healthcare registry (IKNL) 12% of patients did not meet any of the inclusion criteria of any treatment group. Those patients were excluded from the analysis, since they were not treated according to an established schedule as set by experts according to the literature. Out of all patients, 3.7% had an undefined stage. Those patients were also not included in the analysis.

Table 2. Assumptions per treatment group in collecting number of healthcare products.

Treatment group	Assumptions
1. Surveillance	The costs of the mean number of OPD visits per patient in the time period of four years were added to the costs of a surveillance endoscopy.
2. Endoscopic treatment BE 3. Endoscopic treatment EAC	The initial EET was assumed to be finished after two years. Therefore, healthcare products that were declared within two years after the first endoscopic treatment session (RFA and if applicable EMR) were included in the calculation of the costs. Patients with complications were excluded from this calculation, because costs of complications were calculated separately. A median stay at the intensive care unit of 2 days was assumed post-surgery [6]. All T1a patients were assumed to be treated with EET, none of the T1a patients were assumed to be treated otherwise.
4. EAC CROSS regimen	All healthcare products of the first two years after diagnosis were collected, since time until recurrence was assumed to be two years [7]. Of all patients included in this treatment group, 49% is expected to have recurrence and the median survival is estimated to be 43 months. Consequently, for 49% of all patients in this treatment group the costs of group 7 were added, for 51% of patients a yearly OPD visit was assumed for two years after the two years of the initial treatment. A median stay at the intensive care unit of 2 days was assumed post-surgery [6]. Patients were assumed to be in stage 1, 2, or 3 of EAC.
5. EAC definitive chemoradiation	All healthcare products of the first year after diagnosis were collected, since time until recurrence was assumed to be one year [8]. Of all patients included in this treatment group, 86% was expected to have recurrence and the median survival was estimated to be 22 months [9]. Consequently, for 86% of all patients in this treatment group the costs of group 7 were added, for 14% of patients a yearly OPD visit was assumed for two years after the year of the initial treatment. Patients were assumed to be in stage 1, 2, or 3 of EAC.

Table 2. Assumptions per treatment group in collecting number of healthcare products. (*continued*)

Treatment group	Assumptions
6. EAC induction chemotherapy	For patients who have only had induction chemotherapy all healthcare products were used, in which recurrence is assumed to be included, because of the lack of a curative treatment. This group is estimated to be 28% of all patients treated with induction chemotherapy [10]. For patients who had both induction chemotherapy and esophagectomy all healthcare products of the six months after diagnosis were collected, since time until recurrence was assumed to be six months. Of all patients included in this treatment group, 60% was expected to have recurrence and the median survival was estimated to be 21 months. Consequently, for 60% the costs of group 7 were added, for 40% of patients a yearly OPD visit was assumed for one year after the year of the initial treatment. A median stay at the intensive care unit of 2 days was assumed post-surgery [6]. Patients were assumed to be in stage 1, 2, 3, or 4 of EAC.
7. EAC palliative phase	All healthcare products per patient without restriction in time were collected and assigned to be part of the following options for palliative therapy: chemotherapy, external radiotherapy, internal radiotherapy, and an endoscopic stent. Patients were assumed to be in stage 4 of EAC.

Table 3. Mean costs per stage of EAC as declared to insurance companies according to the national registry of the healthcare authorities.

	Stage 1*		Stage 2		Stage 3		Stage 4	
	%	n	%	n	%	n	%	n
Group 2 & 3*	18	19	0	0	0	0	0	0
Group 4	45	49	78	134	79	282	0	0
Only esophagectomy	12	13	1.2	2	0	0	0	0
Group 5	22	24	20	35	20	72	0	0
Group 6	2.8	3	0.6	1	1.1	4	6.3	37
Group 7	0	0	0	0	0	0	94	549
Total n° patients per stage	100%	108	100%	172	100%	358	100%	586
Costs per stage	€ 31,602		€ 42,806		€ 43,127		€ 9,332	

Data are converted from costs per treatment group, according to the proportion of number of patients with EAC and their treatment as registered in the Dutch cancer registry. *This only includes EAC > T1a. Costs for T1a EAC are included separately in the model.

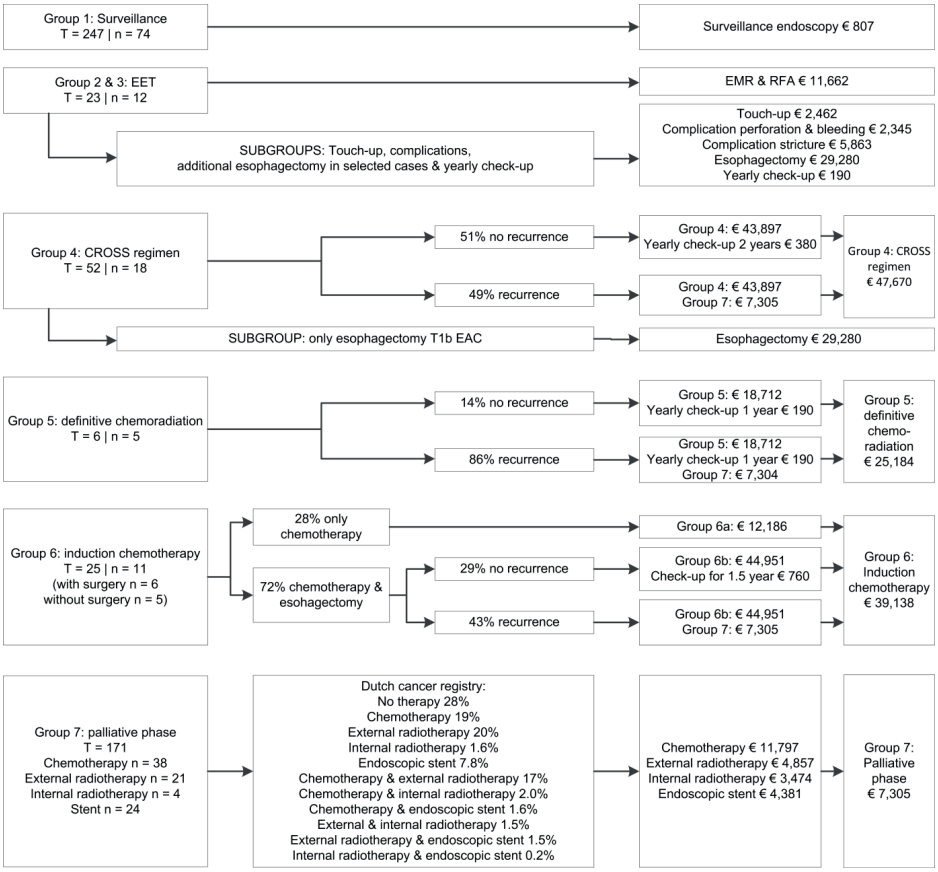

Figure 2. Mean costs per representative patient per treatment group.
EAC: esophageal adenocarcinoma, EET: endoscopic eradication therapy, EMR: endoscopic mucosal resection, n: number of patients included in calculation of costs, RFA: radiofrequency ablation, T: total number of patients identified by search strategy in EPD.

SUPPLEMENTARY TABLES

Supplementary Table 1. Post-treatment surveillance strategies

Patients characteristics	Strategy
Recurrent BE-ND patient	
After CE-IM (state=normal)	Surveillance every 1 year for two years then every 3 years
After non-CE-IM (state=NDBE)	Surveillance at 3, 6, 12 months and then every 1 year*
BE-LGD patients	
After CE-IM (state=normal)	Surveillance every 1 year for two years then every 3 years
After CE-D, non-CE-IM (state=NDBE)	Surveillance every 6 months for one year, every 1 year for two years and then every 3 years
After non-CE-D, non-CE-IM (state=LGD)	Surveillance every 6 months for one year, then every 1 year
BE-HGD/EAC T1a patients	
After CE-IM (state=normal), After CE-D, non-CE-IM (state=NDBE), After non-CE-D, non-CE-IM (state=LGD)	Surveillance at 3, 6, 12 months and then every 1 year*
After non-CE-D, non-CE-IM (state=HGD/EAC T1a)	Esophagectomy

BE: Barrett's esophagus, NDBE: Non-dysplasia Barrett's esophagus, LGD: low-grade dysplasia, HGD: high-grade dysplasia, CE: complete eradication, IM: intestinal metaplasia, D: dysplasia.
* If the state of no-dysplasia was persistent after five years, then surveillance continued every three years.

Supplementary Table 2. Model inputs and sources for the US cost

intervention		Value	Source
Endoscopy		$745	[11]
Initial EET treatment (EMR & RFA)		$5,630	[11]
RFA Touch-Up		$1,012	[11]
EET complication treatment for	Stricture	$1,012	[11]
	Bleeding	$11,815	[12]
	Perforation	$28,533	[13]
Esophagectomy		$48,649	[14, 15]
Annual outpatient visit after esophagectomy		$258	[16]
EAC stage 1 initial care (yearly)		$58,997	[17]
EAC stage 1 terminal care (yearly)		$64,704	[17]
EAC stage 2 and 3 initial care (yearly)		$75,295	[17]
EAC stage 2 and 3 terminal care (yearly)		$77,742	[17]
EAC stage 4 initial care (yearly)		$57,169	[17]
EAC stage 4 terminal care (yearly)		$85,212	[17]
EAC continuous care (yearly)		$4,080	[17]

Supplementary Table 3. Results of the main analysis per 1,000 Barrett's esophagus patients

Strategy		Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)		59	69	+10	66	+7	61	+2	76	+17	72	+13
Prevented EAC deaths		51	56	+5	55	+4	52	+1	60	+9	58	+7
Endoscopies		6,603	9,734	+3,131	8,841	+2,238	7,237	+634	15,163	+8,560	13,757	+7,154
Initial EET		176	235	+59	202	+26	201	+25	278	+102	232	+56
EET touch-ups		99	129	+29	112	+12	112	+13	151	+52	127	+28
Esophagectomy		20	21	+1	21	+2	19	-1	22	+2	23	+3
Complications		24	32	+8	28	+4	27	+3	40	+16	34	+10
Net cost[2] (€m)		4.7	7.0	+2.3	6.2	+1.5	5.3	+0.6	10.6	+6.0	9.4	+4.7
($m)		5.3	8.0	+2.6	7.0	+1.7	6.0	+0.7	12.2	+6.8	10.7	+5.4
LYs gained[2]		311.6	339.6	+28.0	334.1	+22.5	313.6	+2.1	359.2	+47.6	349.4	+37.9
QALYs gained[2]		344.7	374.1	+29.4	369.1	+24.4	346.1	+1.4	392.8	+48.1	383.5	+38.9
Incremental cost per QALY[3]	(€)	N.A.		78,113		60,994		418,830		124,080		121,862
	($)	N.A.		89,257		69,696		478,581		141,781		139,247

ICER: incremental cost-effectiveness ratio, BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, LY: life year, m:million, ND: non-dysplastic, QALY: quality-adjusted life year, EET: endoscopic eradication therapy

1. Difference of the results of these strategies and Dutch guideline strategy are presented in the second column.
2. Costs and (quality-adjusted) life years gained were discounted at an annual rate of 3%.
3. Compared to the Dutch guideline strategy.

Supplementary Table 4. Results of the sensitivity analyses per 1,000 Barrett's esophagus patients

A. Cohort of 50-year-old patients with BE

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	90	104	+13	100	+10	92	+2	113	+23	108	+18
Prevented EAC deaths	80	88	+7	86	+5	82	+1	92	+12	90	+9
Endoscopies	10,179	14,663	+4,484	13,470	+3,291	11,054	+875	22,310	+12,131	20,511	+10,332
Initial EET	241	317	+76	275	+34	272	+31	372	+131	314	+73
EET touch-ups	191	250	+59	218	+26	216	+25	295	+104	249	+58
Esophagectomy	28	29	+2	30	+3	27	-1	30	+3	32	+4
Complications	35	46	+12	40	+6	39	+4	57	+22	49	+14
Net cost[2] (€m)	6.3	9.3	+2.9	8.3	+1.9	7.1	+0.7	13.9	+7.6	12.5	+6.1
($m)	7.2	10.6	+3.3	9.5	+2.2	8.1	+0.8	15.9	+8.7	14.3	+7.0
LYs gained[2]	569.3	615.8	+46.5	606.1	+36.8	573.6	+4.3	647.8	+78.5	631.5	+62.2
QALYs gained[2]	622.5	671.6	+49.1	662.5	+40.0	626.0	+3.5	702.5	+80.0	686.9	+64.4
Incremental cost per QALY[3] (€)	N.A.		59,413		48,643		205,760		94,998		95,328
($)	N.A.		67,889		55,583		235,114		108,551		108,928

B. Cohort of 55-year-old patients with BE

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	75	87	+12	84	+9	77	+2	95	+20	90	+16
Prevented EAC deaths	66	72	+6	70	+5	67	+1	76	+10	74	+8
Endoscopies	8,406	12,276	+3,870	11,205	+2,799	9,187	+781	18,848	+10,442	17,165	+8,759
Initial EET	210	278	+68	240	+30	238	+28	327	+118	274	+65
EET touch-ups	143	187	+44	162	+19	161	+18	220	+78	185	+43
Esophagectomy	24	25	+2	26	+2	23	-1	26	+3	27	+3
Complications	29	39	+10	34	+5	33	+4	49	+19	41	+12
Net cost[2] (€)	5.6	8.2	+2.7	7.3	+1.7	6.2	+0.7	12.4	+6.9	11.0	+5.5
($)	6.3	9.4	+3.0	8.3	+2.0	7.1	+0.8	14.2	+7.9	12.6	+6.3

Supplementary Table 4. Results of the sensitivity analyses per 1,000 Barrett's esophagus patients *(continued)*

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
LYs gained[2]	434.6	472.0	+37.4	464.6	+30.0	438.2	+3.6	497.8	+63.2	485.1	+50.5
QALYs gained[2]	478.1	517.4	+39.4	510.6	+32.5	480.9	+2.8	542.2	+64.1	530.2	+52.2
Incremental cost per QALY[3] (€)	N.A.		67,500		53,860		236,099		107,146		105,177
($)	N.A.		77,129		61,543		269,781		122,431		120,182

C. Cohort of 70-year-old patients with BE

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	27	32	+6	31	+4	28	+1	37	+11	34	+8
Prevented EAC deaths	22	26	+3	25	+2	23	+1	28	+6	27	+4
Endoscopies	3,065	4,707	+1,642	4,192	+1,126	3,459	+394	7,699	+4,633	6,836	+3,770
Initial EET	106	143	+37	121	+15	122	+16	171	+65	140	+34
EET touch-ups	28	36	+7	31	+3	32	+3	41	+13	35	+7
Esophagectomy	12	13	+1	13	+1	11	-1	14	+2	14	+2
Complications	13	18	+5	15	+2	15	+2	22	+9	19	+6
Net cost[2] (€m)	2.5	3.9	+1.4	3.3	+0.9	2.9	+0.4	6.1	+3.7	5.3	+2.8
($m)	2.8	4.4	+1.6	3.8	+1.0	3.3	+0.5	7.0	+4.2	6.0	+3.2
LYs gained[2]	110.3	123.6	+13.3	121.4	+11.1	110.7	+0.5	134.0	+23.8	129.9	+19.6
QALYs gained[2]	123.3	137.1	+13.8	135.3	+12.1	123.3	0.0	146.9	+23.6	143.3	+20.0
Incremental cost per QALY[3] (€)	N.A.		100,605		71,548		23,736,152		154,911		141,311
($)	N.A		114,958		81,755		27,122,394		177,011		161,470

D. Higher progression rate from BE to EAC

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	70	84	+14	80	+11	73	+3	94	+24	89	+19
Prevented EAC deaths	62	70	+8	68	+6	64	+1	75	+12	72	+10
Endoscopies	6,892	9,857	+2,965	8,968	+2,075	7,340	+448	15,245	+8,353	13,830	+6,937

Supplementary Table 4. Results of the sensitivity analyses per 1,000 Barrett's esophagus patients *(continued)*

Strategy		Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Initial EET		189	255	+65	221	+32	216	+27	303	+114	255	+66
EET touch-ups		109	142	+33	125	+16	123	+14	168	+59	143	+34
Esophagectomy		23	25	+2	26	+3	22	-1	27	+4	28	+5
Complications		26	35	+9	30	+5	29	+3	43	+17	37	+11
Net cost[2]	(€m)	4.8	7.0	+2.2	6.2	+1.4	5.3	+0.5	10.6	+5.8	9.4	+4.6
	($m)	5.5	8.0	+2.5	7.1	+1.6	6.0	+0.5	12.2	+6.6	10.8	+5.3
LYs gained[2]		389.3	431.5	+42.3	424.9	+35.6	394.5	+5.3	458.5	+69.3	446.5	+57.3
QALYs gained[2]		430.8	476.8	+46.0	470.4	+39.6	436.1	+5.3	504.3	+73.5	492.5	+61.7
Incremental cost per QALY[3]	(€)	N.A.		47,360		35,121		87,317		79,156		74,532
	($)	N.A.		54,117		40,131		99,774		90,449		85,165

E. Lower progression rate from BE to EAC

Strategy		Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)		50	58	+7	55	+5	51	+1	63	+13	60	+10
Prevented EAC deaths		43	47	+4	45	+3	43	+1	49	+7	47	+5
Endoscopies		6,499	9,613	+3,114	8,728	+2,229	7,133	+635	15,081	+8,582	13,690	+7,192
Initial EET		164	220	+56	187	+23	189	+25	259	+95	214	+50
EET touch-ups		91	118	+27	101	+11	103	+12	139	+48	115	+25
Esophagectomy		17	18	+1	18	+1	16	-1	18	+2	19	+2
Complications		22	30	+8	26	+4	26	+3	38	+15	32	+9
Net cost[2]	(€m)	4.6	6.9	+2.3	6.1	+1.5	5.2	+0.6	10.6	+6.0	9.4	+4.8
	($m)	5.3	7.9	+2.6	7.0	+1.7	6.0	+0.7	12.1	+6.8	10.7	+5.4
LYs gained[2]		253.8	275.0	+21.2	270.5	+16.8	255.6	+1.8	289.5	+35.8	281.8	+28.0
QALYs gained[2]		280.3	301.8	+21.4	298.1	+17.7	281.4	+1.1	314.5	+34.1	307.6	+27.2
Incremental cost per QALY[3]	(€)	N.A.		107,433		84,104		566,097		175,634		175,182
	($)	N.A.		122,760		96,102		646,857		200,690		200,174

Supplementary Table 4. Results of the sensitivity analyses per 1,000 Barrett's esophagus patients *(continued)*

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
F. Lower participation rate in surveillance and endoscopic eradication therapy											
Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	41	49	+8	47	+6	43	+1	56	+15	53	+12
Prevented EAC deaths	36	41	+4	40	+3	37	+1	44	+8	42	+6
Endoscopies	5,724	8,486	+2,763	7,661	+1,937	6,311	+587	12,246	+6,522	11,104	+5,380
Initial EET	131	174	+43	149	+19	148	+17	212	+81	176	+46
EET touch-ups	74	95	+21	83	+9	83	+9	115	+41	97	+23
Esophagectomy	15	16	+1	16	+1	14	-1	17	+2	17	+3
Complications	18	24	+6	21	+3	20	+2	31	+13	26	+8
Net cost[2] (€m)	4.0	5.9	+2.0	5.2	+1.3	4.5	+0.5	8.5	+4.6	7.5	+3.6
($m)	4.5	6.8	+2.3	6.0	+1.5	5.1	+0.6	9.7	+5.2	8.6	+4.1
LYs gained[2]	214.7	237.5	+22.8	233.8	+19.2	215.4	+0.7	257.1	+42.4	250.0	+35.3
QALYs gained[2]	237.5	261.3	+23.8	258.2	+20.7	237.6	+0.1	281.3	+43.8	274.6	+37.1
Incremental cost per QALY[3] (€)	N.A.		83,174		62,007		4,648,332		103,983		96,158
($)	N.A.		95,039		70,853		5,311,472		118,818		109,876
G. Different discount rates for cost and life-years gained[4]											
Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Prevented EAC cases (>T1A)	59	69	+10	66	+7	61	+2	76	+17	72	+13
Prevented EAC deaths	51	56	+5	55	+4	52	+1	60	+9	58	+7
Endoscopies	6,603	9,734	+3,131	8,841	+2,238	7,237	+634	15,163	+8,560	13,757	+7,154
Initial EET	176	235	+59	202	+26	201	+25	278	+102	232	+56
EET touch-ups	99	129	+29	112	+12	112	+13	151	+52	127	+28
Esophagectomy	20	21	+1	21	+2	19	-1	22	+2	23	+3
Complications	24	32	+8	28	+4	27	+3	40	+16	34	+10

Supplementary Table 4. Results of the sensitivity analyses per 1,000 Barrett's esophagus patients *(continued)*

Strategy		Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE[1]	
Net cost[2] (€m)		4.1	6.2	+2.1	5.4	+1.4	4.6	+0.5	9.5	+5.5	8.4	+4.3
($m)		4.6	7.0	+2.4	6.2	+1.5	5.3	+0.6	10.9	+6.3	9.6	+5.0
LYs gained[2]		421.5	459.7	+38.2	451.8	+30.4	424.7	+3.2	486.3	+64.8	472.6	+51.1
QALYs gained[2]		465.5	506.0	+40.4	498.5	+33.0	468.0	+2.5	531.9	+66.4	518.6	+53.1
Incremental cost per QALY[3]	(€)	N.A.		51,772		41,048		217,508		82,434		81,863
	($)	N.A.		59,158		46,903		248,538		94,194		93,542

ICER: incremental cost-effectiveness ratio, BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, LY: life year, m: million, ND: non-dysplastic, QALY: quality-adjusted life year, EET: endoscopic eradication therapy

4. Difference of the results of these strategies and Dutch guideline strategy before rounding are presented in the second column.
5. All discounted at an annual rate of 3%.
6. Compared to the Dutch guideline strategy.
7. Costs were discounted at an annual rate of 4%, and (quality-adjusted) life years were discounted at an annual rate of 1.5%.

Supplementary Table 5. Results of the sensitivity analysis per 1,000 Barrett's esophagus patients incorporating the US costs in the model

H. Cohort of 60-year-old patients with BE

Strategy	Dutch guideline	Intensive for NDBE and LGD[1]		Intensive for NDBE[1]		Intensive for LGD[1]		Very intensive for NDBE and LGD[1]		Very intensive for NDBE	
Prevented EAC cases (>T1A)	59	69	+10	66	+7	61	+2	76	+17	72	+13
Prevented EAC deaths	51	56	+5	55	+4	52	+1	60	+9	58	+7
Endoscopies	6,603	9,734	+3,131	8,841	+2,238	7,237	+634	15,163	+8,560	13,757	+7,154
Initial EET	176	235	+59	202	+26	201	+25	278	+102	232	+56
EET touch-ups	99	129	+29	112	+12	112	+13	151	+52	127	+28
Esophagectomy	20	21	+1	21	+2	19	-1	22	+2	23	+3
Complications	24	32	+8	28	+4	27	+3	40	+16	34	+10
Net cost ($m)[2]	1.8	3.0	+1.3	2.6	+0.9	2.1	+0.3	5.8	+4.0	5.1	+3.4
LYs gained[2]	2.0	3.5	+1.5	3.0	+1.0	2.4	+0.4	6.6	+4.6	5.8	+3.8
QALYs gained[2]	311.6	339.6	+28.0	334.1	+22.5	313.6	+2.1	359.2	+47.6	349.4	+37.9
Incremental cost ($) per QALY[3]	N.A.		43,275		34,937		218,054		83,621		86,191

ICER: incremental cost-effectiveness ratio, BE: Barrett's esophagus, EAC: esophageal adenocarcinoma, HGD: high-grade dysplasia, LGD: low-grade dysplasia, LY: life year, m:million, ND: non-dysplastic, QALY: quality-adjusted life year, EET: endoscopic eradication therapy

8. Difference of the results of these strategies and Dutch guideline strategy before rounding are presented in the second column.
9. All discounted at annual rate of 3%.
10. Compared to the Dutch guideline strategy.

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8

General Discussion

In this chapter, the main findings of the studies included in each part of the thesis are summarized, methodological considerations are described, and the interpretation of the results is provided. Furthermore, this chapter consists of the implications for practice and future research studies, the main conclusions, and recommendations.

MAIN FINDINGS

Part 1. Screening for Barrett's esophagus

Research question 1: Could the use of a minimally invasive cell sampling device for screening of patients with gastroesophageal reflux disease (GERD) symptoms for Barrett's esophagus be cost-effective?

Screening of people with GERD symptoms using a minimally cell sampling device called Cytosponge followed by endoscopic confirmation is a potentially cost-effective option for screening for BE. However, the cost-effectiveness of using the Cytosponge is sensitive to its cost.

In *Chapter* 2, we evaluated the cost-effectiveness of using the Cytosponge for screening of patients with GERD for BE with endoscopic confirmation and compared it with endoscopic screening only.[1] Our findings showed that the Cytosponge screening strategy could reduce the cost of screening by ~30% compared to conventional endoscopy. Although the quality-adjusted life years (QALYs) gained were also reduced, our incremental cost-effectiveness analyses showed that Cytosponge screening is cost effective with incremental cost-effectiveness ratios (ICERs) up to $33,300 per QALY, while screening of patients with endoscopy led to ICERs greater than the commonly accepted willingness-to-pay (WTP) threshold of $100,000 per QALY in the US.

These findings suggest that an initial Cytosponge screening followed by endoscopic confirmation is a potentially cost-effective strategy for screening of a high-risk population for BE, depending on the cost of Cytosponge.

Research question 2: Does the inclusion of unrelated health effects and costs impact the cost-effectiveness of screening for GI cancers?

Unrelated health effects and associated costs may significantly shift cost-effectiveness estimates for cancer screening. Considering them in cost-effectiveness analysis of screening for colorectal cancer (CRC) and EAC may increase the ICERs of recommended screening strategies substantially, so that the currently recommended screening strategies in the US for CRC may no longer be cost effective.

In *Chapter 3*, we used MISCAN models to estimate the impact of unrelated health outcomes and associated costs (e.g., future medical costs or disutility unrelated to the condition under consideration[2]) on cost-effectiveness for two cancer prevention methods, i.e., CRC and EAC screening. We simulated a 40-year-old US population undergoing different colonoscopy screening strategies; and a 60-year-old cohort of US men with GERD undergoing once-only screening with endoscopy or Cytosponge.[1, 3]

Without including unrelated health effects and costs, the optimal cancer prevention strategy for CRC patients was colonoscopy every 10 years from age 50 through 75 years with an ICER of $63,200 per QALY compared to the next effective screening strategy. For EAC screening, Cytosponge and endoscopy screening resulted in ICERs of $26,400 and $107,600 per QALY, respectively. Including unrelated health effects and costs substantially increased ICERs. When we considered the maximum adjustment for unrelated health outcomes and associated costs, we found that the currently recommended CRC screening strategy in the US were no longer cost effective, and the ICERs of Cytosponge and endoscopic screening strategies for EAC nearly doubled.

Part 2. Surveillance of Barrett's esophagus

Research question 3: Is surveillance of individuals with precursor lesions of colorectal, esophageal, gastric, and pancreatic cancers cost effective?

Surveillance for colorectal, esophageal, gastric, and pancreatic cancers may be cost effective; however, for most conditions, the evidence is scant, and the effectiveness basis is weak.

In *Chapter 4*, We conducted a literature review on the cost-effectiveness of surveillance for gastrointestinal (GI) cancer of individuals with a variety of GI conditions, including inflammatory bowel disease (IBD), Barrett's esophagus (BE), gastric precancerous lesions, colorectal adenomas and diverse patients with a high risk of pancreatic neoplasia.[4] We included 21 modeling studies that assessed the cost-effectiveness of surveillance of aforementioned GI conditions. Although studies differed in terms of setting, study populations, surveillance strategies, and health outcomes, most suggested that for high-risk conditions such as BE with high-grade dysplasia (HGD) or treated pancreatic cancer, surveillance with intervals of less than one year is cost effective. For intermediate-risk conditions such as IBD, BE with low-grade dysplasia (LGD), high-risk adenoma, and gastric metaplasia, surveillance every 1-3 years may be more cost effective. For low-risk conditions including small adenomas and non-dysplastic BE (NDBE), surveillance with longer intervals might be appropriate. Although these studies showed that surveillance might be cost effective, it is

worth mentioning that all studies included in this review assumed that surveillance for GI cancers was effective in reducing cancer-specific mortality. The problem with this assumption is that there is no robust evidence showing the effectiveness of surveillance for most of the conditions.

Research question 4: Which management strategy is optimal for patients with BE and low-grade or no dysplasia?

The optimal management strategy for patients with BE and LGD is endoscopic eradication therapy (EET), but only after LGD is confirmed by a repeat endoscopy at 2 months. For BE patients without dysplasia, the optimal strategy is surveillance using a 3-year interval for men and a 5-year interval for women.

In *Chapter 5*, we conducted a comparative modeling analysis to identify the optimal management strategies for BE patients without dysplasia or with LGD.[5] We simulated a no-surveillance strategy and compared it with 78 different strategies for management of patients with NDBE or LGD. In men, management of BE patients prevented up to 75% of EAC cases and consequently decreased EAC mortality up to 88%, while the costs increased substantially compared with no surveillance.

Our analysis showed that strategies without endoscopic confirmation for male LGD patients were not cost effective. For women, only one strategy with surveillance for LGD patients was efficient, while other efficient strategies suggested EET after LGD confirmation. We found that surveillance every 3 years for men with NDBE, and EET for LGD after endoscopic confirmation at 2 months after the first endoscopy, was the optimal management strategy with an ICER of $53,000 per QALY. Our findings suggested a similar strategy for women with LGD; however, the optimal surveillance interval for NDBE patients was 5 years (ICER, $36,000 per QALY) rather than 3 years.

Research question 5: What is the optimal age of last surveillance of patients with non-dysplastic BE considering their competing comorbidities?

The optimal age of last surveillance of patients with non-dysplastic BE without comorbidity is 81 years for men and 75 years for women. However, in case of comorbidities, the optimal stopping ages may be up to 8 years earlier for men and up to 6 years earlier for women.

To answer this question, we conducted a comparative modeling analysis in *Chapter 6*. Using three independently developed models, we simulated 200 US cohorts of patients previously diagnosed with NDBE, varying in age (66 to 90 years), gender, and

comorbidity level[6] (no, mild, moderate, severe). The QALYs gained, and costs from one additional endoscopic surveillance at the current cohort age were calculated versus not performing surveillance at that age. Then we calculated the ICERs for all of the ages to determine the optimal age to discontinue surveillance. We considered the highest age for which the ICER of one more surveillance was still below the WTP threshold of $100,000 per QALY as the optimal age of last surveillance.

Our analysis showed that the benefit of having one more surveillance endoscopy strongly depends on age, gender, and comorbidity status of the patients, while costs were relatively stable. For men with NDBE and no comorbidity, the optimal age of last surveillance was 81 years; however, it was earlier for patients with mild, moderate, and severe comorbidity: 80, 77, and 73 years, respectively. The ages of last surveillance were lower for women than men with NDBE, but the same decreasing trend with increasing comorbidity was found. The optimal ages of last surveillance were 73, 73, and 69 years for women with mild, moderate, and severe comorbidity, respectively, compared to 75 years for patients without comorbidity.

Research question 6: How does the current policy-practice gap in surveillance of patients with BE affect the costs and benefits of the BE management program in the Netherlands?

Surveillance in current practice tends to be more intensive than guidelines. This gap between policy and practice in BE surveillance intervals results in more than 100% higher costs for BE management for a less than 14% increase in QALYs gained per 1,000 BE patients.

The surveillance intervals in practice are shorter than what is recommended in guidelines. To determine how this gap affects the costs and benefits of BE surveillance, we used the MISCAN-EAC model and simulated a cohort of patients with BE in The Netherlands undergoing different management strategies observed in practice to compare the outcomes with those of the Dutch guideline strategy[7] (*Chapter 7*).

Our evaluation of the policy-practice gap in BE surveillance intervals suggested that more intensive surveillance for BE patients can lead to up to 128% higher costs (€2.3-6.0 million per 1,000 patients). However, BE patients gained less than 14% more QALYs compared to the Dutch guideline resulting in incremental cost-effectiveness of more than €78,100 per QALY, which is considerably more than the Dutch willingness-to-pay threshold of €20,000 per QALY. On a population level, this policy-practice gap led to €19-50 million (29-77%) higher healthcare costs in the Netherlands in 2017, due to more endoscopic and treatment procedures.

METHODOLOGICAL CONSIDERATIONS

In this thesis, we have used the MIcrosimulation SCreening Analysis Esophageal adenocarcinoma (MISCAN-EAC) model, which is a discrete-event microsimulation model. Microsimulation models are very helpful for evaluating the impact of health-care interventions such as BE surveillance and screening. This type of modeling enables us to simulate a population, individual by individual, and to follow them from birth to death. The quality and validity of the results from modeling analyses depend on the quality of the model structure and inputs. However, there are not always enough studies available on the natural history of the disease to inform the model. Even if a large number of studies are available, it doesn't guarantee that data from these studies would be usable in the model. It depends on the quality of the studies as well as the type of studies. Furthermore, accurate information on preclinical disease durations and exact disease processes would never be available from literature, because screening/surveillance is only done at specific points in time (and findings often depend on how the test is performed), and disease development cannot be observed continuously. Therefore, usually, some assumptions are required for modeling the disease process. The same is true for EAC modeling.

Available data has been used to inform both the US and the Dutch MISCAN-EAC models (see **Model Appendix)**. We assumed that people with GERD symptoms have a higher risk of developing BE compared to the general population, and EAC can develop only through BE in our model. For BE patients, we assumed the following states: BE with no, low-grade or high-grade dysplasia. Although some studies included data on BE with undefined dysplasia, for simplicity, we decided not to include this state in our model. For EAC in the US model, we assumed local, regional, and distant stages according to the stages used for EAC in the Surveillance, Epidemiology, and End Results (SEER) registry data that was used for model calibration.[8] In the Dutch MISCAN-EAC model, we assumed stages 1-4 based on the data available from the Dutch cancer registry.[9] We also used these data sources to estimate the probability of preclinical cancer to become clinical for each cancer stage, and the survival rate of EAC patients by stage.

One of the controversial issues in BE natural history is the possibility of regression from BE with LGD to NDBE and from HGD to LGD. In MISCAN-EAC models, we have assumed that such BE regression is possible. However, there is no data available on regression transition probabilities. Therefore, during calibration, we have optimized these parameters together with some other unknown natural history parameters, including BE prevalence and average sojourn times between BE states.

Although we have used the best available data as model inputs or to calibrate our model to, there are still uncertainties in some parameters such as BE regression or progression rate of BE towards dysplasia and neoplasia. Therefore, in our studies in the US setting (*Chapters 2, 5, and 6*), we have conducted comparative modeling analysis. In addition to MISCAN-EAC, we have used Esophageal Adeno Carcinoma Model (EACMo) from the Massachusetts General Hospital and the Columbia University Medical Center, and Multistage Clonal Expansion for EAC (MSCE-EAC) model from the Fred Hutchinson Cancer Research Center.[10] All three models are part of the Cancer Intervention and Surveillance Modeling Network (CISNET) in which National Cancer Institute (NCI) sponsored investigators use simulation modeling to improve our understanding of cancer control and to evaluate interventions for prevention and treatment of cancer. Full descriptions of the models are published and available online. [10] These three models are independently calibrated to SEER data while they have different structures and assumptions. For example, two models (MISCAN-EAC and MSCE-EAC) assume that regression from HGD to LGD, and from LGD to NDBE can occur, while the EACMo model does not allow regression. The MSCE-EAC model is based on the molecular and cellular changes that underlie the progression from normal squamous epithelium to BE and to EAC, whereas the other two models are population-based cohort simulations reflecting the clinically identifiable stages leading to EAC development.

Comparative analysis using different independently developed models enables us to validate the results and leads to more robust results than single model analysis. For example, in *Chapter 6* of the thesis, we used the MISCAN-EAC and EACMo models to evaluate the optimal stopping ages for BE surveillance. We found that the EACMo model suggests earlier ages to discontinue surveillance in men and women compared to the MISCAN-EAC model. Therefore, we compared the natural history of the models to understand the underlying reasons better. The cumulative incidence of EAC in NDBE patients is comparable between the EACMo and MISCAN-EAC models. However, EAC cases in the EACMo model occur later than MISCAN-EAC model; therefore, NDBE patients who are still NDBE at later ages, e.g., at age 78 years in the EACMo model will have died of other causes before cancers start to occur. This is the reason that surveillance of NDBE patients at later ages in the EACMo model was not cost-effective compared with MISCAN-EAC model.

In addition to comparative modeling analysis, we have conducted sensitivity analyses to evaluate the robustness of our findings to parameter assumptions in all of the modeling studies, including *Chapter 7* where we only used the Dutch MISCAN-EAC

model. It is also worthwile to mention that in all base case analyses in this theis, costs and utilities were discounted at an annual rate of 3%.

INTERPRETATION OF FINDINGS

Screening or surveillance criteria

The findings of this thesis show that screening for BE and EAC, and some surveillance of BE are cost effective. However, implementation decisions for a screening or surveillance program do not and should not only depend on cost-effectiveness estimates. If we consider the Wilson and Jungner classic screening criteria (***Table 1A***)[11] for choosing a condition for screening or surveillance, we notice that most of the requirements are met for screening for BE and EAC and surveillance of BE. EAC incidence has increased dramatically over the last decades, while survival has remained poor, and therefore it has become a significant health problem. Despite the limited data available on the natural history of BE and EAC, the development trajectory of the disease is partially understood. BE and early-stage EAC are the recognizable stages of EAC, which can be detected early by upper GI endoscopy and biopsy as an appropriate screening or surveillance test. Also, if BE with dysplasia or early-stage EAC is detected, they can be treated by EET to prevent EAC development as recommended by most clinical guidelines. Furthermore, case finding in BE and EAC management is a continuing process where surveillance of BE patients even after treatment is recommended.

The classic criteria were revisited later, and important criteria were added to the list. In addition to benefits, screening or surveillance may have harms such as false-positive test results, complications, overdiagnosis or overtreatments. Therefore criterias such as "the overall benefits of screening should outweigh the harm" and "there should be scientific evidence of screening program effectiveness" were added (***Table 1B***).[11] About the scientific evidence, it is worthwhile to mention that all studies reported the effectiveness of screening for or surveillance of BE are non-randomized or observational studies, including case-control or cohort studies.[12, 13] Although most of these studies showed that screening for or surveillance of BE is effective in reducing EAC mortality, this evidence is not sufficient. The results of these studies may be affected by confounding biases. The ideal study to show the effectiveness of a surveillance/screening program is a randomized controlled trial. However, at this stage, because clinical guidelines recommend screening for BE and EAC, and surveillance of BE patients, randomized clinical trials are no longer deemed ethical. This is where decision modeling comes into play. However, models

can never replace clinical trials, and therefore for future medical interventions it is so important that screening/surveillance should not be implemented until they meet at least the follwing 3 criteria:[14]

- There is evidence on the effectiveness of the intervention
- Benefits of the intervention outweigh harms
- There is evidence on cost-effectiveness of the intervention

For BE screening and surveillance, more research is required to establish the effectiveness and cost-effectiveness of these programs. The results of our modeling analyses in this thesis provide evidence on the effectiveness and cost-effectiveness of screening for BE and EAC, and surveillance of BE patients.

Table 1A. Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Table 1B. The revised screening criteria

• The screening program should respond to a recognized need.
• The objectives of screening should be defined at the outset.
• There should be a defined target population.
• There should be scientific evidence of screening program effectiveness.
• The program should integrate education, testing, clinical services and program management.
• There should be quality assurance, with mechanisms to minimize potential risks of screening.
• The program should ensure informed choice, confidentiality and respect for autonomy.
• The program should promote equity and access to screening for the entire target population.
• Program evaluation should be planned from the outset.
• The overall benefits of screening should outweigh the harm.

Generalizability of our findings

With regard to the cost-effectiveness estimates, we should be aware that these estimates for an intervention in a country depend on the healthcare costs and the willingness-to-pay threshold used in that country. Our analyses in this thesis have been conducted for the US or Dutch setting; however, we believe that our results can be applied to other countries located in North-America or Western Europe. In these countries, the incidence of EAC has also increased substantially over the last decades, and EAC has become the main type of esophageal cancer.[15, 16]

Furthermore, in countries with a lower incidence of EAC, surveillance of BE patients may also be recommended in clinical practice. The expectation is that once people have BE, their risk of progression is not that different between countries. According to the EAC incidence data in the Netherlands and the US, and the results from our studies, we see a similar thing for men and women. While there is a considerable difference in EAC risk, there is a much smaller difference in the progression of BE towards EAC. Therefore, our results regarding BE surveillance can also apply to those countries.

CLINICAL IMPLICATIONS

The findings of the studies included in this thesis have important implications for clinical decisions and policy making for the management of BE patients. While all current international clinical guidelines recommend treatment for BE patients with HGD, they include inconsistent recommendations for BE patients with LGD. Most of these recommendations have been based on expert opinion due to the scarcity of relevant evidence. They also do not include any recommendation for discontinuation of surveillance of NDBE patients.

Our results provide evidence on optimal management strategies for BE patients. For patients with LGD, the results of our analysis showed that in comparison with the treatment of LGD patients by EET, surveillance was not efficient. All three models consistently showed that the optimal management of LGD patients was EET after LGD is confirmed by a repeat endoscopy at 2 months. For NDBE patients, we found that the optimal cost-effective strategy is surveillance at 3-year intervals for men and at 5-year intervals for women.

Our results also provide evidence on the optimal age of last surveillance for NDBE patients. Furthermore, we showed that surveillance of NDBE patients should discontinue earlier in patients with comorbidity and, consequently, with lower life expectancy than in patients without comorbidities. Despite differences across the models in actual stopping ages, our findings provide the age range at which the clinicians and patients can discuss discontinuation of surveillance. In addition to cost-effectiveness, harm-benefit balance is a crucial factor for the decision. Our results draw the attention of the clinician to the fact that discontinuation may be good at some point.

In addition to informing the guidelines, our findings on the potential impact of the policy-practice gap in BE management have implications for policy making to encourage adherence to clinical guidelines. Although there is not enough evidence available for some of the recommendations of guidelines for BE management, our findings indicate that non-adherence to the current guidelines where clinicians conduct more intensive surveillance than recommended may substantially increase the costs of BE management while the benefits are small. Therefore, at first, it is essential to develop policies to improve adherence to the guidelines through incentives. Furthermore, adherence to the guidelines will probably improve with better evidence. Therefore, the guidelines should be improved by including more evidence-based recommendations. The incentive policies and improving guidelines would help to eliminate the policy-practice gap in BE management to reduce the burden of BE management on patients and healthcare resources.

FUTURE RESEARCH

Our research has already answered important questions in the field of BE management; however, there are still some points that need further exploration in future research projects.

Optimization of screening for BE and EAC

In our research on screening of people with GERD symptoms, we have evaluated the cost-effectiveness of using a new sampling device (Cytosponge) as the first-line screening test for BE and EAC, and we showed that it could be a cost-effective alternative to GI endoscopy alone for screening. There are also other promising minimally invasive devices such as unsedated transnasal endoscopy and tethered capsule endoscopy, which can potentially be used as the first-line screening test.[17, 18] Along with the clinical effectiveness of these new technologies, their cost-effectiveness should be evaluated in future research.

In addition to identifying the optimal test for screening, it should be clear who would be eligible for screening and what would be the screening intervals. Current clinical guidelines recommend screening of high-risk people for BE or EAC. These include individuals with at least two of the following risk factors: central obesity, current or past history of smoking, age more than 50 years, and history of BE or EAC in a first-degree relative, according to the American College of Gastroenterology guidelines.[19] Although the recommendations consider age more than 50 years as a risk factor, there is no recommendation for the start age or interval of screening.

Therefore, more clinical research is required to determine the optimal screening strategy.

The presence of several risk factors to develop BE and EAC indicates that screening strategies can be further personalized. Currently, there is a general recommendation to screen people with multiple risk factors. However, if we consider the importance of each risk factor in increasing the risk of BE or EAC and other competing risks, screening strategies could be further customized, which should be considered in future research studies.

Management of BE patients

In *Chapters 5 and 6*, we determined the optimal management strategy for NDBE and LGD patients. Our findings suggest that the optimal strategy differs between NDBE and LGD patients, and between men and women. We also found that the optimal age of last surveillance of NDBE patients varies by comorbidity status of a patient. These results indicate that BE management can be different based on the characteristics of the patients.

Current BE management guidelines are based on the histological grading of BE. Although grading of BE influences the risk of progression towards neoplasia, not all patients within one histological grading category have the same risk of developing EAC. Surveillance endoscopies may enable early detection of HGD or EAC but are also associated with patient burden and costs, and should, therefore, be minimized in those at low risk of progression. For example, surveillance of non-dysplastic patients is generally cost effective,[5] but in patients at low risk of neoplastic progression, the burden of surveillance may outweigh the benefits. Therefore, further personalization of BE management based on the progression risk of BE patients towards EAC might be even more effective and less costly. In addition to dysplasia, BE length, nodularity, inflammation or biomarkers can potentially be used as determinants for the risk of progression towards EAC.[20-22] For example, p53 and SOX2 are the promising biomarkers associated with neoplastic progression. Using these factors for individualization of BE management sounds promising, but more research is needed before it can be implemented in practice.

In our research in *Chapter 5*, we focused on BE management until patients receive EET, but BE patients also receive endoscopic surveillance after EET. Some of the international guidelines include recommendations for such post-treatment surveillance of BE patients; however, these recommendations are based on expert opinion due to lack of evidence on the long-term effectiveness of EET and, consequently,

lack of evidence on the optimal post-treatment surveillance. Besides, none of the existing guidelines include any recommendation for stopping age of post-treatment surveillance. Therefore, current post-treatment surveillance of patients who have received EET is intensive and the same for all patients regardless of their individual risk of recurrence. Future research on BE management should also include studies to determine the long-term efficacy of EET of BE patients to be able to conduct robust cost-effectiveness analyses for the optimization of post-treatment surveillance of BE patients.

Unrelated health effects and costs

In *Chapter 3*, we showed that including unrelated health effects and costs can potentially affect cost-effectiveness estimates of CRC and EAC screening. A limitation of this study was the scarcity of evidence on unrelated health effects and associated costs to incorporate them precisely in the analysis. Due to this uncertainty, we had to consider a range of values for unrelated health effects and associated costs for our analysis. In the low range, the impact on cost-effectiveness estimates was limited, and in the high range, it was quite considerable. Therefore, accurate estimates for unrelated health effects are very important, and we believe that further research is directly needed to ensure reasonable cost-effectiveness estimates.

Furthermore, concerning the shift in cost-effectiveness estimates when we consider unrelated health effects of the interventions, the question is whether commonly accepted WTP thresholds should also be shifted. On the one hand, we may want to do this, because thresholds were set in the time when these unrelated health effects and costs were not considered. On the other hand, a WTP threshold reflects what society is willing to pay for a (quality-adjusted) life year, and this does not change with the thoroughness or completeness of the analyses you perform. The implication of the latter would be that interventions that have been considered cost effective in the past may no longer be deemed cost effective, because the costs of these interventions will increase while benefits decrease. This is an area that requires more future assessment and debate.

CONCLUSIONS

The following conclusions are derived from the results of the thesis:

- First-line screening of people with GERD symptoms using Cytosponge followed by endoscopic confirmation is a potentially cost-effective minimally invasive alternative to conventional endoscopic screening.

- Unrelated health effects and costs affect the cost-effectiveness estimates of GI cancer screening programs significantly.
- If effective, surveillance of patients with IBD, BE, colorectal adenomas, precancerous gastric lesions, neoplastic pancreatic cysts, and treated pancreatic cancer is generally cost effective. However, the evidence base for effectiveness is weak.
- For high-risk conditions such as treated pancreatic cancer, intensive surveillance (i.e., annually) may be cost effective, while for patients with intermediate-risk conditions (i.e., LGD BE, IBD, large adenomas, gastric metaplasia) or with low-risk conditions (i.e., small adenomas or non-dysplastic BE), less intensive surveillance (i.e., every 3-10 years) may be cost effective.
- From a cost-effectiveness perspective, the optimal management strategy for BE patients without dysplasia is endoscopic surveillance using a 3-year interval for men and a 5-year interval for women.
- The optimal age of last surveillance of BE patients without dysplasia varies by gender and comorbidity level of the patients. For non-dysplastic BE patients with no comorbidity, the optimal age of last surveillance is 81 years for men and 75 years for women. However, if they have comorbidities, the optimal stopping ages may be up to 8 years earlier for men and up to 6 years earlier for women.
- For BE patients with LGD, EET is the optimal management strategy for both male and female patients if LGD is confirmed by a repeat endoscopy at 2 months after the first endoscopy.
- Non-adherence of physicians to surveillance guidelines, resulting in earlier surveillance than recommended, may increase the cost of the BE surveillance by more than 100%, while its additional benefits are marginal.

RECOMMENDATIONS

Based on the results and conclusions of the thesis, the following recommendations are provided.

- Low-cost and minimally invasive devices such as Cytosponge should be considered as a potential alternative to endoscopy for screening patients at high risk for BE and EAC.
- Future cost-effectiveness analyses on cancer prevention strategies should consider sensitivity analyses including unrelated health effects and costs, to evaluate the robustness of their cost-effectiveness estimates to these effects.
- Future research should be conducted to determine actual estimates for unrelated health effects to allow more robust determination of cost-effectiveness.

- Prospective (randomized) trials should be conducted on surveillance for GI cancers to confirm the effectiveness and cost-effectiveness of these interventions.
- Prior to the implementation of new devices for BE or EAC screening in clinical practice, more clinical studies and robust cost-effectiveness analyses should be performed.
- Male BE patients without dysplasia should receive surveillance every 3 years, while the surveillance interval for female BE patients without dysplasia can be extended to every 5 years.
- In addition to chronological age, the gender and comorbidity status of BE patients without dysplasia should be considered in clinical decisions about continuing surveillance.
- The possibility of stopping surveillance should be discussed in male non-dysplastic BE patients from age 73 and female non-dysplastic patients from age 69 years. The final decision on when to stop surveillance can be further personalized in this discussion.
- BE patients diagnosed with LGD, should receive a repeat endoscopy after 2 months: if LGD is confirmed at this exam, they should undergo EET followed by surveillance.
- Future research on BE management should focus on clinical studies to determine the long-term efficacy of EET for the treatment of BE patients to allow robust evaluation of optimal post-treatment surveillance of BE patients.
- Appropriate health policies should be developed to encourage physicians to adhere to BE surveillance guidelines to eliminate the policy-practice gap in BE management.

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Model appendix

THE DUTCH AND US MISCAN-EAC MODELS' STRUCTURE AND CALIBRATION

Model overview

The Microsimulation Screening Analysis (MISCAN) esophageal adenocarcinoma (EAC) model is a semi-Markov microsimulation model. The population is simulated individual by individual rather than as proportions of a cohort. This allows future state transitions to depend on past transitions, giving the model a 'memory'. Each person can evolve through discrete disease states. However, instead of modeling yearly transitions between health states with associated transition probabilities, as is generally done in a Markov model, the duration in each state is drawn from an exponential distribution. Although these two approaches lead to similar results, the advantage of the latter approach is that durations in a certain state do not need to be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, onset of Barrett's esophagus (BE), and transitions from one state of disease to another. [1]

The basic structure of the MISCAN-EAC model consists of three main parts:

- Demography part
- Natural history part
- Screening, surveillance and treatment part

Demography Part

The individual life histories are simulated in the demography part of the model. For each person, a birth date and death date due to other causes than EAC is simulated. The distribution of births and deaths can be adjusted to represent the simulated population.

Natural history part

The natural history part of MISCAN-EAC simulates the development of EAC in the population. The US model was calibrated to reproduce Surveillance, Epidemiology, and End Results (SEER) incidence data from 2010-2014 (***Figure 1*.A**),[2] and the Dutch model was calibrated to the Dutch EAC incidence rates per age group, averaged over years 2012-2017 (***Figure 1*.B**).[3]

We assume that EAC develops through BE. At model initiation, each individual in the simulated population is assigned a personal risk index. A minority of the population has symptomatic gastro-esophageal reflux disease (GERD), giving them

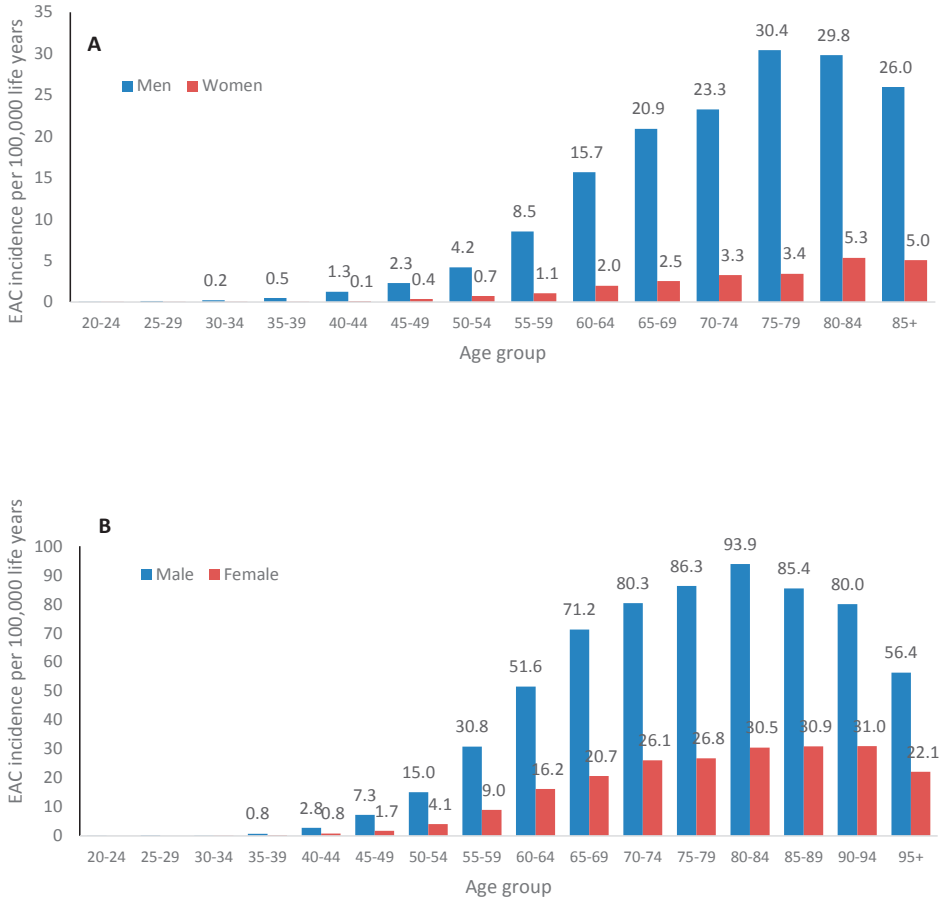

Figure 1. Average esophageal adenocarcinoma (EAC) incidence in the US in years 2010-2014 (A), and in the Netherlands in years 2012-2017 (B)

a higher risk of developing BE during their lifetime.[4, 5] The development of BE is generated according to this personal risk index and an age-specific probabilities of disease onset. Furthermore we distinguish short-segment (SS) and long-segment (LS) BE. The sequence from the onset of BE to EAC diagnosis is governed by sojourn times between the different states. BE starts in a state with no dysplasia (ND), thereafter dysplasia can develop. Two states of dysplasia are defined: low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Indefinite dysplasia was considered as LGD in our model. There is a possibility that regression from HGD to LGD and from LGD to ND occurs. The probability of regression, progression, and the according sojourn times can be calculated as follows:[1]

$Probability\ of\ regression\ in\ state\ i\ = \frac{R_{ir}}{R_{ir}+R_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Probability\ of\ progression\ in\ state\ i = \frac{R_{ip}}{R_{ir}+R_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Sojourn\ time\ in\ state\ i = \frac{1}{R_{ir}+R_{ip}}$, where *i*: current state LGD o*r* HGD: regress, *p*: progress, *R*: rate

From HGD, malignant cells can arise. In the Dutch model they can transform to cancer state T1a. From this state, preclinical malignant cancer stage 1 can develop, which can sequentially progress into preclinical malignant stages 2, 3, and 4. In the US model, HGD can progress to localized preclinical cancer, and then to regional and distant preclinical cancer. In each of these states, there is a probability of the cancer being clinically diagnosed (*i.e.*, because of symptoms). A graphical representation of the structure of the models is shown in ***Figure 2***.

The survival after EAC diagnosis depends on the cancer stage. We used data on survival of EAC patients in the Netherlands diagnosed in years 2010-2013 to inform the modeled survival rates at 1, 3, and 5 years after diagnosis in the Dutch MISCAN-EAC.[6] For the survival of EAC patients in the US MISCAN-EAC model, we used the SEER survival data until 2014.[2]

Screening, surveillance and treatment part

The development of EAC can be interrupted by screening or surveillance. Screening or surveillance can detect BE, dysplasia and preclinical cancer. When BE or dysplasia are detected, they can be removed using treatment. Cancer may be detected in an earlier stage than it would have been otherwise (*i.e.*, in case of clinical diagnosis). In this way screening/surveillance can reduce both EAC incidence and EAC death. Endoscopic eradication treatment (EET) can be used for treatment of BE or early stage EAC patients. We assume that duration of initial EET is 2 years and BE patients receive endoscopic mucosal resection (EMR) and/or radiofrequency ablation. The EET success and recurrence rates are assumed to be dependent on the pre-treatment state of the patients (ND, LGD, HGD/T1a EAC).

For each individual patient, the outcome of the 2-year endoscopic treatment phase is randomly drawn based on the disease state at the start of the treatment. In case of treatment failure, the patient remains in endoscopic surveillance at an interval based on their pre-treatment dysplastic grade. In case of treatment success, the patient transits to a state of complete eradication of dysplasia with either persistent

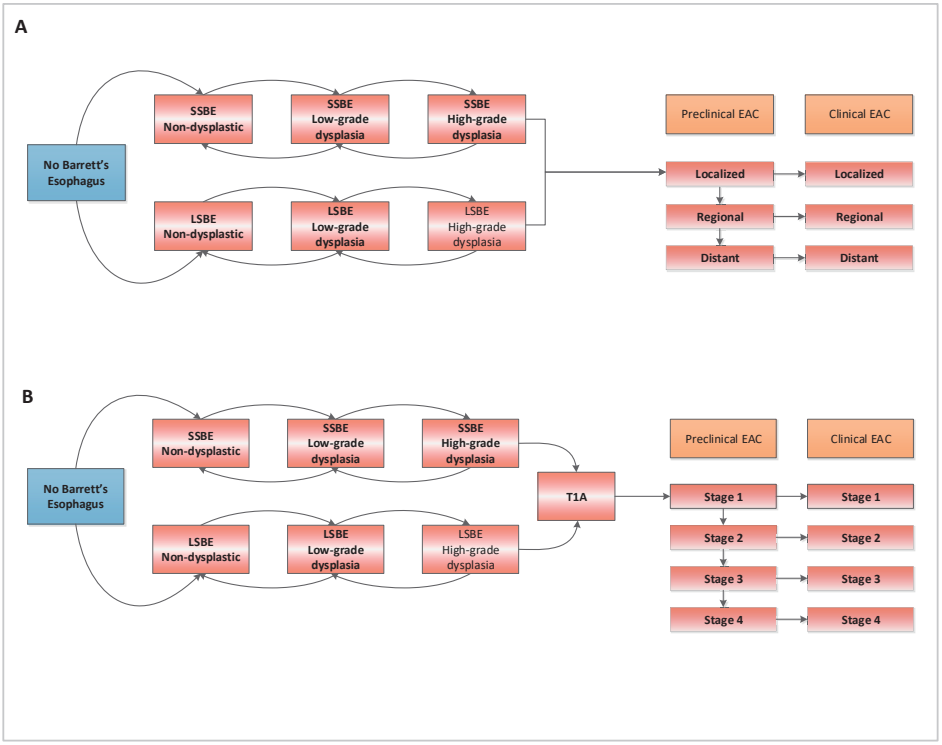

Figure 2. The structure of US MISCAN-EAC Model (**A**) and Dutch MISCAN-EAC model (**B**)
EAC: esophageal adenocarcinoma, LSBE: long-segment Barrett's esophagus, SSBE: short-segment Barrett's esophagus, T1a: esophageal adenocarcinoma T1a

metaplasia (CE-D) or intestinal metaplasia (CE-IM). In the former case, we assume that the patients would have the same assumptions as our natural history model, only without the distinction between short-segment and long-segment. In the latter case, the patient stays in the CE-IM state for a sojourn time randomly selected from an exponential distribution. If the patient transits to next state because of recurrence or progression, a new RFA is applied followed by post-treatment surveillance.

Integration of the three model components

For each individual, the demography part of the model simulates a time of birth and a time of death from other causes than EAC, creating a life history without EAC. Subsequently the onset of BE is simulated for some of the individuals. Most individuals do not develop any dysplasia. In case of progressive BE, dysplasia may develop and HGD transforms into a malignant state, causing symptoms and eventually resulting in death from EAC. If a person dies from EAC before he would die from other causes, his death age is adjusted accordingly.

After the life history of a person has been adjusted for the natural history of disease, it can also be adjusted for the effects of screening and surveillance, which can detect BE with or without dysplasia. When BE is treated successfully, the individual does not develop cancer according to the original life history because the precursor has been removed. In that case, the individual may die from other causes, or the individual may again develop BE and EAC, and still die because of EAC. The effect of a screening or surveillance intervention is the difference in life years between the simulation without the intervention and the simulation with the intervention.

Model quantification and calibration

In this part, the parameters that we used in the different parts of the model and the methods that we have used to calibrate them, are described. The main sources that we used for the calibration process for the Dutch MISCAN-EAC model were EAC incidence rates per age group in the Netherlands, averaged over years 2012-2017, and the ProBar study, which is a multicenter prospective cohort study in the Netherlands.[7] In this study, 783 patients with BE (≥2 cm) were included and followed under endoscopic surveillance according to the guidelines of the American College of Gastroenterology with a median follow-up of 7.6 years. In this study, neoplastic progression (*i.e.*, development of HGD or EAC) in BE patients was determined during follow-up.

The US model was calibrated to reproduce Surveillance, Epidemiology, and End Results (SEER) EAC incidence data 2010-2014. In addition, we used the available literature to set other calibration targets such as BE progression rate.

Demography parameters

There are two types of demography parameters: birth tables and life tables. For the birth tables, we assumed that all individuals were born at 1957 or 1950 in the Dutch and the US models, respectively. The life tables for the Dutch model were derived from the life tables published by Statistics Netherlands, and for the US model from the tables published by the National Center for Health Statistics.[8, 9] We assumed everyone to die at or before age 100.

Natural history parameters

For both models, we assumed that the prevalence of symptomatic GERD is around 20%.[10-13] Another fixed parameter in the model was the proportion of BE patients who have symptomatic GERD. We assumed that individuals with GERD symptoms make up 60% of the BE patient population.[14, 15] Other parameters differed across the models as follows.

One of the calibration targets in the Dutch MISCAN-EAC model was the maximum BE prevalence at ages 50-70. It was set to 12% in the male population and 7% in the female population. There is limited evidence available on precise prevalence of BE in the Netherlands, but based on expert opinion we feel it would not be higher than these percentages.[16] For the US model, we didn't assume any upper limits for BE prevalence during calibration.

Using the ProBar study, we estimated that from the male BE patients, 1.4% were HGD, 13.1% were LGD, and 85.5% were NDBE. From the female BE patients, we estimated that 0.5% were HGD, 9.7% were LGD, and 89.8% were NDBE. Both distributions were used as calibration targets in the Dutch model.[7] SSBE and LSBE were assumed to have similar proportions of LGD and HGD. Furthermore, the EAC incidence was calibrated to the EAC incidence rates in the Netherlands in years 2012-2017.[3] EAC was assumed to be diagnosed in stages 1, 2, 3, and 4 in 17%, 13%, 31%, and 40% of cases in men, and 17%, 15%, 30%, and 38% of cases in women, respectively.[7]

For the US model, we estimated the proportion of NDBE, LGD and HGD in a BE population at 88.4%, 9.4% and 2.2%, respectively, based on the available literature [15, 17-28] We used these percentages as calibration targets in the US MISCAN model. Furthermore, the EAC incidence was calibrated to the EAC incidence rates in the US in years 2010-2014.

We adjusted the screening part of the Dutch model in order to reproduce the characteristics of the ProBar study design by implementing realistic surveillance and diagnostic inaccuracy as observed in this study.[7] BE with or without LGD was detected at index endoscopy. Surveillance was stopped when HGD or EAC was found. As the SSBE population in the ProBar cohort does not cover the total SSBE population in our model (ProBar only included ≥2cm) the progression rates were taken as an upper bound for these populations. The annual progression rates as calibration targets were calculated after a follow-up of 13 years using a weighted average of follow-up years (***Figure 6***).

In the US model, we set the annual progression rates of BE (NDBE and LGD) towards EAC to 0.0018 and 0.0075 for men and women, respectively.[29-31] To calibrate the progression rates based on the rates derived from the results of the available studies, [29-31] we used a one-time screening examination at age 65 to detect patients with NDBE or LGD. The diagnosed NDBE and LGD patients underwent surveillance, getting their next endoscopy after 2 or 1.4 years, respectively. After the first surveillance endoscopy, 46% of the patients did not adhere to the next endoscopy, and were

not offered any subsequent surveillance in our model. The remaining patients in the surveillance cohort were offered surveillance every 3 years (NDBE), 1 year (LGD) and 3 months (HGD) until cancer detection or death. The calculation of the annual progression rates was calculated after 5 years.

Calibration process

During the optimization the Pearson chi-square Goodness of fit function was minimized. The deviation of all calibration targets (e.g., EAC incidence rates per age group, annual progression rate from BE to HGD and EAC, proportions of dysplasia and average BE prevalence at ages 50-70) was summed to calculate the overall Goodness of fit of the model given a certain set of parameters. The search for new parameter values was performed following the Nelder-Mead simplex method.

Calibration results

The parameters used in the models are presented in ***Tables 1 and 2*** for the Dutch and the US models, respectively.

Figures 3 and 4 show the age-specific EAC incidence calibration targets in years 2012-2017 in the black diamonds,[3] and the results of the model in the blue (male) and red female) lines, respectively. ***Figure 5*** presents the prevalence of BE in Dutch male and female population in absence of screening or surveillance for BE (natural history).

At baseline in the ProBar study, the median age was 59 for men, and 65 for women. When replicating the ProBar study, we could assess the progression rate in a 59-year-old male and 65-year-old female BE (ND+LGD) cohort towards HGD and EAC. The results are presented in ***Figure 6***.

The calibration results of the US model are shown in ***Figures 7-10***.

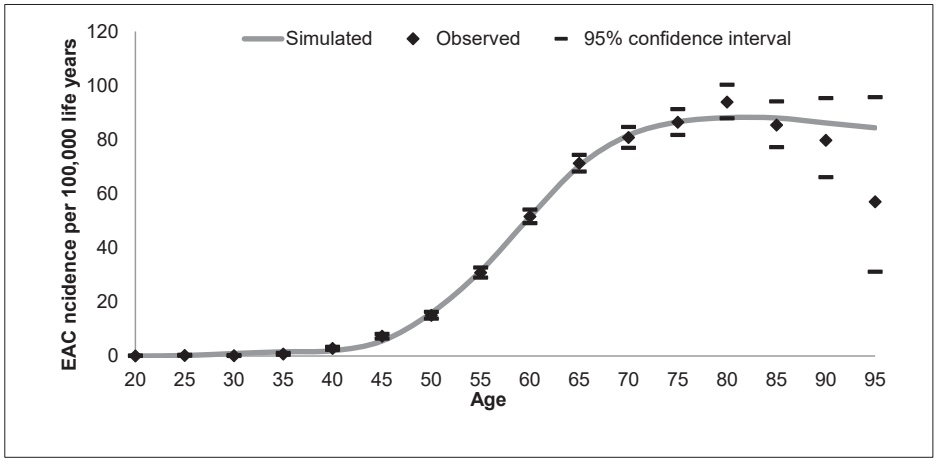

Figure 3. Age-specific EAC incidence in Dutch male population (Observed vs simulated) in the absence of screening and surveillance (natural history)

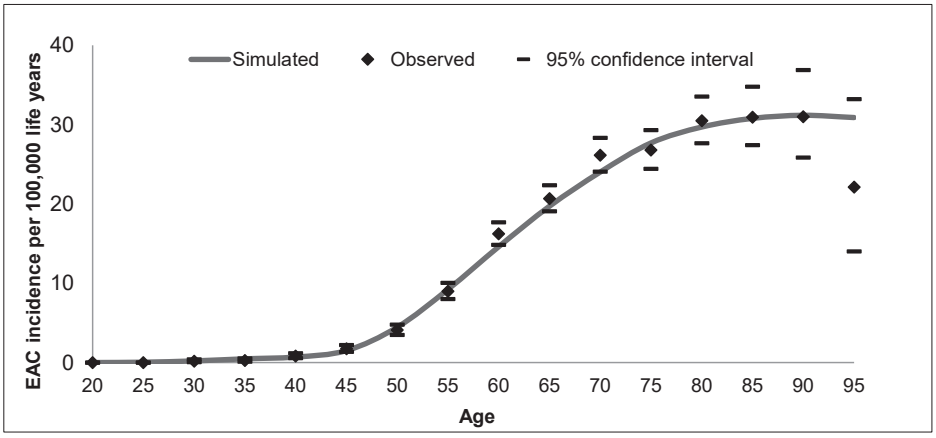

Figure 4. Age-specific EAC incidence in Dutch female population (Observed vs simulated) in the absence of screening and surveillance (natural history)

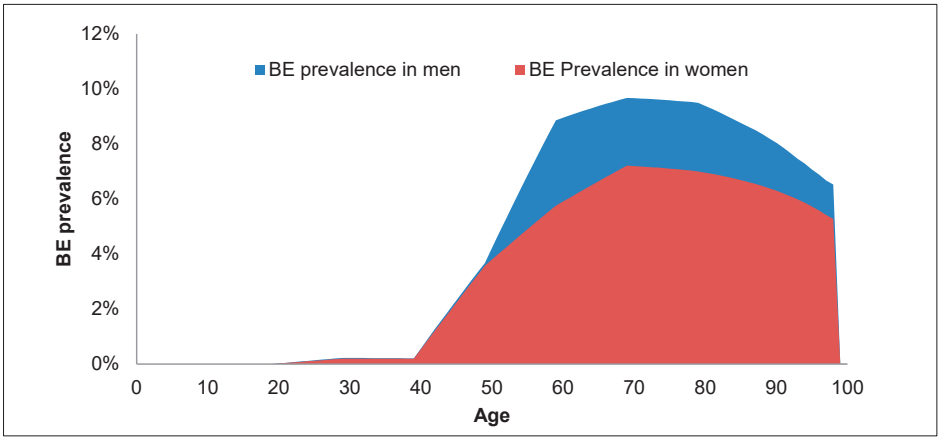

Figure 5. Barrett's esophagus (BE) prevalence in the absence of screening and surveillance (natural history) in the Dutch popualtion

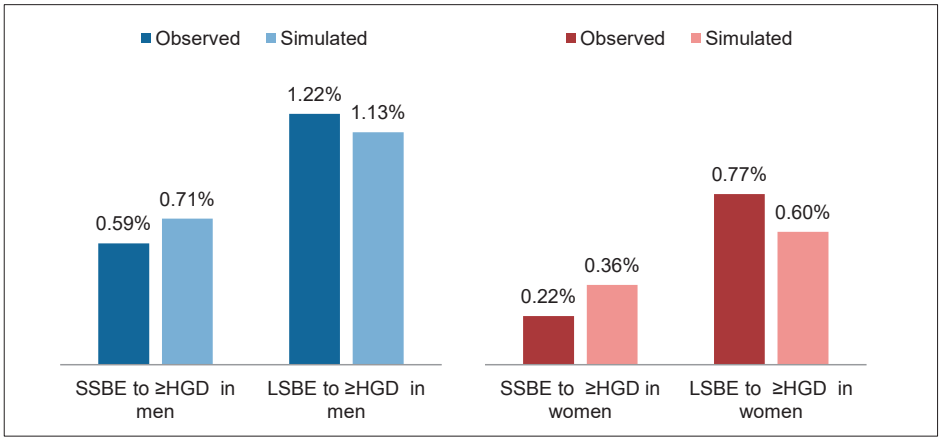

Figure 6. Annual progression rate from short-segment (SS) or long-segment (LS) Barrett's esophagus towards high-grade dysplasia or esophageal adenocarcinoma (EAC) in men and women (Dutch model)

Table 1. Parameters used in the Dutch model

Model parameter	Male model	Female model	Parameter characteristics
Symptomatic GERD prevalence	20% [10-13]	20% [10-13]	Fixed input
Fraction of BE cases found in symptomatic GERD population	60% [14, 15]	60% [14, 15]	Fixed input
BE prevalence age 50-70	4-10%	4-7%	Optimized
Average duration between one state to the next state (years)			
SSBE to SSLGD	18.6	38.1	Optimized
SSLGD to SSHGD	3.3	6.7	Optimized
SSHGD to T1a	2.6	5.4	Optimized
LSBE to LSLGD	11.3	23.1	Optimized
LSLGD to LSHGD	2.0	4.1	Optimized
LSHGD to T1a	1.6	3.3	Optimized
T1a to preclinical stage 1 EAC	1.4	1.4	Optimized
Regression transition probability			
LGD to NDBE	79.5%	79.5%	Optimized
HGD to LGD	24.4%	24.4%	Optimized

BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; GERD: Gastroesophageal Reflux disease; HGD: high-grade dysplasia; LGD: low-grade dysplasia; LS: long-segment; NDBE: non-dysplastic Barrett's esophagus; SS: short-segment

Table 2. Parameters used in the US model

Model parameter	Male model	Female model	Parameter characteristics
Symptomatic GERD prevalence	20% [10-13]	20% [10-13]	Fixed input
Fraction of BE cases found in symptomatic GERD population	60%[14, 15]	60% [14, 15]	Fixed input
Average duration between one state to the next state (years)			
SSBE to SSLGD	53.8	89.9	Optimized
SSLGD to SSHGD	9.0	15.1	Optimized
SSHGD to localized EAC	4.2	7.0	Optimized
LSBE to LSLGD	28.5	47.6	Optimized
LSLGD to LSHGD	4.8	8.0	Optimized
LSHGD to localized EAC	2.2	3.7	Optimized
Regression transition probability			
LGD to NDBE	31.5%	79.5%	Optimized
HGD to LGD	54.7%	24.4%	Optimized

BE: Barrett's esophagus; EAC: esophageal adenocarcinoma; GERD: Gastroesophageal Reflux disease; HGD: high-grade dysplasia; LGD: low-grade dysplasia; LS: long-segment; NDBE: non-dysplastic Barrett's esophagus; SS: short-segment

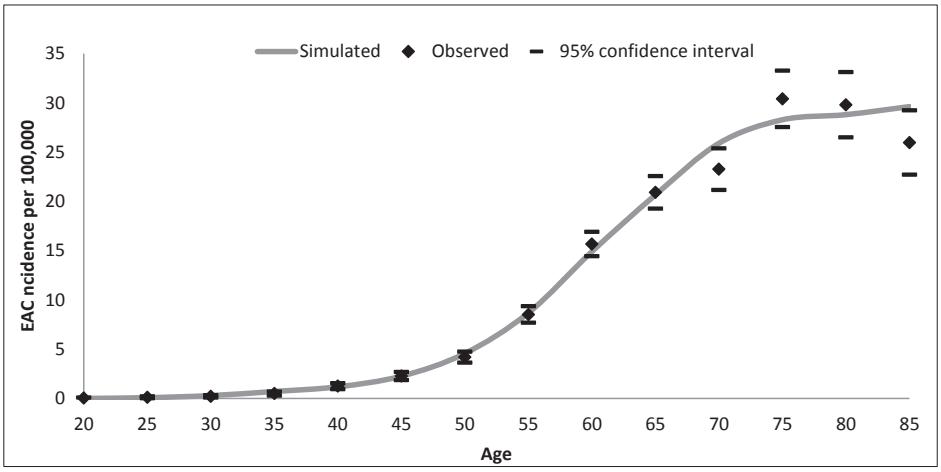

Figure 7. Age-specific EAC incidence in US male population 2010-2014 (Observed vs simulated) in the absence of screening and surveillance (natural history)

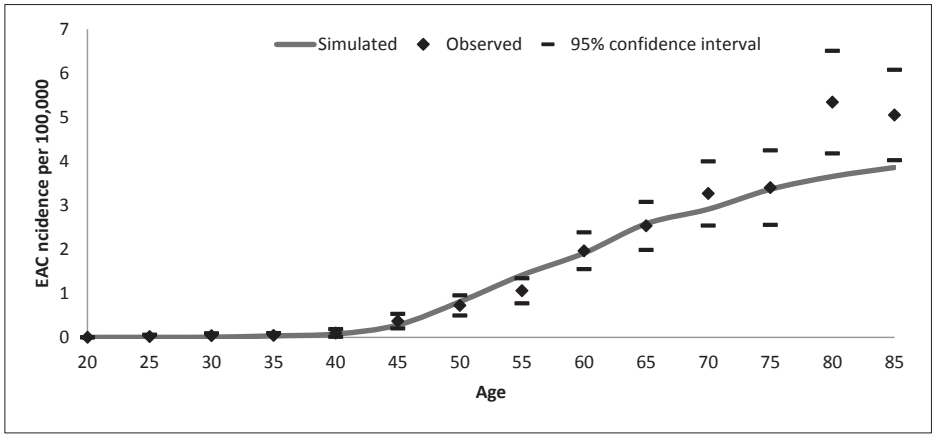

Figure 8. Age-specific EAC incidence in US female population 2010-2014 (Observed vs simulated) in the absence of screening and surveillance (natural history)

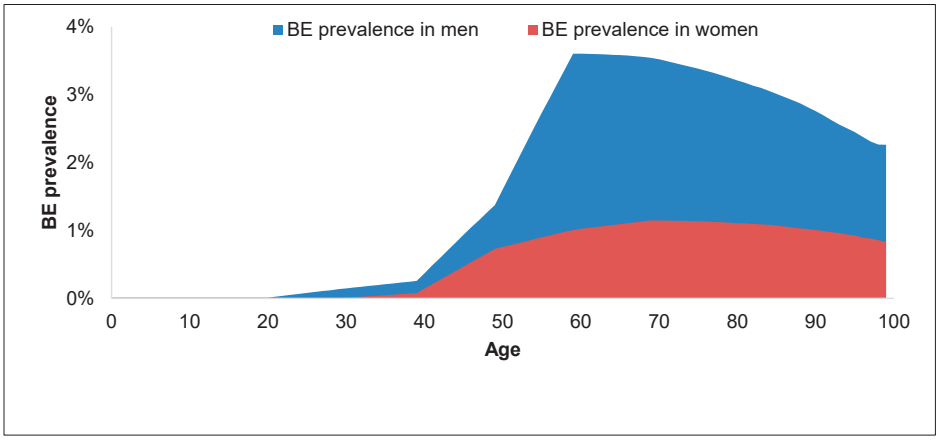

Figure 9. Barrett's esophagus (BE) prevalence in the absence of screening and surveillance (natural history) in the US population

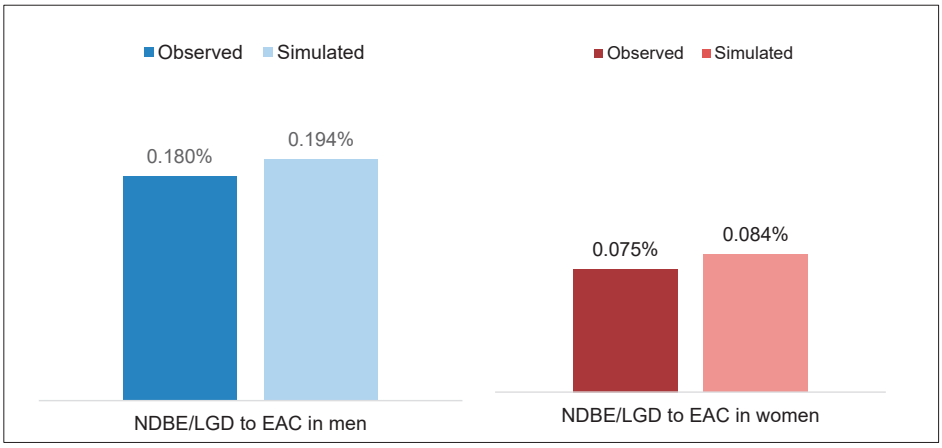

Figure 10. Annual progression rate from non-dysplastic Barrett's esophagus (NSBE) or low-grade dysplasia (LGD) towards esophageal adenocarcinoma (EAC) in men and women (US model)

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Summary

SUMMARY

Introduction

Esophageal adenocarcinoma (EAC) is the most common type of esophageal cancer in Western countries. EAC incidence and mortality have increased significantly in recent decades, which was particularly evident in high-income countries such as the US and the Netherlands. Various risk factors are associated with EAC, of which Barrett's esophagus (BE) is the most important one. Targeted screening of well-defined high-risk populations using an upper gastrointestinal (GI) endoscopy is recommended by several clinical practice guidelines in the world. Although GI endoscopy is considered to be a safe procedure, it carries a low risk of adverse events. Therefore, less invasive methods such as Cytosponge have been suggested for screening for BE and EAC.

In addition to screening, once BE is diagnosed, surveillance is recommended. BE surveillance can detect dysplasia or invasive carcinoma. Generally, in the absence of dysplasia, surveillance is recommended, while in the presence of dysplasia, either surveillance or endoscopic treatment is recommended. However, there are discrepancies in guidelines' recommendations, particularly in terms of management of BE patients with low-grade dysplasia (treatment or surveillance) and intervals for surveillance of BE patients without dysplasia. Furthermore, there are no recommended stopping ages for surveillance. One of the reasons for the discrepancies in guidelines around the world is the lack of clinical studies evaluating the effectiveness of surveillance. At this stage, because clinical guidelines recommend BE surveillance, randomized clinical trials are no longer deemed ethical. This is where decision modeling comes into play, which can generate a wealth of information about the benefits, harms, and costs of different screening and surveillance strategies.

In this thesis, we have used the Microsimulation Screening Analysis Esophageal Adenocarcinoma (MISCAN-EAC) model to conduct cost-effectiveness analyses on BE screening and surveillance strategies. In the first part, we have focused on screening for BE and evaluated the cost-effectiveness of using Cytosponge as a minimally invasive method to screen high-risk people for BE. Then we assessed the impact of including unrelated health effects and costs on our cost-effectiveness estimates. In the second part, we synthesized the literature on the cost-effectiveness of surveillance recommendations and evaluated several ways to further improve the cost-effectiveness of surveillance by optimizing several aspects of BE management, including optimal management of BE patients with LGD or no dysplasia, and stopping age of surveillance of non-dysplastic BE patients. Subsequently, we evaluated

how the lack of adherence to surveillance guidelines for BE patients can impact cost-effectiveness estimates.

Screening for Barrett's esophagus

In *Chapter* 2, we evaluated the cost-effectiveness of using Cytosponge with endoscopic confirmation for the screening of patients with gastroesophageal reflaux disease symptoms for BE and compared it with endoscopic screening only. Our findings showed that the Cytosponge screening strategy could reduce the cost of screening by almost 30% compared to conventional endoscopy. Our results suggest that an initial Cytosponge screening followed by endoscopic confirmation is a potentially cost-effective strategy for screening of a high-risk population for BE, depending on the cost of the Cytosponge test.

In *Chapter 3*, we used the results from both *Chapter 2* and a study on colorectal cancer (CRC) screening to estimate the impact of unrelated health outcomes and associated costs (e.g., future medical expenses or disutility unrelated to the condition under consideration) on cost-effectiveness for BE/EAC and CRC screening. When we considered the maximum adjustment for unrelated health outcomes and associated costs in the model, we found that the currently recommended CRC screening strategy in the US (colonoscopy every 10 years from age 50 through 75 years) was no longer cost effective, and the ICERs of Cytosponge and endoscopic screening strategies for BE nearly doubled.

Surveillance of Barrett's esophagus

In *Chapter 4*, we conducted a literature review on the cost-effectiveness of surveillance for gastrointestinal (GI) cancer of individuals with a variety of GI conditions. Although the reviewed studies differed in terms of setting, study population, surveillance strategies, and health outcomes, most suggested that at least some surveillance of individuals with GI precursor lesions may be cost effective. However, for most conditions, the evidence was scant, and the effectiveness basis was weak.

In *Chapters 5 and 6*, we conducted comparative modeling analysis to optimize the management of BE patients using independently developed models. Our findings showed that the optimal management strategy for patients with BE and LGD is endoscopic eradication therapy (EET), but only after LGD is confirmed by a repeat endoscopy at 2 months. For patients with non-dysplastic BE, the optimal strategy is surveillance using a 3-year interval for men and a 5-year interval for women. Concerning the optimal age of last surveillance of patients with non-dysplastic BE, our findings showed that it depended strongly on age, gender, and comorbidity status

of the patient. For men with non-dysplastic BE and no comorbidity, the optimal age of last surveillance was 81 years; however, it was earlier for patients with mild, moderate, and severe comorbidity: 80, 77, and 73 years, respectively. The ages of last surveillance were lower for women than men, but the same decreasing trend with increasing comorbidity was found. The optimal ages of last surveillance were 73, 73, and 69 years for women with mild, moderate, and severe comorbidity, respectively, compared to 75 years for women without comorbidity.

The surveillance intervals for BE patients in practice are often shorter than recommended in guidelines. In *Chapter 7*, we determined how this policy-practice gap affects the costs and benefits of BE surveillance. We used the MISCAN-EAC model and simulated a cohort of patients with BE in the Netherlands undergoing different management strategies observed in practice to compare the outcomes with those of the Dutch guideline strategy. This gap between policy and practice in BE surveillance intervals resulted in more than 100% higher costs for BE management for a less than 14% increase in quality-adjusted life-years gained per 1,000 BE patients.

Interpretation of findings

Although the findings of this thesis show that screening for BE and EAC, and surveillance of BE patients are cost effective, implementation decisions for a screening or surveillance program do not and should not only depend on cost-effectiveness estimates. To implement a screening or surveillance program, the following criteria should be met:

- There is evidence on the effectiveness of the program
- The benefits of the program outweigh the harms
- There is evidence on the cost-effectiveness of the program

For BE screening and surveillance, more clinical research is required to establish the effectiveness of these programs. In the meantime, the results of our modeling analyses provide guidance on further improvements to the management of BE.

Our analyses have been conducted for the US or Dutch setting; however, we believe that our results can be applied to other countries located in North-America or Western Europe. In these countries, the incidence of EAC has also increased substantially over the last decades, and EAC has become the primary type of esophageal cancer. Furthermore, in countries with a lower incidence of EAC, surveillance of BE patients may also be recommended in clinical practice. The expectation is that once people have BE, their risk of progression is not that different between countries. Therefore, our results regarding BE surveillance can also apply to those countries.

Conclusions and recommendations

Based on the results of the thesis, the following conclusions are derived:

- First-line screening of people with GERD symptoms using Cytosponge followed by endoscopic confirmation is a potentially cost-effective minimally invasive alternative to conventional endoscopic screening.
- Unrelated health effects and costs affect the cost-effectiveness estimates of GI cancer screening programs significantly.
- If effective, surveillance of patients with IBD, BE, colorectal adenomas, precancerous gastric lesions, neoplastic pancreatic cysts, and treated pancreatic cancer is generally cost effective. However, the evidence base for effectiveness is weak.
- For high-risk conditions such as treated pancreatic cancer, intensive surveillance (i.e., annually) may be cost effective, while for patients with intermediate-risk conditions (i.e., LGD BE, IBD, large adenomas, gastric metaplasia) or with low-risk conditions (i.e., small adenomas or non-dysplastic BE), less intensive surveillance (i.e., every 3-10 years) may be cost effective.
- From a cost-effectiveness perspective, the optimal management strategy for BE patients without dysplasia is endoscopic surveillance using a 3-year interval for men and a 5-year interval for women.
- The optimal age of last surveillance of BE patients without dysplasia varies by gender and comorbidity level of the patients. For non-dysplastic BE patients with no comorbidity, the optimal age of last surveillance is 81 years for men and 75 years for women. However, if they have comorbidities, the optimal stopping ages may be up to 8 years earlier for men and up to 6 years earlier for women.
- For BE patients with LGD, EET is the optimal management strategy for both male and female patients if LGD is confirmed by a repeat endoscopy at 2 months after the first endoscopy.
- Non-adherence of physicians to surveillance guidelines, resulting in earlier surveillance than recommended, may increase the cost of the BE surveillance by more than 100%, while its additional benefits are marginal.

Based on the results and conclusions of the thesis, we recommed the following:

- Low-cost and minimally invasive devices such as Cytosponge should be considered as a potential alternative to endoscopy for screening patients at high risk for BE and EAC.
- Future cost-effectiveness analyses on cancer prevention strategies should consider sensitivity analyses including unrelated health effects and costs, to evaluate the robustness of their cost-effectiveness estimates to these effects.
- Future research should be conducted to determine actual estimates for unrelated health effects to allow more robust determination of cost-effectiveness.

- Prospective (randomized) trials should be conducted on surveillance for GI cancers to confirm the effectiveness and cost-effectiveness of these interventions.
- Prior to the implementation of new devices for BE or EAC screening in clinical practice, more clinical studies and robust cost-effectiveness analyses should be performed.
- Male BE patients without dysplasia should receive surveillance every 3 years, while the surveillance interval for female BE patients without dysplasia can be extended to every 5 years.
- In addition to chronological age, the gender and comorbidity status of BE patients without dysplasia should be considered in clinical decisions about continuing surveillance.
- The possibility of stopping surveillance should be discussed in male non-dysplastic BE patients from age 73 and female non-dysplastic patients from age 69 years. The final decision on when to stop surveillance can be further personalized in this discussion.
- BE patients diagnosed with LGD, should receive a repeat endoscopy after 2 months: if LGD is confirmed at this exam, they should undergo EET followed by surveillance.
- Future research on BE management should focus on clinical studies to determine the long-term efficacy of EET for the treatment of BE patients to allow robust evaluation of optimal post-treatment surveillance of BE patients.
- Appropriate health policies should be developed to encourage physicians to adhere to BE surveillance guidelines to eliminate the policy-practice gap in BE management.

SAMENVATTING

Introductie

Oesofageaal adenocarcinoom (OAC) is het meest voorkomende type slokdarmkanker in Westerse landen. De incidentie en mortaliteit van OAC zijn de afgelopen decennia sterk toegenomen. Deze toename was vooral duidelijk te zien in landen met een hoog inkomen zoals de Verenigde Staten en Nederland. Verschillende risicofactoren worden geassocieerd met OAC, waarvan Barrett-slokdarm (BS) de belangrijkste is. Diverse richtlijnen en aanbevelingen wereldwijd adviseren dat individuen met een verhoogd risico op OAC, zoals mensen met reflux en obesitas, gescreend worden met gastro-intestinale (GI) endoscopie. Hoewel GI-endoscopie beschouwd wordt als een veilige procedure, bestaat er toch een klein risico op nadelige incidenten, zoals perforatie. Daarom wordt veel onderzoek verricht naar minder invasieve methodes voor screening, zoals bijvoorbeeld de Cytosponge.

Wanneer een patiënt met BS is gediagnosticeerd, wordt intensieve surveillance met GI-endoscopie aanbevolen. Tijdens die surveillance kan vervolgens dysplasie of invasief carcinoom gevonden worden, waarvoor (endoscopische) behandeling wordt aanbevolen. De aanbevelingen in de verschillende richtlijnen zijn echter niet eenduidig, en verschillen vooral met betrekking tot management van BS-patiënten met laaggradige dysplasie (behandeling of surveillance) en intervallen voor surveillance bij patiënten zonder dysplasie. Verder zijn er geen aanbevelingen met betrekking tot de leeftijd waarop surveillance eventueel beëindigd zou kunnen worden. Een van de redenen voor de verschillen in richtlijnen over de wereld is het gebrek aan klinische studies die de effectiviteit van surveillance evalueren. Doordat klinische richtlijnen BS-surveillance aanbevelen, worden gerandomiseerde klinische studies in deze fase ook niet meer ethisch geacht. Dit is een situatie waarin 'decision modeling' gebruikt kan worden om lacunes in informatie op te vullen, en voordelen, nadelen en kosten van verschillende screening- en surveillance strategieën door te rekenen.

In dit proefschrift, maken we gebruik van het decision model 'Microsimulation Screening Analysis Esophageal Adenocarcinoma (MISCAN-EAC)' om een kosteneffectiviteitsanalyse uit te voeren naar verschillende BS-screening en surveillance strategieën. In het eerste deel van dit proefschrift ligt de focus op screening naar BS en is de kosteneffectiviteit geëvalueerd van Cytosponge als minimaal invasieve methode voor het screenen van mensen met een hoog risico op BS. Vervolgens is de impact van niet-gerelateerde gezondheidseffecten en kosten op de kosteneffectiviteit van BS en darmkanker screening onderzocht. In het tweede deel, hebben we een overzicht gegeven van de literatuur over de kosteneffectiviteit van surveillance

aanbevelingen en verschillende manieren geëvalueerd om de kosteneffectiviteit van de surveillance te verbeteren door verschillende aspecten van BS management te optimaliseren, inclusief management van BS-patiënten zonder of met alleen laaggradige dysplasie, en de stopleeftijd van surveillance bij BS-patiënten zonder dysplasie. Tot slot hebben we de impact geschat die het gebrek aan naleving van surveillance richtlijnen heeft op de kosten en effecten van BS surveillance in Nederland.

Screening voor Barrett-slokdarm

In *Hoofdstuk 2*, hebben we de kosteneffectiviteit van twee screenmethoden voor BS geëvalueerd bij patiënten met gastro-oesofageale reflux: Cytosponge en conventionele endoscopische screening. Onze bevindingen lieten zien dat de kosten van Cytosponge screening bijna 30% lager zijn dan van conventionele endoscopie. Hierdoor is Cytosponge screening een potentieel kosteneffectieve screening strategie bij hoog risico individuen voor BS. Dit resultaat was wel sterk afhankelijk van de kosten van de Cytosponge test.

In *Hoofdstuk 3*, hebben we de impact van niet-gerelateerde gezondheidseffecten en bijbehorende kosten (bijvoorbeeld invaliditeit of toekomstige medische kosten die geen verband houden met de betreffende aandoening) op de kosteneffectiviteit van screening voor BS/OAC en colorectaal carcinoom (CRC) berekend. Hierbij maken we gebruik van de resultaten uit *Hoofdstuk 2* en van data uit een studie over CRC screening. Na het toepassen van een maximale correctie voor niet-gerelateerde gezondheidseffecten en bijbehorende kosten bleek de huidige aanbevolen CRC-screening strategie in de VS (coloscopie elke 10 jaar vanaf 50 tot 75 jaar) niet langer kosteneffectief. Ook de incrementele kosteneffectiviteitsratio van Cytosponge en endoscopische BS screening verdubbelde bijna.

Surveillance van Barrett-slokdarm

In *Hoofdstuk 4*, hebben we een literatuurstudie uitgevoerd naar de kosteneffectiviteit van surveillance voor GI kanker bij individuen met verschillende gastro-intestinale aandoeningen. Ondanks dat de gebruikte studies verschilde in setting, studiepopulatie, surveillance strategie en gezondheidsuitkomsten, duidden de meeste resultaten erop dat een bepaalde mate van surveillance bij individuen met gastro-intestinale voorlopers van kanker kosteneffectief kan zijn. Voor de meeste aandoeningen is het bewijs voor de potentiële effectiviteit van surveillance echter zeer zwak.

In *Hoofdstuk 5 en 6,* hebben we met verschillende onafhankelijk ontwikkelde modellen de beste behandelstrategie voor BS geëvalueerd. Onze resultaten laten zien dat de optimale behandelstrategie voor patiënten met BS met laaggradige dysplasie bestaat

uit endoscopische eradicatietherapie (EET). Dit is alleen het geval indien de laaggradige dysplasie door een surveillance endoscopie na 2 maanden is bevestigd. Voor mannelijke patiënten met BS zonder dysplasie is de optimale strategie endoscopische surveillance met een interval van 3 jaar. Voor vrouwen met BS zonder dysplasie is een 5-jaars interval optimaal. De optimale leeftijd voor de laatste surveillance bij patiënten met BS zonder dysplasie, is sterk afhankelijk van leeftijd, geslacht, en comorbiditeit. Voor mannen met BS zonder dysplasie en zonder comorbiditeit is de optimale leeftijd van de laatste surveillance 81 jaar. Bij patiënten met milde, gemiddelde en ernstige comorbiditeit ligt deze leeftijd lager: respectievelijk 80, 77 en 73 jaar. De optimale leeftijd voor de laatste surveillance ligt lager bij vrouwen dan bij mannen. De optimale leeftijd voor de laatste surveillance voor een vrouw zonder comorbiditeit is 75 jaar. De optimale leeftijd voor de laatste surveillance voor vrouwen met milde, gemiddelde en ernstige comorbiditeit is respectievelijk 73, 73 en 69 jaar.

De surveillance intervallen voor patiënten met BS zijn in de praktijk vaak korter dan aanbevolen in de richtlijnen. In *Hoofdstuk 7*, hebben we het effect van deze afwijkende intervallen op de kosten en op de mogelijke voordelen van BS-surveillance geanalyseerd. We hebben het 'MISCAN-EAC model' gebruikt om een cohort Nederlandse BS patiënten te simuleren welke verschillende screen/surveillance strategieën ondergingen die in de praktijk beschreven zijn. De uitkomsten hiervan zijn vergeleken met een simulatie waarbij de strategie uit de Nederlandse richtlijn werd aangehouden. De discrepantie tussen BS surveillance volgens de richtlijn en in de praktijk resulteerde in een toename van meer dan 100% van de kosten van BS management. Tegelijkertijd zagen we slechts een stijging in Quality Adjusted Life Years (QALY) van minder dan 14%.

Interpretatie van de resultaten

Hoewel de resultaten van dit onderzoek laten zien dat BS/OAC screening en surveillance kosteneffectief is, hangt een beslissing over het wel of niet implementeren van een dergelijk screen/surveillance programma niet alleen af van de kosteneffectiviteit. Alvorens een screening of surveillance programma te implementeren, moet aan volgende criteria worden voldaan:

- Er is bewijs voor de effectiviteit van screening/surveillance
- De voordelen van screening/surveillance wegen op tegen de nadelen
- De screening/surveillance is kosteneffectief

Op dit moment ontbreekt voor veel GI aandoeningen, inclusief BS, onomstotelijk bewijs van effectiviteit, maar wordt het niet langer ethisch geacht om dit in ge-

randomiseerde klinische studies te onderzoeken. In dit soort situaties geven de resultaten van onze modelanalyse sturing in het verbeteren van de aanpak van BS.

Onze analyses zijn uitgevoerd voor de Amerikaanse en Nederlandse setting. Onze resultaten zijn echter ook breder toepasbaar in andere landen in Noord-Amerika en West-Europa. In deze landen is de laatste decennia een vergelijkbare toename in OAC incidentie opgetreden en is OAC het voornaamste type slokdarmkanker geworden. Daarnaast zijn onze resultaten voor de surveillance van BS wellicht ook toepasbaar in landen met een lagere OAC incidentie, omdat we verwachten dat de lagere incidentie vooral wordt veroorzaakt door een lagere prevalentie van BS, maar dat het risico op progressie binnen BE patiënten wellicht niet verschilt tussen landen.

Conclusies en aanbevelingen

Naar aanleiding van de resultaten uit dit proefschrift, hebben we de volgende conclusies getrokken:

- Eerstelijns screening van mensen met gastro-oesofageale reflux symptomen middels Cytosponge is een potentieel kosteneffectief en minimaal invasief alternatief voor conventionele endoscopische screening.
- Niet-gerelateerde gezondheidseffecten en kosten hebben een significant effect op de potentiële kosteneffectiviteit van screening programma's voor gastrointestinale kankers.
- Surveillance van patiënten met IBD, BS, colorectale adenomen, non-maligne maaglaesies, neoplastische pancreascysten en behandeld pancreascarcinoom kan kosteneffectief zijn als de surveillance effectief is. Het bewijs voor deze effectiviteit is echter zwak.
- Intensieve surveillance (b.v. jaarlijks) kan voor mensen met hoog-risico aandoeningen, zoals bijvoorbeeld behandeld pancreascarcinoom, kosteneffectief zijn. Voor mensen met een gemiddeld-risico (d.w.z. laaggradige dysplasie BS, IBD, grote adenomen, gastrische metaplasie) of laag-risico aandoening (d.w.z. kleine adenomen, BS-patiënten zonder dysplasie) kan minder intensieve surveillance (elke 3-10 jaar) kosteneffectief zijn.
- Vanuit het perspectief van kosteneffectiviteit is de optimale managementstrategie voor BS-patiënten zonder dysplasie endoscopische surveillance met een interval van 3 jaar voor mannen en een interval van 5 jaar voor vrouwen.
- De optimale leeftijd voor de laatste surveillance van BS-patiënten zonder dysplasie verschilt naar geslacht en comorbiditeit. Voor BS-patiënten zonder comorbiditeit is de optimale leeftijd van laatste surveillance 81 jaar voor mannen en 75 jaar voor vrouwen. Echter, wanneer er sprake is van comorbiditeit ligt de

optimale eindleeftijd voor surveillance tot zo'n 8 jaar eerder voor mannen en 6 jaar eerder voor vrouwen.
- EET is de optimale managementstrategie voor mannen en vrouwen met BS met laaggradige dysplasie mits de laaggradige dysplasie bevestigd is in een surveillance endoscopie 2 maanden na initiële diagnose.
- Afwijken van de surveillance richtlijnen door artsen in de kliniek, met als gevolg eerdere surveillance dan aanbevolen, kan leiden tot een kostenverhoging van de BS-surveillance van meer dan 100%, terwijl de toename in voordelen minimaal is.

Aan de hand van de resultaten en conclusies van dit proefschrift, bevelen wij het volgende aan:
- Voordelige en minimaal invasieve screeningsmethoden zoals de Cytosponge moeten overwogen worden als een alternatief voor endoscopie screening van patiënten met een hoog risico op BS en OAC.
- Toekomstige kosteneffectiviteitsanalyses op het gebied van kankerpreventie moeten sensitiviteitanalysen opnemen op niet-gerelateerde gezondheidseffecten en bijbehorende kosten om de robuustheid van hun schattingen voor deze factoren te bepalen.
- Er is verder onderzoek nodig om de hoogte van niet-gerelateerde gezondheidseffecten en bijbehorende kosten vast te stellen voor een exactere bepaling van de kosteneffectiviteit van preventieve interventies.
- Er zijn prospectieve (gerandomiseerde) studies nodig om de effectiviteit en kosteneffectiviteit van surveillance voor GI kankers te bevestigen.
- Voordat er nieuwe BS/OAC screenmethoden worden geïmplementeerd moeten er meer klinische studies en robuuste kosteneffectiviteitsanalysen worden verricht.
- Mannen met BS zonder dysplasie moeten elke 3 jaar surveillance ondergaan terwijl dit interval voor vrouwen verlengd kan worden naar elke 5 jaar.
- Naast leeftijd moeten ook geslacht en comorbiditeit een rol spelen in de beslissing om surveillance bij BS patiënten zonder dysplasie te beëindigen of juist voort te zetten.
- Bij mannen met BS zonder dysplasie kan vanaf leeftijd 73 besproken worden om surveillance eventueel te beëindigen. Bij vrouwen ligt deze leeftijd op 69 jaar. Het definitieve besluit om surveillance te beëindigen moet in overleg tussen patiënt en arts genomen worden op basis van individuele voorkeuren van de patiënt.
- BS-patiënten met laaggradige dysplasie moeten na 2 maanden opnieuw een endoscopie ondergaan. Indien de aanwezigheid van laaggradige dysplasie tijdens deze endoscopie wordt bevestigd moet een EET verricht worden gevolgd door surveillance.

- De focus van toekomstig onderzoek m.b.t. BS-management moet zich richten op klinische studies naar de lange-termijn effectiviteit van EET als behandeling van BS patiënten. Hierna kan evaluatie van optimale post-EET surveillance voor BE patiënten geëvalueerd worden.
- De beroepsgroep van MDL-artsen en verzekeraars zouden samen (financiële) prikkels moeten ontwikkelen om artsen te stimuleren de BS-surveillance richtlijnen na te leven en zo de discrepantie tussen praktijk en richtlijnen te elimineren.

PUBLICATIONS

This thesis

Omidvari AH, Hazelton WD, Lauren BN, Naber SK, Lee M, Ali A, Seguin C, Kong CY, Richmond E, Rubenstein JH, Luebeck GH, Inadomi JM, Hur C, Lansdorp-Vogelaar I. The optimal age to stop endoscopic surveillance of Barrett's esophagus patients based on gender and comorbidity: a comparative cost-effectiveness analysis. *Submitted*.

Omidvari AH, Lansdorp-Vogelaar I, de Koning HJ, Meester RGS. Impact of unrelated health and cost outcomes on the cost-effectiveness of cancer screening; A model exploration. *Submitted.*

Omidvari AH, Roumans CAM, Naber SK, Kroep S, Wijnhoven BPL, Gaast AV, de Jonge PJ, Spaander MCW, Lansdorp-Vogelaar I. The Impact of the Policy-Practice Gap on Costs and Benefits of Barrett's Esophagus Management. *American Journal of Gastroenterology*. 2020;115(7):1026-35.

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Other Publications

Peterse EFP, Meester RGS, de Jonge L, **Omidvari AH**, Alarid-Escudero F, Knudsen AB, Zauber AG, Lansdorp-Vogelaar I. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. J Natl Cancer Inst. 2020.

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Rezayat SM, Boushehri SV, Salmanian B, **Omidvari AH**, Tarighat S, Esmaeili S, Sarkar S, Amirshahi N, Alyautdin RN, Orlova MA, Trushkov IV, Buchachenko AL, Liu KC, Kuznetsov DA. The porphyrin-fullerene nanoparticles to promote the ATP overproduction in myocardium: 25Mg2+-magnetic isotope effect. Eur J Med Chem. 2009;44(4):1554-69.

ABOUT THE AUTHOR

Amir Houshang Omidvari was born on September 17, 1985, in Esfahan, Iran. He completed his primary and secondary education in Esfahan in 2003. For higher education, he perused Medicine at Tehran University of Medical Sciences. Besides Medicine, he obtained a Master of Public Health (MPH). During his education, he received the title and prize as "Top National Medical Student" awarded by the Ministry of Health and Medical Education, and he ranked 4th in the Third National Medical Sciences Student Olympiad in Health System Management in Iran. After graduation in 2012, he worked with different healthcare organizations as a physician-researcher and a healthcare quality improvement consultant.

In 2013, he joined an International MPH Course in Health Development at the Royal Tropical Institute in Amsterdam. In the same period, Amir wrote a proposal on researching how various factors of the health system influence the choice of delivery method to address the increasing trend of the Cesarean Section rate. For this proposal, he was awarded a Welcome Trust Global Health Clinical Research Training Fellowship grant at Imperial College London. Subsequently, as a Research Fellow, he collaborated with the National Institute for Health and Care Excellence (NICE) in London until 2016.

In 2016, he was offered a scientific researcher/Ph.D. position at the Department of Public Health at the Erasmus MC University Medical Center Rotterdam. In this position, he investigated the cost-effectiveness of screening for and surveillance of Barrett's esophagus using a comparative modeling approach. The results of these investigations are included in this thesis.

PHD PORTFOLIO

PhD student	AmirHoushang Omidvari
Erasmus MC department	Public Health
Research School	Netherlands Institute for Health
PhD period	2016-2020
Promotor	Prof.dr. H.J. de Koning
Copromotor	Dr. I. Lansdorp-Vogelaar

	Year	Place	Workload (ECTS)
General and Specific NIHES courses in Erasmus MC			
Scientific Integrity	2016	Netherlands	0.3
Scientific writing	2018	Netherlands	3
Career support workshop	2018	Netherlands	0.5
Planning and evaluation of screening	2016	Netherlands	1.4
Health Economics	2017	Netherlands	0.7
Health Technology assessment	2017	Netherlands	5.0
Advanced topics in decision making in Medicine	2020	Netherlands	2.4
Using R for statistics in Medical Research	2020	Netherlands	1.3
Seminars and workshops			
Seminars at the department of Public Health, Erasmus MC	2016-2020	Netherlands	5.7
Society of medical decision making, hands-on model calibration in R	2018	Canada	0.1
Society of medical decision making, microsimulation modeling in R	2018	Canada	0.1
Presentations			
Presentations at Cancer Intervention and Surveillance Modeling Network (CISNET) meetings	2016-2020	USA	6.0
Presentations at internal research meetings at department of Public Health, Erasmus MC	2016-2020	Netherlands	1.2
Oral presentation, OESO, 14th World Conference Global perspectives in Esophageal diseases	2017	Switzerland	0.6
Oral presentation, 25th United European Gastroenterology Week	2017	Spain	0.6
Oral and poster presentations, 26th United European Gastroenterology Week	2018	Austria	1.2
Oral presentation, Society for Medical Decision Making Meeting	2018	Canada	0.6

Grant and review activities			
Grant proposal for ZonMw	2020		1.0
Value in Health	2016		0.2
OncoTarget	2016		0.2
Clinical and Experimental Gastroenterology	2018		0.2
American Journal of Gastroenterology	2020		0.2
Teaching			
Planning of Screening and Surveillance	2020	Netherlands	0.1

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