Published in final edited form as:

Med Decis Making. 2015 August ; 35(6): 726–733. doi:10.1177/0272989X14551640.

THE IMPACT OF UNCERTAINTY IN BARRETT'S ESOPHAGUS PROGRESSION RATES ON HYPOTHETICAL SCREENING AND TREATMENT DECISIONS

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Abstract

Background—Estimates for the annual progression rate from Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) vary widely. In this explorative study, we quantified how this uncertainty impacts the estimates of effectiveness and efficiency of screening and treatment for EAC.

Design—We developed three versions of the UW/MISCAN-EAC model. The models differed with respect to the annual progression rate from BE to EAC (0.12% or 0.42%) and the possibility of spontaneous regression of dysplasia (yes or no). All versions of the model were calibrated to the observed Surveillance, Epidemiology, and End Results (SEER) esophageal cancer incidence rates from 1998 to 2009. To identify the impact of natural history we estimated the incidence and deaths prevented as well as numbers needed to screen (NNS) and treat (NNT) of a one-time perfect screening at age 65 that detected all prevalent BE cases, followed by a perfect treatment intervention.

Results—Assuming a perfect screening and treatment intervention for all BE patients, the maximum EAC mortality reduction (64–66%) and the NNS per death prevented (470–510) were similar across the three model versions. However, three times more people needed to be treated to prevent one death (24 vs. 8) in the 0.12% regression model compared to the 0.42% progression model. Restricting treatment to those with dysplasia or only high grade dysplasia (HGD) resulted in smaller differences in NNT (2–3 to prevent one EAC case) but wider variation in effectiveness (mortality reduction of 15–24%).

Conclusion—The uncertainty in the natural history of the BE to EAC sequence influenced the estimates of effectiveness and efficiency of BE screening and treatment considerably. This uncertainty could seriously hamper decision making about implementing BE screening and treatment interventions.

Keywords

Barrett's esophagus; esophageal adenocarcinoma; population-based modeling; progression rates; incidence; screening; prevalence

Introduction

Over the past four decades, the incidence of esophageal adenocarcinoma (EAC) has rapidly increased. Barrett's esophagus (BE) is a precursor of EAC [1]. In BE, normal cells of the esophagus are replaced by intestinal metaplasia, which may progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD) or adenocarcinoma [2]. Despite this concern, little is known about the prevalence of BE in the population and the time course of progression to EAC. There are several unknown crucial characteristics of the epidemiology of BE to EAC sequence in the population that may have large influences on the estimates of effectiveness and efficiency of BE screening and treatment. First, estimates for the annual progression rate from BE to EAC vary widely in the literature within a range of 0.07%–3.6% [3–5]. Until recently, a progression rate of 0.42% annual progression was assumed most plausible [6, 7]. However, several large recently published population-based studies suggest that the progression rate is actually much lower (~0.12%) [8–10]. Selection bias, publication bias, study size and differences in follow up years and cohort characteristics all contribute to the difficulty of comparing and validating these estimates. Secondly, there are large differences in the estimates of the prevalence of BE in the population (0.34%–25%) [11]. Differences in BE definitions over time and between countries are an important bottleneck for obtaining consistent estimates. Thirdly, there are indications that BE with dysplasia might regress. Several studies have shown disappearance of dysplasia in BE surveillance cohorts [6, 12]. Regression has also been demonstrated in well-conducted studies with expert pathologists [13]. Disappearance perceived in subsequent biopsies could be the result misclassification because of subjective interpretation of LGD and HGD by pathologists or of sampling errors.

With the introduction of endoscopic mucosal resection and radiofrequency ablation, endoscopic therapy for BE with HGD is being increasingly viewed as first-line treatment [14]. However, the uncertainty in the natural history of EAC may have large influences on the expected effectiveness and efficiency of such interventions.

In this study we used micro simulation modeling to explore how uncertainty in the risk of EAC development in patients with BE impacts the expected effectiveness and efficiency of screening and treatment intervention.

Methods

The UW/MISCAN-EAC model

The UW/MISCAN-EAC model was developed as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). A detailed description can be found in Appendix A. In brief, the model simulates the life histories of a large population of individuals from birth to death. Part of the population has symptomatic gastro-esophageal reflux disease (GERD) which is defined as weekly heartburn and/or acid regurgitation.

These individuals are at increased risk to develop BE. However, BE can also develop in the absence of GERD symptoms (RR = 6.0 GERD to BE compared to non-GERD to BE, resulting from the assumption that 60% of the BE patients have symptomatic GERD [5]). Depending on age, sex and baseline individual risk, low-grade dysplasia may develop from non-dysplastic (ND) BE, which may later progress to high-grade dysplasia. Although most individuals with BE will never develop cancer, malignant cells can arise from HGD, transforming to localized EAC which can progress sequentially into regional and distant EAC. In each cancer stage there is a probability of the cancer diagnosis due to the development of symptoms versus staying asymptomatic and progressing undetected into the next stage. Persons may die of other causes at any time during their lifetime (figure 1).

Model quantification

In order to quantify the effect of different natural history assumptions we developed three different model versions: low-progression model, high-progression model, and regression model. The natural history assumption on progression from BE to EAC is different in each model. Our *low-progression model* considers a low progression rate from BE (ND+LGD) at age 65 to EAC (0.12% annually within a five-year follow up), consistent with recently published studies [15–17]. The *high-progression model* considers a higher progression rate (0.42% annually), consistent with published reviews [18–20]. These two model structures include only progressive transitions. The *regression model* additionally includes the possibility to regress from HGD to LGD and from LGD to no dysplasia and considers a low progression rate (0.12% annually from BE (ND+LGD) at age 65 to EAC within a five-year follow up). These main contrasts in model structures and the annual progression rate calibration target between the three models versions are shown in Table 1. In addition to the varying progression rates from BE to EAC, all models were calibrated to the age-specific esophageal cancer incidence as observed in the Surveillance, Epidemiology, and End Results (SEER) Program for 1998–2009 (without assuming secular trends), the amount of LGD and HGD in the 60–65 year old BE population and the estimated average sojourn time from undetected to detected EAC for the total EAC population. An overview of all calibration targets and the resulting natural history characteristics for each model version can be found in the appendix (table A2). The BE prevalence was optimized in each model in order to match the EAC incidence while accounting for the differences in progression rates and model structure assumptions.

Perfect screening and perfect treatment intervention strategies

A hypothetical perfect screening and treatment intervention was introduced in the three alternative models. We modeled perfect screening and treatment interventions in order to study the effect of the alternative models independently from limitations in test performance and treatment outcomes. The cohort was assumed to be screened with a perfect test (i.e. sensitivity and specificity for BE and neoplasia of 100%, irrespective of symptomatic and non-symptomatic patients) at age 65. All preclinical cancers were detected and treated depending on the stage of EAC at the time of detection. After screening one of three perfect treatment strategies was applied for people with BE. Perfect treatment is defined as an intervention that ensures BE is effectively removed and EAC will not develop during the lifetime of the treated patient. All residual cases of EAC will therefore develop in patients

without BE at the time of screening who developed BE and EAC within 15 years after that screening. In the first treatment strategy all BE patients with or without dysplasia were treated (*BE treatment*). The second treatment strategy provided no treatment for non-dysplastic BE patients, but only for LGD and HGD patients (*dysplasia treatment*). In the final treatment strategy only HGD patients receive treatment (*HGD treatment*).

Outcomes

We compared model variants on the outcomes of BE prevalence and EAC incidence by age group. The effectiveness of BE screening and treatment for all three treatment strategies was compared by the reduction in EAC incidence and EAC mortality. The efficiency of screening and treatment was examined by comparison of the number of screenings and treatments required, and number needed to screen and treat to prevent one EAC case of death. A sensitivity analysis was performed to compare the impact of hypothetical interventions in different age groups.

This study was funded by the National Cancer Institute.

Results

The BE prevalence was highest in the model with regression [3.3% for age 60–65] followed by low progression [2.9% for age 60–65] and high progression [1.3% for age 60–65] (figure 2).

The differences in EAC incidence and mortality reduction from screening and treating all BE were negligible between the three models (table 2) but were more pronounced for dysplasia and HGD treatment. The maximum clinical incidence reduction was greatest in the strategy incorporating treatment of all patients with BE [58%–62%], followed by dysplasia treatment [26%–42%] and HGD treatment [4%–13%].

Differences in the EAC development in the untreated BE population directly reflect differences in the progression rates between the models. In case of treatment limited to dysplasia 7.5% of the ND BE developed into EAC in the high-progression model, whereas in the low progression and the regression models less than 3.5% developed into EAC (figure 3).

The number of treatments differ in each model because this is influenced by the variation in BE prevalence. As a consequence, the number of treatments required to treat all patients with BE is 3-fold higher in the regression model compared with the high-progression model, which requires the fewest number of treatments. Given this variation in number of treatments and the minor differences in effectiveness of screening and treatment, large differences are seen in the numbers needed to treat to prevent one EAC case (NNT/case) and numbers needed to treat to prevent one EAC death (NNT/death). The all-BE treatment strategy is most efficient in the high-progression model (NNT/death is 8.5), followed by the low-progression model (NNT/death is 19.1) and the regression model (NNT/death is 24.3) (figure 4). Almost no differences in the efficiency of HGD treatment are found between the three models.

Additional sensitivity analyses were performed on the age of initial screening and treatment. In the case of treatment of all BE the incidence and mortality reductions were inversely associated with the initial age of screening; BE treatment in older age groups was less effective. Differences between the models in mortality reduction ranged from 5% to 34% for intervention age 75 compared to intervention age 55. The differences between the models in NNT/death ranged from 2.1- to 2.9- fold for the different intervention ages (appendix, table A3).

Discussion

This study demonstrates that the current uncertainty surrounding BE progression is unlikely to lead to large differences in estimates of the effectiveness of BE screening and treatment in the strategy of treatment for all patients with BE. However, if treatment is restricted to BE patients with dysplasia, treatment effectiveness varies widely and is dependent on BE progression assumptions. Furthermore, the resources required to gain that effectiveness vary considerably when treating all BE: screening and treating of all BE requires up to 3 times more patients to be treated per death prevented in a situation with regression compared to a situation with high progression. Finally, the smaller number of patients treated when limiting therapy to patients with dysplasia results in smaller differences in the efficiency of treatment between the models when following the patients for a fifteen-year period.

BE prevalence differs considerably between the models (1%–3% at age 60–65). This difference is explained by differences in assumptions about BE progression. In case of low progression, a higher BE prevalence is needed compared with high progression, in order to calibrate to the same SEER-based cancer incidence. Because of this dependency the real progression rate parameter could be estimated if the real BE prevalence in the population would be known, and vice versa. Unfortunately, estimates for both parameters differ widely and estimates in all three models lie well within the plausible range published in the literature. Based on published data the estimated plausible range for BE prevalence is assumed to be within 1.6–6.8% [21], which overlaps our simulation estimates. Our study shows that with a high BE prevalence there are more treatments required to obtain the same effectiveness of treatment in terms of cancer and death reduction.

Screening and treatment interventions for all BE patients or patients with dysplasia result in a larger reduction in EAC incidence than EAC mortality due to the risk of death from competing causes. When performing screening and limiting treatment to HGD patients just a small proportion of cancer incidence and deaths is reduced because of HGD treatment. Hence, a large proportion of death reduction from this strategy is due to early detection of malignancies at screening.

We focused on the potential effectiveness of treatment using simulation modeling of a hypothetical perfect intervention. We have used the approach that mirrors the maximal clinical incidence reduction (MCLIR)[1]; this theoretical approach identifies how and where differences in model structures manifest in their results. Here the estimated incidence and mortality reductions correspond to the maximum possible clinical benefit in EAC incidence achievable by screening and treatment of BE lesions. We did not implement a “real-life”

intervention in our model because there is a paucity of data on treatment results of LGD and BE. Our point was merely to illustrate the impact of uncertainty in natural history on screening and treatment of BE in general. However, our study results can be generalized to (cost-) effectiveness of real-life interventions: the relative impact of the differences between model structures in this study can be directly translated to relative differences in effectiveness of real-life interventions.

Previous research found that both the progression rate from BE to EAC and the BE prevalence in the population were among the variables causing at least 10% variation in the incremental cost-effectiveness ratio [2], while our studies suggest that up to 70% variation in the effectiveness of treatment interventions may be due to differences in progression assumptions and BE prevalence. Two large cost-effectiveness studies on treatment of BE have been published [3] [4]. Both studies concluded cost-effective surveillance and treatment scenarios are present for treatment of HGD, but treatment of ND and LGD BE is far more expensive and not cost-effective. When comparing differences in NNT/death and NNS/death between our models with literature for other screening programs, we found that outcomes for efficiency of screening in terms of numbers needed to invite (NNI) are reported for breast cancer screening. A recent meta-analysis reported 1904 NNI/death, with a large 95% confidence interval between 929 and 6378 NNI/death [5]. Thus, the reported variation of NNI/death within the 95% confidence interval holds a 7-fold variation, while our results reported variation between models up to 3-fold for the NNT/death. Modeling studies reporting the influence of the uncertainty of input parameters and model structures on cancer screening also showed considerable differences for effectiveness of screening. The study that compared various models with different structures and input assumptions for the simulation of colonoscopy screening showed that the MCLIR after disease removal at age 65–80 varied from 51% to 90% between models [6], implying a difference of 80% in incidence reduction between models. In our study the largest differences were seen in case of HGD treatment resulting in a difference of 230% in incidence reduction. A recent paper investigated the benefits and harms of computed tomography lung cancer screening strategies by five comparative simulation models. Differences in modeling results for the number of persons who were no longer dying of lung cancer varied between 177 and 863 per 100,000 individuals [7], which is a 5-fold difference in mortality reduction. Our study showed a maximum of 1.6-fold difference between the mortality reduction of the models.

This study has three limitations that are noteworthy. First, for each model additional parameters apart from the BE incidence must be recalibrated. Therefore, some differences in model outcomes might be due to slightly different estimates in parameters such as preclinical sojourn times and the dysplastic proportion in the BE population. When calibrating the high-progression model the model compensates by shortening the sojourn times. This resulted in a high percentage of dysplastic patients in the total BE population. Thus, it was not feasible to reach the main calibration target of a high progression in combination with a low proportion of LGD in BE (calibration target of 9%). Consequently optimization of the high-progression model resulted in a high proportion of LGD patients (17%). However, most differences in these other parameters are small (appendix table A2) and therefore not likely to greatly influence results.

Second, this analysis is restricted to white males. We focused on this group because the majority of published data are derived from this group and including nonwhites and females to the analyses would add more uncertainty to the models. Third, for this analysis we have focused on differing progression rates from BE to EAC and have not accounted for other changes and uncertainties in variables, such as secular trend assumptions and assumptions concerning the preclinical sojourn times. Incorporating a secular trend could have effects on different parts of the model. It is not known whether these effects would be totally or partly caused by an increase in BE incidence or in a higher progression towards EAC in the BE population; thus, we decided not to model these effects. Since the preclinical to clinical sojourn times is a small part of the total BE to EAC sojourn time sequence the impact of varying the preclinical sojourn time is expected to be small compared to the current analysis.

Our analysis highlights the importance of research to diminish the uncertainty in BE prevalence and progression rate to malignancy in BE patients. Because these variables are closely correlated a reliable estimate of either would substantially reduce current uncertainty. Identification of the progression rate to malignancy using a Barrett's surveillance cohort to observe cancer development is difficult. Therefore we suggest a study to accurately estimate BE prevalence since this type of study does not require long-term follow-up and would be able to provide an answer to this important question in a shorter time frame.

In conclusion, our analysis illustrates that there is great uncertainty in the efficiency of treatment for Barrett's esophagus despite small variation in the effectiveness of therapy. This is due to the large variation in the numbers needed to treat based on the differing progression rates. Limiting treatment to patients with BE and HGD reduces the variability induced by uncertainty in progression. Estimates of the effectiveness and efficiency of BE screening and treatment will be highly speculative until this uncertainty is resolved.

Acknowledgments

We would like to thank the CISNET consortium.

Financial Support:

(U01 CA152926)¹

Abbreviations

BE	Barrett's esophagus
EAC	esophageal adenocarcinoma
HGD	high-grade dysplasia
LGD	low-grade dysplasia
ND	no dysplasia

¹Financial support for this study was provided entirely by a grant from the National Cancer Institute. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

GERD gastro-esophageal reflux disease

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Appendix

MODEL OVERVIEW

The UW/MISCAN-EAC model is a semi-Markov microsimulation model for esophageal adenocarcinoma (EAC). The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the UW/MISCAN-EAC model generates durations in states. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to similar results as a Markov model with yearly transition probabilities. The advantage of the MISCAN approach is that durations in a certain state

need not necessarily 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, Barrett's incidence, and transitions from one state of disease to another.

The basic structure of the UW/MISCAN-EAC model is separated in three main parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.

Demography Part

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

Natural history part

The natural history part of UW/MISCAN-EAC simulates the development of EAC in the population. To vary the underlying structural assumptions of the model, we developed two options for the natural history part, the first one being the *progression* model and the second one being the *regression* model. The current models used in this paper do not include an increasing secular trend for the EAC increasing incidence over time. Because the focus of this paper is on effectiveness and efficiency, we decided that it could be best compared with the simulation of a cohort excluding secular trend effects before and after 1998–2009.

Progression model—We assume that EAC develops through precursor Barrett's Esophagus (BE). For each individual in the simulated population a personal risk index is generated. A minority of the population has symptomatic gastro-esophageal reflux disease (GERD), giving them a higher risk of developing BE during their lifetime. The development of BE is generated according to this personal risk index and an age specific incidence of onset. 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 (LGD) and High Grade dysplasia (HGD). From High Grade dysplasia, malignant cells can arise that can transform from this stage to preclinical localized EAC, which can sequentially progress into Regional and Distant preclinical EAC. In each of these three states, there is a probability of the cancer being diagnosed. The sojourn times between these described states are exponentially distributed, and in some states (BE ND, BE LGD and BE HGD) age dependent. Because most sojourn times extend beyond the demography-generated age of death from other causes, only a small proportion of the population develop EAC from BE. The survival after clinical diagnosis depends on the cancer stage, and the year of diagnosis (period effect reflecting survival improvement over time).

Regression model—In the regression model an additional possibility to transit between states is added. BE still starts with no dysplasia, thereafter LGD and HGD can develop. From HGD, malignant cells can arise with can transform this stage to preclinical localized EAC. In the regression model, however, there is a possibility that regression from HGD to LGD and from LGD to ND occurs. The probability to regress or progress is dependent on a transition rate matrix, and is therefore also influenced by the sojourn time. The probability of regression, progression and the according sojourn times can be calculated as follow:

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 or HGD, r : regress, p : progress, R : rate

Screening part

The development of EAC can be interrupted by screening. Screening can detect BE, the dysplasia states and preclinical cancers. BE and dysplasia can be removed using treatment. Usually the cancers will be found in an earlier stage than with clinical diagnosis. In this way screening reduces EAC incidence or EAC death.

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 of other causes than EAC, creating a life history without EAC. Subsequently the onset of BE is simulated for that individual. For most individuals no dysplasia is generated. In the case of progressive BE, dysplasia may develop and HGD transforms into a malignant carcinoma, causing symptoms and eventually resulting in death from EAC. When a person dies from EAC before he dies from other causes, his death age is adjusted accordingly.

After the life history of a person is adjusted for EAC, the history can also be adjusted for the effects of screening. During screening BE with or without dysplasia is removed by a hypothetical treatment. This results in a combined life history for EAC in the presence of screening. BE is removed at the time of screening and this individual does not develop cancer because the precursor has been removed. Therefore the person dies from other causes and the effect of screening is the difference in life-years in between the simulation without screening and the simulation with screening.

MODEL QUANTIFICATION

For this analysis we developed three different models varying in model structure and natural history assumptions.

DEMOGRAPHY PARAMETERS

There are two types of demography parameters: birth tables and life tables. The life tables were derived from the life tables published by the National Center for Health Statistics [1].

NATURAL HISTORY PARAMETERS

The parameters for the natural history are directly estimated from data or fit to reference data, based on expert opinion, or calibrated to fit the model. The average prevalence rate of symptomatic GERD is around 20% [2–5]; therefore we have a fixed input parameter for which 20% of the total population suffers from symptomatic GERD.

The onset of BE was fitted per age group, we call this an optimized parameter. The parameter is relaxed and its final value results from the optimal calibrated model. Asymptomatic BE (no GERD symptoms) is a calibration target of the model, calibrated to be 40% of the total prevalence of BE in the model [6, 7] .

The exponential scale parameter for the time from a preclinical state to clinical detection is restricted within the range of 2–9 years for each individual [8, 9]. When evaluating the whole simulated population, the average time from onset of preclinical cancer to the diagnosis of clinical EAC is calibrated to be within the range of 4 – 5 years, which is a calibration target of the model.

Using published studies we estimated the proportion of LGD and HGD in a BE population (table A1), being 2.2% HGD 9.4% LGD, and 88.4% non-dysplastic BE, which were used as calibration targets in the models. Furthermore, the EAC incidence is calibrated to the total SEER esophageal cancer incidence rates from 1998 to 2009.

There are two assumptions that differ between the models. The first assumption differs in the natural history parameter of the yearly progression rate from BE (ND+LGD) to EAC, which was assumed 0.12% or 0.42% and set as a different calibration target in the models. The second assumption differs in the used model structure for the possibility to regress. We optimized the regression probabilities for the transitions from LGD to ND and from HGD to LGD to fit the calibration targets.

In the calibration process, all input assumptions are taken into account. Table A2 contains a summary of the model input, calibration values and its data sources, and the calibration results for the natural history. The BE prevalence is not specified and therefore allowed to optimize for each model, which results in varying estimations. Other optimized parameters are the exponential sojourn times and in case of regression, the regression probabilities.

SCREEN PARAMETERS

We have used a one-time perfect screening examination at age 65 in the simulation, in which every person is correctly categorized as having no BE, BE, LGD, HGD and EAC. Perfect treatment is modeled to manage patients depending on their treatment strategy. The first strategy includes treatment for all patients in whom BE is diagnosed with and without dysplasia; the second strategy treats only dysplastic patients (LGD and HGD); the final strategy treats only patients with high-grade dysplasia. When treatment is performed it is

assumed the person will never develop BE again and will die of other causes than EAC. The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage.

CALIBRATION PROCESS

The UW/MISCAN-EAC model is calibrated to fit several calibration targets in order to optimize the unknown natural history parameters. For all three models, the incidence of BE per 10-year age group, the sojourn times in BE ND and the sojourn times in the preclinical states have to be optimized. In the progression models the sojourn times in LGD and HGD must also be included in the parameters to optimize, where in the regression model the transition rates of regression and progression in LGD and HGD must be included.

During the optimization the Pearson chi-square Goodness of fit function was minimized on the basis of the number of observed and expected rates. The deviation of each of the four main calibration targets (SEER-EAC incidence rates per age group, annual progression rate from BE to EAC, proportions of dysplasia and average preclinical sojourn time) were summed to calculate the overall Goodness of fit of the model given a certain set of parameters. The search for new parameters was performed following the Nelder-Mead simplex method.

The regression and progression transition probabilities are highly correlated with the progression rate from BE towards EAC, which hampers the ability to identify these parameters. Although there are a large number of feasible parameters solutions, there is one optimal parameter solution resulting in the best fit which can be found in the calibration process [10].

VALIDATION OF MORTALITY RATES

The model-projected EAC mortality rates are estimated using incidence-based mortality rates by cancer stage reported in SEER. A direct comparison of model-projected EAC mortality and EAC mortality in SEER is not possible, because SEER does not distinguish mortality from EAC vs mortality from esophageal squamous cell carcinoma. Even if this distinction were possible, the appropriateness of stage migration effects of screening could not be validated with SEER data: SEER does not distinguish method of diagnosis and the estimated percentage of EAC diagnosed by screening or surveillance (7.6%) is too small to test a hypothesis of stage migration.

Figure 1.

Graphical representation of the UW/MISCAN-EAC model RR = Relative Risk

Figure 2.

A | EAC incidence for each alternative model compared to the background EAC incidence from SEER for each age group

B | The BE prevalence for each alternative model for each age group

Figure 3.
EAC development in the untreated BE population in the three models after removal of the dysplasia treatment cases and HGD treatment cases

Figure 4.
Representation of the number needed to treat to prevent one EAC death for each model in each treatment strategy

Figure A1.

The BE prevalence for each alternative model for each age group. Figure A shows the BE prevalence for non-dysplastic and dysplastic patients, figure B shows the BE prevalence including only dysplasia patients, figure C shows the BE prevalence of the high grade dysplastic group only.

Table 1

Contrasting assumptions and calibration targets for three versions of the UW/MISCAN-EAC model

	Low-progression model	High-progression model	Regression model
Contrast in Model structure	Only progression between states	Only progression between states	Regression in dysplasia states possible
Contrast in Calibration Target	0.12% annual progression rate BE to EAC	0.42% annual progression rate BE to EAC	0.12% annual progression rate BE to EAC

Table 2

Effectiveness and efficiency, age 65–80

Incidence reduction		BE treatment		Dysplasia treatment		HGD treatment	
low progression		62%		42%		13%	
high progression		58%		36%		4%	
regression		58%		26%		8%	
Mortality reduction							
low progression		66%		51%		24%	
high progression		64%		46%		15%	
regression		63%		36%		19%	
Screening efficiency		NNS/case	NNS/death	NNS/case	NNS/death	NNS/case	NNS/death
low progression		470	628	692	822	2,273	1,739
high progression		510	663	827	925	8,389	2,748
regression		503	667	1,139	1,171	3,842	2,274
Treatment efficiency		NNT/case	NNT/death	NNT/case	NNT/death	NNT/case	NNT/death
low progression		14.3	19.1	2.4	2.8	1.8	1.4
high progression		6.5	8.5	2.3	2.5	3.0	1.0
regression		18.3	24.3	5.2	5.3	2.3	1.3

Number needed to screen to prevent one case: NNS/case, Number needed to screen to prevent one death: NNS/death, Number needed to treat: NNT

Table A1

Estimation of LGD and HGD prevalence within the BE population at age 60–65

Author	Sample size	LGD prevalence	Rate	Sample Size	HGD prevalence	Rate
Bonelli [11]	205	18		205	0	
Clark, Ireland [12]	70	8		70	3	
Conio [13]	177	4		177	3	
GOSPE [7]	69	6		69	1	
Hirota, Loughney [14]	63	5		63	1	
Katz, Rothstein [15]	102	5		-	-	
Rex, Cummings [16]	65	3		65	0	
Sharma, Weston [17]	177	17		177	3	
Sharma, Morales [18]	59	5		59	0	
Spechler, Robbins [19]	115	4		-	-	
Weston, Krmpotich [20]	60	15		60	0	
Weston, Krmpotich [21]	108	20		108	8	
Weston, Badr [22]	99	18		99	6	
Total	1369	128	9.35%	1152	25	2.17%

Table A2
Natural history assumptions and results for the three versions of the UW/MISCANEC model

Model parameter/value	Value low-progression model	Value high-progression model	Value Regression model	Source	Parameter characteristic*
Symptomatic GERD prevalence	20% of the total population	20% of the total population	20% of the total population	Prevalence studies [2–5]	Fixed input
BE from symptomatic GERD population	60% of total BE is from symptomatic GERD population	60% of total BE is from symptomatic GERD population	60% of total BE is from symptomatic GERD population	Published estimates [6, 7]	Fixed Input
Sojourn times preclinical cancer (years)	2–9	2–9	2–9	Published estimates [8, 9]	Fixed Input
BE prevalence age 60–64 [†]	2.9%	1.3%	3.3%	Optimized BE onset per 10 year age group	Optimized parameter
Percent of LGD in total BE at age 60–65	8.3%	17.3%	10.8%	Derived from published studies (table A1)	Calibration target: 9.4%
Percent of HGD in total BE at age 60–65	2.5%	2.6%	1.6%	Derived from published studies (table A1)	Calibration target: 2.2%
Annual progression rate from BE (ND+LGD) to EAC	0.12%	0.42%	0.12%	Published meta-analysis [23–28] <i>Definition: 5 year follow up from age 65</i>	Calibration target: 0.12%, 0.42% and 0.12% respectively
Average time BE to LGD (years) [‡]	16.0	12.2	10.7	Optimized exponential sojourn times: BE to LGD	Optimized parameter
Average time LGD to HGD (years)	6.4	6.0	2.7	LGD to HGD	
Average time HGD to Preclinical Localized (years)	2.7	1.2	1.8	HGD to Preclinical Localized	
Average sojourn time to preclinical cancer (years)	4.7	4.8	4.7	Published estimates [8, 9]	Calibration target: 4–5 years
Regression transition probability P(LGD to ND)	n.a.	n.a.	76% 15%	Optimized regression transition probability	Optimized parameter

Model parameter/value	Value low- progression model	Value high- progression model	Value Regression model	Source	Parameter characteristic [*]
P(HGD to LGD)					

n.a.: Not applicable;

^{*} Fixed input: the parameter is defined as a fixed input of the model, Optimized parameter: the parameter is relaxed and is optimized during calibration of the model, the value is a results of the model;
Calibration target: the model is calibrated to fit the fixed calibration targets as good as possible;

[†] Figure A1 shows the BE and dysplasia prevalence's of the models more specifically per age group;

[‡] The average duration between one state to the next state.

Table A3

Effectiveness and efficiency for varying intervention ages in case of BE treatment

	age 55–70	age 65–80	age 75–90
Incidence reduction			
low progression	71%	62%	47%
high progression	67%	58%	43%
regression	65%	58%	47%
Mortality reduction			
low progression	70%	66%	46%
high progression	66%	64%	43%
regression	69%	63%	58%
Screening efficiency			
	NNS/case	NNS/death	NNS/case
low progression	590	869	470
high progression	605	883	510
regression	633	851	503
Treatment efficiency			
	NNT/case	NNT/death	NNT/case
low progression	14.2	21.0	14.3
high progression	6.5	9.4	6.5
regression	16.4	22.1	18.3

Number needed to screen to prevent one case: NNS/case, Number needed to screen to prevent one death: NNS/death, Number needed to treat: NNT