Supporting Information

# Appendix: Model profiles and endoscopic ablation modeling

Esophageal adenocarcinoma (EAC) is an important cancer to model because EAC incidence has increased over five-fold in the U.S. since 1975, risk factors driving these increasing trends are not well understood, current surveillance methods identify only a small fraction of individuals that later become EAC incident cases, and survival of EAC incident cases is generally very poor.

In brief, each model computes the life histories of a population of hypothetical individuals from birth (UW-MISCAN and FHCRC) or age 20 (MGH) to death and has a natural history component that tracks the progression of esophageal disease or precursor states preceding adenocarcinoma. All three models include the following health states: healthy, GERD symptoms, BE without dysplasia, BE with dysplasia, preclinical cancer, clinically diagnosed cancer, and death. The UW-MISCAN and MGH models further categorize dysplasia in BE into low-grade dysplasia (LGD) and high-grade dysplasia (HGD). In the current study, all EAC models followed a BE cohort. EAC would be diagnosed when no interventions are assumed if symptoms prompted endoscopic evaluation (*clinical EAC*). However, natural history can be interrupted by surveillance and/or endoscopic ablative therapy. These interventions allow for early detection on cancer, which potentially improves the survival of patients when diagnosed in an early malignant state.

For this study, the EAC CISNET models have been extended to predict the effectiveness and efficiency of surveillance and treatment for diagnosed BE patients, focusing on the impact of endoscopic ablative treatment on long term EAC mortality, with risk stratification by gender, age and dysplastic grade. Additionally the models evaluate the efficiency of the therapy in terms on surveillance endoscopies and treatments required.

The modeling approach for calculating the survival period after diagnosis of surveillance detected EAC and clinical EAC differs between the three models. The FHCRC model explicitly models the number of EAC surgeries (esophagectomies), which has more favorable outcomes for surveillance-detected patients, and generate a survival probability for these patients. The survival for clinically diagnosed patients is determined using calibration of SEER incidence and mortality. The MGH and the ERASMUS/UW models use the SEER-9 survival data that differ by cancer stage at the time of diagnosis. For surveillance detected EAC patients, the models adjust the survival according to malignant stage.

**MGH Model**

EACMo is a population-level Markov state transition model that depicts the natural history of EAC. A detailed description of this model can be found on the CISNET website. In order to allow for greater clinical realism particularly around endoscopic radiofrequency ablation (RFA), a microsimulation module was developed to augment the natural history model for this analysis. This appendix provides a description of this module and its implementation of the relevant screening, surveillance and treatment strategies.

A simulation was first run of the entire U.S. population within the population-level natural history model. When patients from the 1950 cohort reached the designated age (60 in the base case) for the beginning of screening the subpopulation with BE was identified and sequestered from simulation. The characteristics of this subpopulation were then used to initialize an individual-level microsimulation, which continued to simulate the progression of the disease in the presence of endoscopic surveillance and RFA treatment. Individual patients were simulated from the start of screening until death or age 100; the outcomes were then aggregated and combined with the output of the population-level simulation to produce the final results.

Prior to RFA treatment patients within the microsimulation could progress each cycle according to the transition probabilities of the natural history model. Endoscopy was performed at scheduled intervals based on detected health state; patients could receive RFA treatment based on the treatment strategy being analyzed, which was contingent on histologic status detected by endoscopic biopsy. The outcome (CE-IM, CE-D, or treatment failure) at the end of the initial treatment period was determined by a single random draw. Endoscopic surveillance schedules post-ablation depended on both the outcome of treatment and the pre-ablative health state of the patient.

In the event of treatment failure, patients remained in their pre-ablative health state, underwent endoscopic surveillance according to the same schedule prior to ablation, and received no further attempts at RFA treatment, essentially returning to their prior states. These patients could progress to more advanced disease states based on the transition probabilities from the natural history model.

Patients who received successful or partially successful treatment did not progress according to the natural history transition probabilities. Instead, there was a constant probability each cycle that a patient would undergo a recurrence event. When a recurrence event occurred, a second random draw based on a distribution would be performed to determine the post-recurrence state. Once in a post-recurrence state the patient could again progress in the same way as in the natural history model. If a patient was found by endoscopy and biopsy to have progressed beyond their diagnosed post-ablation state – that is, if endoscopic surveillance detected that a recurrence event had occurred – but had not yet progressed to cancer, the patient could receive touch-up RFA treatment, up to a maximum of 3 touchups after the end of the initial 2 year treatment period. Touch-up RFA was implemented in the same way as initial treatment in terms of the efficacy of ablation, the schedule of surveillance after treatment, and the modeling of recurrence.

**ERASMUS/UW-EAC Model**

The basic assumptions and model profile of the ERASMUS/UW-EAC model can be found on the CISNET website. Additional modules for modeling the characteristics of endoscopic ablation were inserted to the model. For endoscopic ablation, the outcome of the initial two-year endoscopic treatment for each individual patient is randomly drawn at the start of the treatment. In case of treatment failure, the patient remains in endoscopic surveillance at an interval in accordance to their pre-ablative dysplastic grade. In case of treatment success, the patient will be in complete eradication of dysplasia with persistent metaplasia (CE-D) or complete eradication of dysplasia and intestinal metaplasia (CE-IM) after two years. In the first case, we assume that the patient is in the BE non-dysplastic (ND) phase having the same assumptions as our natural history model. In the latter case, the patient stays in the CE-IM state for sojourn time randomly selected from an exponential distribution. If the patient transits to the next state (recurrence/progression), they will immediately transit to the state of histological recurrence. Furthermore, the patient will have a higher probability of recurrence in a higher state if the patient would have developed EAC in the natural history model. After generating this new life-history for this individual, the model simulated the surveillance according to the inputs after RFA. Surveillance can detect recurrent stages of BE and dysplasia and EAC. In the case of recurrent stages of BE, a new endoscopic ablation sequence is inserted, and the process as described is started again; generating new life histories for the patient. In this new life history the durations and probability of developing EAC are set. After determining this new life history, surveillance is inserted in the model according to post-RFA surveillance intervals described in the common input parameters. A maximum number of three touch ups is allowed.

**FHCRC: MSCE-EAC Multiscale Screening Model**

The multistage clonal expansion (MSCE) model for EAC includes an initial stochastic transition rate to convert a section of the normal squamous epithelium in the esophagus to generate a BE segment, with separate transition rates for individuals with or without gastroesophageal reflux disease (GERD). Cells within the BE segment are assumed to be at risk for progression through a multistage clonal expansion process to develop EAC. The MSCE-EAC model includes two rate-limiting mutations to transform BE cells to premalignant cells that undergo a slow clonal expansion process, followed by a third rate-limiting mutation to generate malignant cells that also undergo clonal expansion, but at a faster rate. In contrast to earlier multistage clonal expansion (MSCE) formulations of the EAC incidence model ([46](#_ENREF_46), [47](#_ENREF_47)) the MSCE-EAC multiscale screening model includes the explicit computation of the number and sizes of premalignant (HGD) clones and their spatial appearance within an idealized crypt-structured BE segment as a function of how long a patient had BE.([48](#_ENREF_48)) This description also includes the stochastic development of malignant clones representing preclinical cancer, which may be detected on a biopsy as a screen-detected cancer case. Symptomatic, incident cancers occur by a stochastic detection process. Biological parameters were estimated via likelihood maximization fitting EAC incidence data ([17](#_ENREF_17)).

The MSCE-EAC model simulates the joint distribution of premalignant and malignant clones sizes before cancer is detected in a symptomatic patient. Thus, we are able to predict the potential presence (or absence) of malignant cells in biopsies that harbor a sufficiently large number of dysplastic crypts to be subjected to closer examination for the presence of malignant cancer. The results presented in the main text are based on use of the standard (Seattle) biopsy protocol which requires quadrant biopsies every 1-2 cm along the BE segment. Factors contributing to the sensitivity for detection of HGD or cancerous lesions include the minimum aberrant tissue fraction in the biopsy necessary for diagnosis, the spacing between biopsy samples, and the size of biopsy forceps. The general efficacy of biopsy sampling remains highly uncertain due to variability in biopsy sampling between practitioners and due to considerable uncertainties in the histological assessment of the biopsied tissues. For the Results in the main text, we employed a biopsy detection sensitivity of 40% (see ([48](#_ENREF_48)) for details on the definition of diagnostic sensitivity). For the 60 year old screened males with BE, this assumption yields a prevalence of 2.8% for initial screen-detected cancers and 4.7% for initial HGD cases.

FHCRC: Surveillance and RFA Treatment

During surveillance, the MSCE-EAC model explicitly simulates the growth (in numbers) of any and all BE crypts, HGD crypts, and malignant crypts as a BE patient ages. For each patient, given a randomly generated size of the BE segment and simulated number and sizes of the neoplastic lesions at any given time, we also simulate the biopsy procedure at every surveillance screen to determine a possibly different diagnosis based on the highest grade of tissue found on biopsy. After a simulated screen of a BE patient for detection of HGD and preclinical EAC at a specified screening age, the MSCE-EAC model also allows the explicit modeling of an ablative treatment, such as radio frequency ablation (RFA). Specifically, assuming that ablation decimates the number of BE, dysplastic, and malignant crypts by specific fractions, the simulation modifies the size of a patient’s BE segment along with any concurrent HGD and/or malignant lesions during ablative treatment. For the results shown in the main text, we assumed an efficacy of 70% removal of all cell types during an RFA treatment or touch-up based on calibration to published recurrence rates during surveillance ([13](#_ENREF_13), [19](#_ENREF_19))

FHCRC: Survival

Once a malignant lesion is screen-detected, a BE patient may undergo surgery, whether endoscopic mucosal resection or esophagectomy. We utilized data from the Surveillance and End Results (SEER) registry to model cause-specific EAC survival and cure rate trends by stage and age category (ages 50-59, 60-60, 70-84), using the CANSURV program to fit a lognormal survival model to the data while estimating temporal trends on the shape and cure parameters. ([49](#_ENREF_49)) After controlling for age and stage, survival for men and women did not differ significantly, but the estimated cure rates for local stage diagnosis were significantly higher than for regional or distant diagnoses. The all-stage EAC survival curves for each age category were adjusted to account for ablation or surgical resection by fitting the cure model parameters based on a study of 430 patients undergoing ablation and 1586 patients undergoing esophagectomy that were identified in SEER between 1998-2009 ([50](#_ENREF_50)). Separate models were developed for EAC cause specific survival by age group, with or without ablation or surgical resection, while accounting for censoring and other cause death by matching cure rates at 2003.5 (midpoint of the 1998-2009 SEER follow-up data from Wani et al.) at age 63.4 (mean patient age for surgical resection), or age 70.5 for ablation.

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# Appendix table 1. Input & sensitivity parameters

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Base values** | | | **Lower value** | | | **Upper value** | | |
| Durability of successful treatment | | | | | | | | | |
|  | **Pre-treatment histology** | | | **Pre-treatment histology** | | | **Pre-treatment histology** | | |
|  | NDBE | IND/LGD | HGD | NDBE | IND/LGD | HGD | NDBE | IND/LGD | HGD |
| Annual recurrence probability | 7.0% | 10.7% | 10.0% | 3.5% | 5.4% | 5.0% | 14.0% | 21.5% | 20.0% |
| Efficacy of the initial treatment | | | | | | | | | |
| Success of therapy in pre-treatment HGD patients | | | | | | | | | |
| *CE – IM and CE-D* | 0.89  0.04  0.07 | | | 0.78  0.07  0.15 | | | 0.94  0.02  0.04 | | |
| *Non CE-IM, CE-D* |
| *Non-CE-IM and Non-CE-D* |
|  |
| Success of therapy in pre- treatment LGD patients | | | | | | | | | |
| *CE – IM and CE-D* | 0.98  0.02 | | | 0.96  0.04 | | | 0.99  0.01 | | |
| *Non-CE-IM and Non-CE-D* |
|  |
| Success of therapy in pre- treatment n NDD patients | | | | | | | | | |
| *CE – IM* | 0.97  0.03 | | | 0.94  0.06 | | | 0.98  0.02 | | |
| *Non CE-IM* |
| Halting surveillance after a period of observed good health post-treatment | | | | | | | | | |
|  | Until death or age 80 (follow patients up to age 100) | | | STOP surveillance when 5 year remained CE-IM, after achievement CE-IM of initial endoscopic therapy | | | STOP surveillance when 10 year remained CE-IM, after achievement CE-IM of initial endoscopic therapy | | |
|  |
| EET costs | | | | | | | | | |
| Initial Treatment | $5630 | | | $2815 | | | $11260 | | |
| Touch Up | $1012 | | | $506 | | | $2024 | | |
|  |  | | |  | | |  | | |
| Cancer treatment costs | | | | | | | | | |
| Localized Initial care | $58997 | | | $24499 | | | $117994 | | |
| Localized Terminal care | $64704 | | | $32352 | | | $129408 | | |
| Regional Initial care | $75295 | | | $37648 | | | $150590 | | |
| Regional Terminal care | $77742 | | | $38871 | | | $155484 | | |
| Distant Initial care | $57169 | | | $28585 | | | $114338 | | |
| Distant Terminal care | $85212 | | | $42606 | | | $170424 | | |
| Continuous care | $4080 | | | $2040 | | | $8160 | | |
|  |  | | |  | | |  | | |
|  |  | | |  | | |  | | |

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

# Appendix table 2. Post-treatment surveillance strategies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient characteristic | **Surveillance interval** |  |  | **Source** |
| Surveillance endoscopy interval after CE-IM of HGD patient (state = NORMAL) | Q3 months for one year then q6 months for one year then annual | | | ([51](#_ENREF_51)) |
| Surveillance endoscopy interval after CE-IM of LGD patient (state = NORMAL) | Q6 months for 2 years then annually for 2 years, then every three years | | | *Expert consensus\** |
| Surveillance endoscopy interval after CE-IM of NDBE patient (state = NORMAL) | every three years | | | *Expert consensus\** |
| Surveillance endoscopy interval after CE-D, none CE-IM of HGD patient (state=IM/BE ND) | Q3 months for one year then q6 months for one year then annual | | | *Expert consensus\** |
| Surveillance endoscopy interval after CE-D, none CE-IM of LGD patient (state=IM/BE ND) | Q3 months for one year then q6 months for one year then annual | | | *Expert consensus\** |
| Surveillance endoscopy interval after non CE-D, none CE-IM of HGD patient (state = HGD) | Every three months | | | *Expert consensus\** |
| Surveillance endoscopy interval after non CE-D, none CE-IM of LGD patient (state = LGD) | q6 months for one year then annual | | | *Expert consensus\** |
| Surveillance endoscopy interval after none CE-IM of ND patient (state = ND) | Every three years | | | *Expert consensus\** |

BE: Barrett’s esophagus, ND: No dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia, IND: indefinite dysplasia, EGD: esophagogastroduodenoscopy, CE: complete eradication, IM: intestinal metaplasia, D: dysplasia, RFA: radiofrequency ablation, EAC: esophageal adenocarcinoma

\*Expert consensus: panel of experts NS; SS; JI; CH; JR

# Appendix table 3. All Female results: Incremental numbers needed to treat to prevent one EAC death per strategy and model

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Incremental NNT/Death | **FHCRC** | | | **MGH** | | | **ERASMUS/UW** | |  |
|  | Reference strategy | | | Reference strategy | | | Reference strategy | | |
| Strategy: | S | HGD | LGD | S | HGD | LGD | S | HGD | LGD |
| HGD | 31 |  |  | 57 |  |  | 114 |  |  |
| LGD |  |  |  | 169 | 1,027 |  | 295 | 516 |  |
| BE | 101 | 177 |  | 248 | 1,060 | 1,100 | 282 | 380 | 256 |

EAC: esophageal adenocarcinoma, Strategies: NH:Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

# Appendix table 4. All Male surveillance start age 50, 60 and 70: Incremental numbers needed to treat to prevent one EAC death per strategy and model

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Incremental NNT/Death | | | | | | | | | |
| Age 50-100 | **FHCRC** | | | **MGH** | | | **ERASMUS/UW** | |  |
|  | Reference strategy | | | Reference strategy | | | Reference strategy | | |
| Strategy: | S | HGD | LGD | S | HGD | LGD | S | HGD | LGD |
| HGD | 31 |  |  | 36 |  |  | 31 |  |  |
| LGD |  |  |  | 93 | 320 |  | 72 | 181 |  |
| BE | 71 | 110 |  | 118 | 299 | 274 | 74 | 140 | 83 |
| Age 60-100 | **FHCRC** | | | **MGH** | | | **ERASMUS/UW** | |  |
|  | Reference strategy | | | Reference strategy | | | Reference strategy | | |
| Strategy: | S | HGD | LGD | S | HGD | LGD | S | HGD | LGD |
| HGD | 34 |  |  | 39 |  |  | 28 |  |  |
| LGD |  |  |  | 107 | 347 |  | 73 | 162 |  |
| BE | 99 | 180 |  | 142 | 316 (dominated) | 288 | 89 | 168 | 179 |
| Age 70-100 | **FHCRC** | | | **MGH** | | | **ERASMUS/UW** | |  |
|  | Reference strategy | | | Reference strategy | | | Reference strategy | | |
| Strategy: | S | HGD | LGD | S | HGD | LGD | S | HGD | LGD |
| HGD | 37 |  |  | 43 |  |  | 30 |  |  |
| LGD |  |  |  | 130 | 391 |  | 92 | 193 |  |
| BE | 170 | 412 |  | 200 | 409 | 424 | 116 | 181 | 171 |

EAC: esophageal adenocarcinoma, Strategies: NH:Natural History strategy; S: Surveillance strategy, HGD: Endoscopic ablative therapy for HGD diagnosed patients strategy; LGD: Endoscopic ablative therapy for dysplasia diagnosed patients strategy; BE: Endoscopic ablative therapy for all BE diagnosed patients strategy

**Appendix Figure legends**

Appendix figure 1| BE patient flow diagram for the various treatment strategies.

Appendix figure 2 | Progression rates in each model. The figure shows the development from BE to EAC in terms of progression rates in case of no interventions, which is, in the natural history of the disease. The cumulative progression rates towards EAC are shown following patients from age 60 having a certain initial phase (NDBE, LGD or HGD).

Appendix figure 3| The incremental number needed to treat to prevent 1 EAC death (NNT/Death) per model for the various sensitivity analyses. The incremental outcomes of two strategies are shown: the additional treatments needed to prevent 1 EAC death in case of HGD treatment compared to the strategy where only surveillance is applied (grey dots). Next to this, the incremental NNT/death when applying treatment to all BE patients compared to treatment for only HGD patients is presented (black dots). The lines represent the base case value.