# The Impact of Endoscopic Eradication for Barrett’s Esophagus on Esophageal Adenocarcinoma: a Comparative Modeling Analysis

*Short title: Endoscopic eradication of Barrett’s Esophagus*

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Word count:

The study was supported by the National Cancer Institute. The funding source had no role in the study design, conduct, and reporting.

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**Abstract (419:260 words)**

**Background & Aims:** Esophageal adenocarcinoma (EAC) incidence increased dramatically over the past 40 years in Western countries and neither EAC incidence nor mortality has plateaued. New techniques for endoscopic eradication of the EAC precursor Barrett’s esophagus (BE) such as radiofrequency ablation (RFA) are utilized to prevent progression to EAC. The efficacy and durability of endoscopic eradication are reported, but the intermediate-term impact of eradicative treatment and recurrent disease on EAC incidence and overall mortality reduction has not been analyzed with comprehensive and robust simulation models using this recently updated clinical data. In this study we analyzed the impact of RFA for endoscopic eradication of BE with or without dysplasia on EAC incidence and mortality using a comparative simulation modeling approach.

**Methods:** This study includes the predictive modeling of endoscopic eradicative treatment (EET) using three previously established population-based EAC models calibrated to NCI-SEER data. The modeling of clinical aspects of EET was based on available clinical data for RFA and endoscopic mucosal resection (EMR). We simulated a hypothetical cohort of 60-year-old patients with BE for whom multiple management strategies were tested, selected on initial dysplasia status and evaluated the simulation outcomes for EAC incidence and mortality reduction; required surveillance endoscopies and treatments including RFA and EMR and numbers of treatments needed to avert one EAC death (NNT/death). Additionally, we calculated the incremental cost effectiveness ratio (ICER) for the varying management strategies in costs per quality-adjusted life-year (QALY).

**Results**: A strategy to endoscopically eradicate BE with high-grade dysplasia will decrease EAC incidence by 50% (range 46%-58%) and EAC mortality by 47% (41%-53%) with NNT/death of 29 (23-44). If all BE (dysplastic and non-dysplastic) were eradicated, EAC incidence would incrementally decrease by 83% (81%-86%) and mortality by 81% (74%-85%). However, this reduction in EAC was associated with a five-fold increase in the number of treatments with an incremental NNT/death of 221 (168-316). Dominant strategies when assuming a 3% discount rate, in the models including simulation of dysplastic treatment, were HGD treatment, dysplastic treatment and all BE treatment with ICERS of $13141-19809, $27481-119008, and $125645-184575 respectively. The model only including HGD and all BE treatment resulted in a dominant strategy of ND treatment with an ICER of $8018. Halting post-treatment surveillance after a recurrence-free period of 5-10 years has a negligible influence on NNT/death when eradicating only patients with HGD. The main limitation of our study is the extrapolation of shorter-term EET clinical data to long-term results.

**Conclusions:** The resources needed to achieve EAC mortality reduction increase substantially as patients with lower severity of disease are selected for treatment. From a resource efficiency perspective, the large NNT/death and the results of our cost-effectiveness analysis suggests that treatment benefits justify endoscopic eradication only among BE patients with HGD.

*Key words: Radiofrequency ablation; Simulation modeling; Cost effectiveness*

# Introduction

The incidence of esophageal adenocarcinoma (EAC) has risen dramatically over the past four decades in the U.S. and much of the Western world, and unlike many other cancers, neither EAC incidence nor mortality has plateaued.([1](#_ENREF_1)) Barrett’s Esophagus (BE), in which the normal squamous epithelium of the distal esophagus is replaced by an intestinal-type columnar epithelium, is a precursor for EAC.([2](#_ENREF_2)) Most societal guidelines recommend BE patients undergo endoscopic surveillance with tissue biopsy to grade the severity of precursor lesions and detect curable neoplasia.([3](#_ENREF_3), [4](#_ENREF_4)) BE with no dysplasia progresses to EAC at a rate of less than 0.5% per year ([5](#_ENREF_5)), while BE with high-grade dysplasia progresses at a rate of 6%-19% per year.([6](#_ENREF_6))

New techniques for endoscopic eradication of BE such as endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) have become more widely utilized with the aim of preventing progression to EAC. Current American Gastroenterological Association (AGA) guidelines unequivocally recommend endoscopic eradicative therapy only for patients with high grade dysplasia (HGD).([7](#_ENREF_7)) The incremental benefit for this therapy on low grade dysplasia (LGD) and particularly non-dysplastic (ND) BE patients remains uncertain. Recent reports suggesting RFA decreases cancer incidence among subjects with BE and LGD might prompt increased utilization of eradicative therapy in this lower-risk population.([8](#_ENREF_8)) There is a growing evidence base regarding the efficacy and durability of RFA treatment.([9-15](#_ENREF_9)) The increasing availability of long-term data affords us the opportunity to analyze the impact of eradicative treatment on EAC incidence and overall mortality reduction using comprehensive and robust simulation models.

The National Cancer Institute’s (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) includes three modeling groups who independently developed population-based models for the natural history of BE and EAC that share common calibration targets (Surveillance, Epidemiology, and End Results (SEER) cancer incidence and mortality data)([16](#_ENREF_16)) and were previously cross-validated through comparative modeling exercises.([17](#_ENREF_17)) Unique to CISNET is the ability to compare outcomes between models with differing structural assumptions, such as progression and regression from dysplasia, or the incorporation of molecular mechanisms of cancer development in the model structure. Sensitivity analyses on natural history assumptions and underlying model structures are thus built into our comparative modeling approach, strengthening our confidence in model results.

The aim of our current study was to analyze the impact of endoscopic eradication therapy on EAC mortality in a BE population. Specifically, we sought to describe the impact of multiple different strategies utilizing eradication therapy on EAC incidence and mortality and to estimate the number of surveillance endoscopies and treatments required to produce potential clinical benefits. In addition, we performed a cost-effectiveness analysis to describe the concrete impact of the various strategies on health resources.

**Methods**

*CISNET-EAC models*

Three distinct models for EAC were used to quantitatively estimate the effectiveness and efficiency of endoscopic ablative therapies. These EAC models were developed independently but have been refined through comparative modeling using common population benchmarks such as SEER incidence and mortality within NCI’s CISNET modeling consortium. The models are the Multistage Clonal Expansion for EAC (MSCE-EAC) Model from the Fred Hutchinson Cancer Research Center (Seattle, WA) (**FHCRC model**), 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**). The CISNET-EAC models differ by modeling approach and structure, but all use a common set of calibration data on EAC incidence by age, stage, and calendar year from SEER (1975–2009). The FHCRC model uses a biological cell-based approach combining likelihood and microsimulation methods that focus on cell kinetics (mutations, cell division, death or apoptosis) including initiation of cells followed by clonal expansion, extinction, and biopsy-based detection of premalignant and malignant clones. The MGH model is a hybrid Markov state transition/ microsimulation model, and the Erasmus/UW model is a discrete-event microsimulation model. All three models assume a step-wise progression from ND BE towards dysplasia and EAC. The MGH and Erasmus/UW models include two grades of dysplasia: LGD and HGD, whereas the FHCRC model includes a singular grade of dysplasia: HGD.

For this analysis, all groups modified their original models to include additional modules containing the clinical details of RFA ablation and subsequent surveillance and management. Detailed technical profiles of each model are available online([18](#_ENREF_18)) and specific details about modeling endoscopic eradication are included the appendix.

Highlight definition differences between the models that would influence the results

*Population simulated*

Hypothetical cohorts for males and females and for 50-, 60- and 70-year old patients diagnosed with BE were followed for EAC incidence and mortality until death or age 100. Endoscopic surveillance and eradication therapy were discontinued at age 80. The cohorts analyzed were stratified by initial dysplasia status (high grade dysplasia-HGD; low-grade dysplasia-LGD; BE no dysplasia- ND). Cancer risk was dependent on calendar year, birth cohort, age, and sex. Each model was calibrated to reproduce the cancer risks according to available SEER EAC incidence data.

*Simulated strategies*

We modeled and analyzed 5 strategies described in Table 1. In the ‘Natural History’ (NH) strategy there was no endoscopic screening or surveillance; patients came to medical attention only when a clinical cancer was diagnosed, at which point they would receive standard treatment. When a cancer was diagnosed, survival was modeled according to SEER survival data or survival of esophagectomy, depending on the modeling group (see Appendix). The ‘Surveillance’ (S) strategy is that previously recommended by numerous societal guidelines prior to the widespread availability of endoscopic eradication therapy. The majority of societal guidelines base the interval of surveillance endoscopy solely on the histological grade of biopsy samples.([7](#_ENREF_7)) The three endoscopic eradication treatment strategies varied by the histological point at which endoscopic eradication is first performed. In the ‘HGD’ strategy, patients with BE underwent endoscopic surveillance until HGD was detected on endoscopic biopsy, at which point the patient underwent treatment (figure 1). In the ‘LGD’ strategy, patients underwent treatment when any dysplasia (HGD or LGD) was detected on biopsy. In the ‘BE’ strategy, all BE patients underwent treatment at the start of the simulation regardless of degree of dysplasia.

*Treatment characteristics*

The efficacy and complications associated with endoscopic eradication therapy (EET) for BE were based on recently published data([19](#_ENREF_19), [20](#_ENREF_20)) and expert opinion (Table 2). Initial RFA treatment took place over a two-year period, and was in 55% of the patients preceded by EMR. Possible outcomes at the end of this period were complete eradication of intestinal metaplasia (CE-IM), complete eradication of dysplasia (CE-D), or treatment failure (persistence of IM and/or D). After treatment failure, patients received endoscopic surveillance at pre-treatment intervals and were not given additional treatments. After treatment success (CE-IM or CE-D) patients were subject to a modified surveillance regimen that included additional endoscopies in the years immediately after the initial treatment period, with later endoscopies following at less frequent regular intervals. Full details of the post-treatment surveillance strategy for each treatment outcome and pre-treatment state are shown in the appendix. Following successful treatment patients could recur to BE, to their pre-treatment state or to a more advanced disease state. The probability of recurrence to BE was assumed to be constant over time and the distribution of post-recurrence states depended on the patient’s pre-treatment state as estimated from observed clinical data (Table 2). Patients with recurrences detected during post-treatment surveillance received “touch-up” RFA treatment (defined as circumferential or focal endoscopic RFA performed after the initial treatment period) and were monitored for further recurrences according to the post-treatment schedule described above. Patients were limited to a maximum of three touch-ups. The model accounted for complications of endoscopy and ablation including perforation and stricture. A graphical representation of the simulated treatment strategies can be found in the figure 1 and in the appendix.

*Costs and quality of life*

The cost effectiveness analyses were conducted from a health care perspective. The costs for endoscopies and EET were based on reimbursement costs (Table 2). The costs for complications and cancer care were derived from literature. We adjusted all costs to reflect the 2015 level using the U.S. Consumer Price Index. ([21](#_ENREF_21)) Data on quality of life (utility loss) were derived from literature and were used to convert absolute life-years of each strategy into quality-adjusted life-years (QALYs).

*Outcomes*

The main outcomes were presented for a 60-year-old male cohort (additional outcomes for female and various ages are shown in the appendix). The primary outcomes were EAC incidence and mortality reduction; total numbers of surveillance endoscopies and endoscopic eradicative treatments; numbers of treatments needed to avert one EAC death (NNT/death); life years gained; and complications of endoscopy and treatment. The NNT/death was calculated as the total number of ablative treatments divided by the number EAC deaths averted by a given strategy. We incorporated the total number of treatments needed to prevent one death because multiple treatments were needed per patient. Presenting the results as the number of patients needed to treat would underestimate the overall resources. Treatments included the number of EMR and RFA treatments. Incremental results compared the NNT/death for a given strategy to the next-least invasive strategy by dividing the number of additional treatments by the additional EAC mortality reduction in the more invasive strategy.

We quantified the effectiveness of each strategy in terms of QALY and associated costs, applying the conventional 3% discount rate to both.([22](#_ENREF_22)) We calculated the incremental cost effectiveness ratio (ICER) for the various strategies by calculating the difference in cost between the intervention strategies with the natural history strategy, divided by the change in QALYs.

*Sensitivity analysis*

We repeated our five base strategy simulation analyses with half and twice the base-case assumptions for the durability of successful treatment. For the efficacy of the initial treatment we derived upper- and lowerbound values from literature (appendix Table 1). In addition, we analyzed the effect of halting surveillance after a period of observed good health post-treatment (appendix Table 1). As for costs, we repeated our base simulation analyses with half and twice the base-case assumptions for cancer treatment costs, and EET treatment costs.

# Results

*EAC incidence and mortality*

Without surveillance, 85-134 EAC cases and 57-92 EAC deaths (ranges reflect differences between models) were expected to occur in 1,000 60-year old male BE patients (Table 3a). In all three models, surveillance led to down-staging and an average EAC mortality reduction of 26%; however, there was a 28% increase in cancer detection due to overdiagnosis (surveillance-detected EAC that would not have become clinically observed due to death from non-cancer causes).

The relative impact of the different treatment strategies was consistent across models. Compared to the surveillance only strategy, the HGD treatment strategy resulted in an average decrease in EAC diagnosis of 50% in the three models (range 47%-58%) and EAC mortality reduction of 47% (range 41%-53%). The LGD treatment strategy (simulated by the MGH and ERASMUS/UW models only) resulted in a decrease in EAC diagnosis by 70% (range 68%-72%) and EAC mortality by 70% (range 68%-72%). Treating all BE patients at age 60 decreased the number of EAC cases by 83% (range 81%-86%) and the EAC mortality by 81% (range 74%-85%) (figure 2).

*Resources required*

The number of treatments differed across models, but showed similar patterns for each treatment strategy. On average 891 (range 884-928) treatments (including EMR, ablative treatments and touch-ups) needed to be performed in the HGD strategy. Also treating LGD patients increased the number of treatments by more than 200% to approximately 3,228 treatments (figure 3). Extending treatment to all BE patients further increased required treatments to 4,944 (range 4,911 -5,019).

*Efficiency of treatment*

The significant increase in treatments diminished the efficiency per treatment for the more inclusive strategies. The NNT/death for HGD treatment was a mean of 34 (range 28-39). In this strategy, relatively few treatments were required, resulting in a high mortality reduction (range 41%-53%). In contrast, the incremental NNT/death for LGD compared to HGD treatment was 347 and 162 in the MGH and ERASMUS/UW models, respectively. The incremental NNT/death for BE compared to HGD treatment was 180, 316, and 168 in the FHCRC, MGH, and the ERASMUS/UW models, respectively (table 3b). Furthermore, compared to HGD, BE would require 23,325 additional treatments to save 1 additional year of life, and would induce 551 complications to save 1 year of life.

*Cost-effectiveness analysis*

The results of the Erasmus/UW model reflect higher costs for the natural history strategy compared to the MGH model. In combination with relatively higher impact of the treatment strategies on the increase QALYs, this results in lower ICERs than the MGH model. Without surveillance, the costs were $4701-$6068 for 13.26-14.74 discounted QALYs (ranges reflect differences between models). HGD treatment reflected an increase in life expectancy by 0.22-0.36 and an increase in costs by $3055-$3338-, resulting in an ICER of $9342-$13,885 per QALY. In both models (MGH and Erasmus/UW) the life expectancy for a BE patients is increased for strategies when treatment is applied to less severe dysplastic grades, however these strategies are also more expensive (Table 3b).

*Sensitivity analysis*

For the HGD treatment strategy, the results of our models were robust to sensitivity analysis. Comparing incremental NNT/death for the BE strategy with the HGD strategy, the results were most sensitive to the durability of successful treatment and for halting surveillance after a period recurrence-free post-treatment surveillance. However, halting post-treatment surveillance after a recurrence-free period of 5-10 years had negligible influence on NNT/death in the HGD strategy (see Appendix). The sensitivity analyses for both EET and cancer costs had high impact on the ICERS and the dominant strategies. ….. (see appendix)

# Discussion

Our study shows that endoscopic eradication of HGD, specifically RFA, could result in substantial reductions in EAC incidence and mortality. However, extending treatment eligibility to patients with lower grades of dysplasia substantially increases the use of eradication therapy while diminishing the incremental effectiveness. This results in an unfavorable number needed to treat to prevent one EAC death if a strategy treating all patients with BE (including HGD, LGD and NDBE) is utilized.

The finding that EET may reduce EAC incidence and mortality is not surprising as the efficacy of the treatment is reported to be high and associated complication rates are relatively low. The more relevant issues to applying this therapy on a population basis are related to healthcare resource utilization, over-testing and over-treatment. Evaluation of the NNT to achieve additional mortality reduction for each strategy demonstrates eradicative therapy for patients with low-grade or no dysplasia results in diminishing returns. However, the mortality reduction that can be achieved by including non-dysplastic patients in the treatment strategy does not require substantially more treatments per cancer death averted compared to ablating patients with LGD. It appears that the diminishing impact of treatment expansion is due to the likelihood that ND and LGD patients will eventually receive treatment if they develop HGD. The additional deaths prevented by expansion of treatment result from cases that are rapidly developing EAC, or that are misclassified. In these instances, the HGD may not be diagnosed at endoscopy and it makes sense to treat these patients in an early stage.

Two models performed cost effectiveness analyses in addition to the main simulations to identify the costs and QALYs incurred by each strategy. Both models identify that performing surveillance alone is a costly strategy, while performing EET reduced overall costs and increased QALYs.

The model results were most sensitive for the duration of successful treatment. Furthermore, all models support the decision to stop offering surveillance to HGD patients five years after successful RFA. All sensitive analyses had a relatively larger impact on the treatment strategies for low-grade and absent dysplasia.

Explanation differences between models:

LGD prevalence/ definition HGD and cancer in FH model

Previously published cost-effectiveness studies agree that endoscopic eradication therapy is cost-effective when offered to HGD BE patients.([23-25](#_ENREF_23)). One previous study evaluated the cost-effectiveness of RFA on varying dysplastic grades of BE, concluding that endoscopic ablative therapy was only cost-effective when offered to dysplastic BE patients.([25](#_ENREF_25)) Our study similarly showed eradicative treatment is effective for all patients, and that treating patients with less severe or no dysplasia demands a major amount of resources. Prior studies used a single Markov model informed by clinical data available at the time of publication, but were not calibrated to US SEER incidence and mortality data. Our study used three simulation models that were independently calibrated to SEER data, which better equips them to assess cancer control strategies and patient guidelines.

A major strength of this study is the comparative modeling approach, which uses results from independently developed models with common calibration targets. The comparative modeling approach helps to resolve major differences in model outputs and to understand model uncertainties, and has been used in other CISNET comparative modeling analyses.([17](#_ENREF_17), [26](#_ENREF_26), [27](#_ENREF_27)) With this approach we were able to not only perform sensitivity analyses on the parameter estimates, but also on structural assumptions such as the possibility of regression from dysplasia, the incorporation of multiscale elements such as clonal expansion and other variations in the natural history of BE and EAC. Hence, although there are initial differences between our models when considering absolute malignant development and mortality among BE patients, this analysis showed considerable consistency between the models on the relative effectiveness and the NNT/death, demonstrating the robustness of our findings. Finally, we used the latest RFA data available in the field, collaborating with experts to verify the analysis and model inputs.

Our study is subject to several limitations. First, all of our models depict the biological progression following a specific sequence: BE without dysplasia, BE with dysplasia, preclinical cancer, and detected cancer. Although this is the commonly accepted paradigm for EAC carcinogenesis, not all EACs may follow this prescribed sequence in reality and alternative, heterogeneous pathways may exist within this paradigm.([28](#_ENREF_28), [29](#_ENREF_29)) Second, the simulated endoscopic eradication results are dependent on assumptions about the durability and efficacy of endoscopic ablation. Recognizing these limitations, we have used the latest and best data available.([30](#_ENREF_30)),([31](#_ENREF_31)) Our baseline assumption for efficacy on the initial treatment was based on data from ten of the best centers in the US in a highly regulated randomized controlled trial, which may raise the concern whether our models are too optimistic. However, our sensitivity analysis showed relatively low sensitivity for differing assumptions of efficacy of the initial treatment. Although we have used the latest available data regarding EET and more specifically RFA, limited availability of long-term outcomes necessitated translation of shorter-term data into model inputs to make longer-term projections. The accuracy of these projections may impact model outcomes. However, sensitivity analyses of these projections using a broad range of potential variables demonstrated our results are robust. Thirdly, we have not incorporated the absolute excess risk of death in the BE cohort. More data is becoming available showing that the relative increased risk of all causes death was 21% for BE patients compared to the general population.([32](#_ENREF_32)) The majority of these deaths were actually not due to esophageal cancer, which reflects a higher competing risk for other cause mortality in BE patients resulting in lower EAC mortality rates.Finally, the definition of LGD is subject to large uncertainty because of interpretation bias. The models based the prevalence and progression rate of LGD to best available data, mainly from the U.S. Recently, Duits et al ([33](#_ENREF_33)) showed that when LGD is confirmed by experts, the risk for malignant progression is significantly higher than generally thought. When our models would assume that LGD is indeed approximating the malignant progression rate of HGD, the conclusions of our study may become more favorable towards EET treatment for LGD patients.

This study provides clinically important results about the effectiveness of RFA. A strategy focusing only on cancer control with no consideration of cost would mandate treatment of all patients with BE given the 79% cancer mortality reduction expected under this approach. However, the primary utility of our study is in the projections of resource utilization necessary to achieve this goal. Our analysis highlights the large increment in endoscopic treatment numbers necessary to include LGD and NDBE patients in a population-based treatment program. These results may allow health policy decision makers to prioritize the use of this therapy in treatment algorithms based on their willingness to pay for the gains in cancer prevention outlined above, as well as the costs associated with its use in different healthcare systems. Furthermore, the large number of repeated endoscopic treatments represents a significant burden to individual patients. Lastly, it is expected that there will be a significant increase in esophageal stricture complications; however, these strictures are rarely serious and usually amenable to endoscopic treatment.

In conclusion, our comparative modeling analyses indicate that EET is an effective means of reducing EAC incidence and mortality. Benefit is predicted to be achieved across all patients with BE; however, the efficiency of eradication is substantially reduced if patients with LGD and no dysplasia are treated, and substantially more healthcare resources are required to avert a cancer death in these settings. These findings were consistent across all three esophageal CISNET models and were robust to sensitivity analyses of RFA efficacy and durability. Our results add further evidence to support RFA therapy to patients with HGD, and suggest that strategies targeting less severe disease will require close scrutiny for cost-effectiveness. Efficiency of care would be greatly enhanced through improved methods to stratify risk of cancer in lesser forms of dysplasia and, therefore to better identify individuals who would benefit most from endoscopic therapy.

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# Funding statement

The study was supported by the National Cancer Institute: U01 CA-152926 and the National Science Foundation DGE-0718124: KC. The funding source had no role in the study design, conduct, and reporting.

# Abbreviations

BE Barrett’s Esophagus

CE-D Complete eradication of dysplasia

CE-IM Complete eradication of intestinal metaplasia

EAC Esophageal adenocarcinoma

EET Endoscopic Eradicative Therapy

HGD High grade dysplasia

LGD Low grade dysplasia

ND No dysplasia

NNT/death Number of treatments needed to prevent one death

RFA Radiofrequency ablation

# Tables

**Table 1. Characteristics of simulated interventions on Barrett’s esophagus patient cohort**

|  |  |  |  |
| --- | --- | --- | --- |
| Strategy | **NDBE patients** | **LGD patients** | **HGD patients** |
| Natural History (NH) | No intervention | No intervention | No intervention |
| Surveillance (S) | Surveillance endoscopy with biopsies every 3 years | Surveillance endoscopy with biopsies every 6 months in the first year, thereafter every year | Surveillance endoscopy with biopsies every 3 months |
| BE surveillance and HGD treatment (HGD) | Surveillance endoscopy with biopsies every 3 years | Surveillance endoscopy with biopsies every year | Endoscopic eradication therapy followed by surveillance\* |
| BE surveillance and Dysplasia treatment (LGD) | Surveillance endoscopy with biopsies every 3 years | Endoscopic eradication therapy followed by surveillance\* | Endoscopic eradication therapy followed by surveillance\* |
| BE treatment (BE) | Endoscopic eradication therapy followed by surveillance\* | Endoscopic eradication therapy followed by surveillance\* | Endoscopic eradication therapy followed by surveillance\* |

BE: Barrett’s esophagus, ND: No dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia

\*All post-treatment surveillance intervals can be found in E-table 2

**Table 2. Common input parameters**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter/Definition | **Value** |  |  | **Source** |
| Complications of therapy |  |  |  |  |
| Complication rate from EGD | 0.00013 |  |  | ([34](#_ENREF_34), [35](#_ENREF_35)) |
| Stricture rate with RFA at year 3 | 0.076 |  |  | ([36](#_ENREF_36)) |
| Perforations with RFA | 0.0005 |  |  | ([4](#_ENREF_4), [37-41](#_ENREF_37)) |
| Proportion of patients receiving EMR treatments before RFA | 0.55 |  |  | ([15](#_ENREF_15)) |
| Success of therapy in pre-treatment HGD patients | | |  | ([19](#_ENREF_19)) |
| *CE – IM and CE-D* | 88.89% |  |  | ([19](#_ENREF_19)) |
| *Non CE-IM, CE-D* | 3.70% |  |  | ([19](#_ENREF_19)) |
| *Non-CE-IM and Non-CE-D* | *7.41%* |  |  | ([19](#_ENREF_19)) |
| Success of therapy in pre-treatment LGD patients | | |  | ([19](#_ENREF_19)) |
| *CE – IM and CE-D* | 98.08% |  |  | ([19](#_ENREF_19)) |
| *Non CE-IM, CE-D* | 0.00% |  |  | ([19](#_ENREF_19)) |
| *Non-CE-IM and Non-CE-D* | *1.92%* |  |  | ([19](#_ENREF_19)) |
| Success of therapy in pre-treatment NDBE patients | | | | ([20](#_ENREF_20)) |
| *CE – IM* | 96.77% |  |  | ([20](#_ENREF_20)) |
| *Non-CE-IM* | 3.23% |  |  | ([20](#_ENREF_20)) |
| Recurrence rates by baseline histologic grade and grade of recurrence |  |  |  | (28,29) |
| Annual recurrence rates after CE-IM |  |  |  | (28,29) |
| Pre-treatment NDBE | 7% |  |  |  |
| Pre- treatment IND/LGD | 11% |  |  |  |
| Pre- treatment HGD | 10% |  |  |  |
| Recurrence histology pre- treatment NDBE |  |  |  | (28,29) |
| NDBE | 92% |  |  |  |
| IND/LGD | 6% |  |  |  |
| HGD | 2% |  |  |  |
| IMC/EAC | 0% |  |  |  |
| Recurrence histology pre- treatment LGD |  |  |  | (28,29) |
| NDBE | 82% |  |  |  |
| IND/LGD | 14% |  |  |  |
| HGD | 2% |  |  |  |
| IMC/EAC | 2% |  |  |  |
| Recurrence histology pre- treatment HGD |  |  |  | (28,29) |
| NDBE | 69% |  |  |  |
| IND/LGD | 15% |  |  |  |
| HGD | 10% |  |  |  |
| IMC/EAC | 6% |  |  |  |

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

**Table 2b. Common input parameters costs and utilities**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter/Definition Costs | **Value** |  |  | **Source** |
| Endoscopy | $670 |  |  |  |
| EET Treatment\* | $5630 |  |  |  |
| RFA Touch Up | $1012 |  |  |  |
| Stricture | $1012 |  |  |  |
| Perforation | $28553 |  |  | ([25](#_ENREF_25)) |
| Stricture complication | $8792 |  |  |  |
| Localized Initial care | $58997 |  |  | ([42](#_ENREF_42" \o "Yabroff, 2008 #178)) |
| Localized Terminal care | $64704 |  |  |  |
| Regional Initial care | $58997 |  |  |  |
| Regional Terminal care | $77742 |  |  |  |
| Distant Initial care | $57169 |  |  |  |
| Distant Terminal care | $85212 |  |  |  |
| Continuous care | $4080 |  |  |  |
| Parameter/Definition Utility | | | |  |
| Endoscopy | 1 day, 0.7 |  |  | *(*[*43*](#_ENREF_43)*)* |
| EET Treatment1 | 30 days / 2 year, 0.7 |  |  |  |
| RFA Touch Up | 7 days, 0.7 |  |  |  |
| Stricture | 1 day, 0.7 |  |  |  |
| Perforation | 7 days, 0.7 |  |  |  |
| Stricture complication | 7 days, 0.7 |  |  |  |
| Localized Initial care (yearly) | 0.838 |  |  | ([44](#_ENREF_44), [45](#_ENREF_45)) |
| Localized Continuous and Terminal care (yearly) | 0.96 |  |  |  |
| Regional care (yearly) | 0.654 |  |  |  |
| Distant care (yearly) | 0.395 |  |  |  |

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

Costs of EMR, RFA treatments and Touch ups within the first two years (initial treatment period)

1 Within the initial treatment period we assume that there are multiple treatments and touch us resulting in on average 16 days utility of 0.7.