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Radiofrequency Ablation of Barrett's Esophagus Reduces Esophageal Adenocarcinoma Incidence and Mortality in a Comparative Modeling Analysis

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The incidence of esophageal adenocarcinoma (EAC) has risen dramatically during the past 4 decades in the United States and much of the Western world.[1] Most clinical guidelines recommend patients with Barrett's esophagus (BE) undergo endoscopic surveillance with tissue biopsy to grade the severity of precursor lesions and detect curable neoplasia.[2] In addition, techniques for endoscopic eradication treatment of BE, such as endoscopic mucosal resection and radiofrequency ablation (RFA), have increasingly been used to limit progression to EAC.[3]

The National Cancer Institute's (NCI) Cancer Intervention and Surveillance Modeling Network (CISNET) includes 3 esophageal cancer modeling groups who have independently developed population-based models for the natural history of BE and EAC[4]; these models have been validated by calibration to NCI Surveillance Epidemiology and End Results data and by numerous comparative modeling exercises.[5] The aim of the current study was to use the CISNET models to perform a comparative modeling analysis to determine the effectiveness and cost-effectiveness of an RFA-centered endoscopic eradication treatment strategy for management of a population of patients with BE. We sought to test and assess the impact of multiple strategies using endoscopic 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 assess the various strategies from a healthcare utilization perspective. Detailed technical profiles of each model are available on the NCI CISNET website, and details regarding the methods are available in a downloadable pdf file (Supplementary Materials).[6]

Methods

In our base case analysis, the simulated cohort was composed of men born in 1950 with BE diagnosed at age 60. Patients were tracked for EAC incidence and mortality until death by any cause or age 100. Endoscopic surveillance and eradication therapy were discontinued after age 80. Risk of progression to cancer was dependent on calendar year, birth cohort, age, and sex. Outcomes for each strategy analyzed included EAC incidence and mortality, total numbers of surveillance endoscopies and endoscopic eradicative treatments, numbers of treatments needed to avert one EAC death (NNT/death), unadjusted and quality-

[a]Authors share co-first authorship. [b]Authors share co-senior authorship.

Abbreviations used in this paper: BE, Barrett's esophagus; CISNET, Cancer Intervention and Surveillance Modeling Network; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NCI, National Cancer Institute; NNT/death, number of treatments needed to prevent one death; QALY, quality-adjusted life year; RFA, radiofrequency ablation.

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adjusted life years, number of complications from endoscopy and treatment, and total costs. The NNT/death was calculated as the total number of ablative treatments divided by the number of EAC deaths averted by a given strategy. Because many patients require multiple treatments, the total number of treatments required provides a better estimate of resource utilization than the number of patients who required treatment. Treatments included the total number of endoscopic mucosal resection and RFA treatments. Incremental results compared the NNT/death for a given strategy with the next least invasive strategy by dividing the number of additional treatments by the additional EAC mortality reduction in the more invasive strategy.

Cost-effectiveness analyses were conducted from a third-party payer perspective. Quality of life (utility values) were derived from literature and used to convert absolute life years of each strategy into quality-adjusted life years (QALYs). We quantified the effectiveness of each strategy in terms of QALYs and associated costs, applying the conventional 3% discount rate to both. Incremental cost-effectiveness ratios were calculated between strategies as the ratio of incremental cost to incremental gain in QALYs. Comprehensive details of model inputs or parameter estimates including methods for derivations are available online.[6]

Results

Table 1 summarizes the 5 strategies for the management of BE. Figure 1 presents the highlighted modeling results for the strategies for each of the 3 modeling groups with the end points of EAC incidence and mortality. The model analysis found that the impact of the different treatment strategies, measured relative to a baseline of surveillance alone, was consistent across all 3 models. High-grade dysplasia (HGD) treatment resulted in an average decrease in EAC incidence of 51% (range, 46%–54%) and an EAC mortality reduction of 44% (range, 39%–49%). In terms of NNT/death, HGD treatment was the most efficient, with a mean of 44 (range, 30–56). In this strategy, relatively few treatments were required to achieve a substantial reduction (range, 39%–49%). In contrast, the incremental NNT/death for low-grade dysplasia (LGD) compared with HGD treatment was 346 and 166 in the MGH and ERASMUS/UW models, respectively. The LGD treatment strategy (simulated by the MGH and ERASMUS/UW models only) resulted in a decrease in EAC incidence by 63% (range, 58%–67%) and EAC mortality by 58% (range, 53%–62%). Treating all BE patients at age 60 decreased the number of EAC cases by 71% (range, 68%–79%) and the number of EAC deaths by 68% (range, 58%–81%). This strategy was resource intensive, with NNT/death of 350 (range, 253–518) compared with HGD treatment alone and an incremental cost-effectiveness ratio of $182,093–$422,256/QALY, which is above a $100,000/QALY willingness-to-pay threshold. Model predictions diverged on the cost-effectiveness of treatment for LGD. Additional results of our modeling analyses including unadjusted life expectancy, costs per strategy, and sensitivity analyses on key parameter inputs and surveillance assumptions are available online.[6]

Discussion

In conclusion, our results strongly confirm the current guidelines that endorse endoscopic eradication therapy for patients with HGD.[2] Our divergent results for LGD highlight the need for a better understanding of the uncertainties surrounding the LGD health state.[7] Benefits

Table 1. Characteristics of Simulated Interventions on BE Patient Cohort

Strategy	NDBE patients	LGD patients	HGD patients
Natural history	No intervention	No intervention	No intervention
Surveillance without RFA treatment (S strategy)	Surveillance endoscopy with biopsies every 3 y	Surveillance endoscopy with biopsies every 6 mo in first year, thereafter every year	Surveillance endoscopy with biopsies every 3 mo
BE surveillance with treatment for HGD only (HGD strategy)	Surveillance endoscopy with biopsies every 3 y	Surveillance endoscopy with biopsies every year	RFA therapy followed by surveillance[a]
BE surveillance with treatment for all dysplasia (LGD strategy)	Surveillance endoscopy with biopsies every 3 y	RFA therapy followed by surveillance[a]	RFA therapy followed by surveillance[a]
Treatment for all BE patients (BE strategy)	RFA therapy followed by surveillance[a]	RFA therapy followed by surveillance[a]	RFA therapy followed by surveillance[a]

NDBE, BE with no dysplasia.
[a]All post-treatment surveillance intervals can be found in E-table 5.[6]

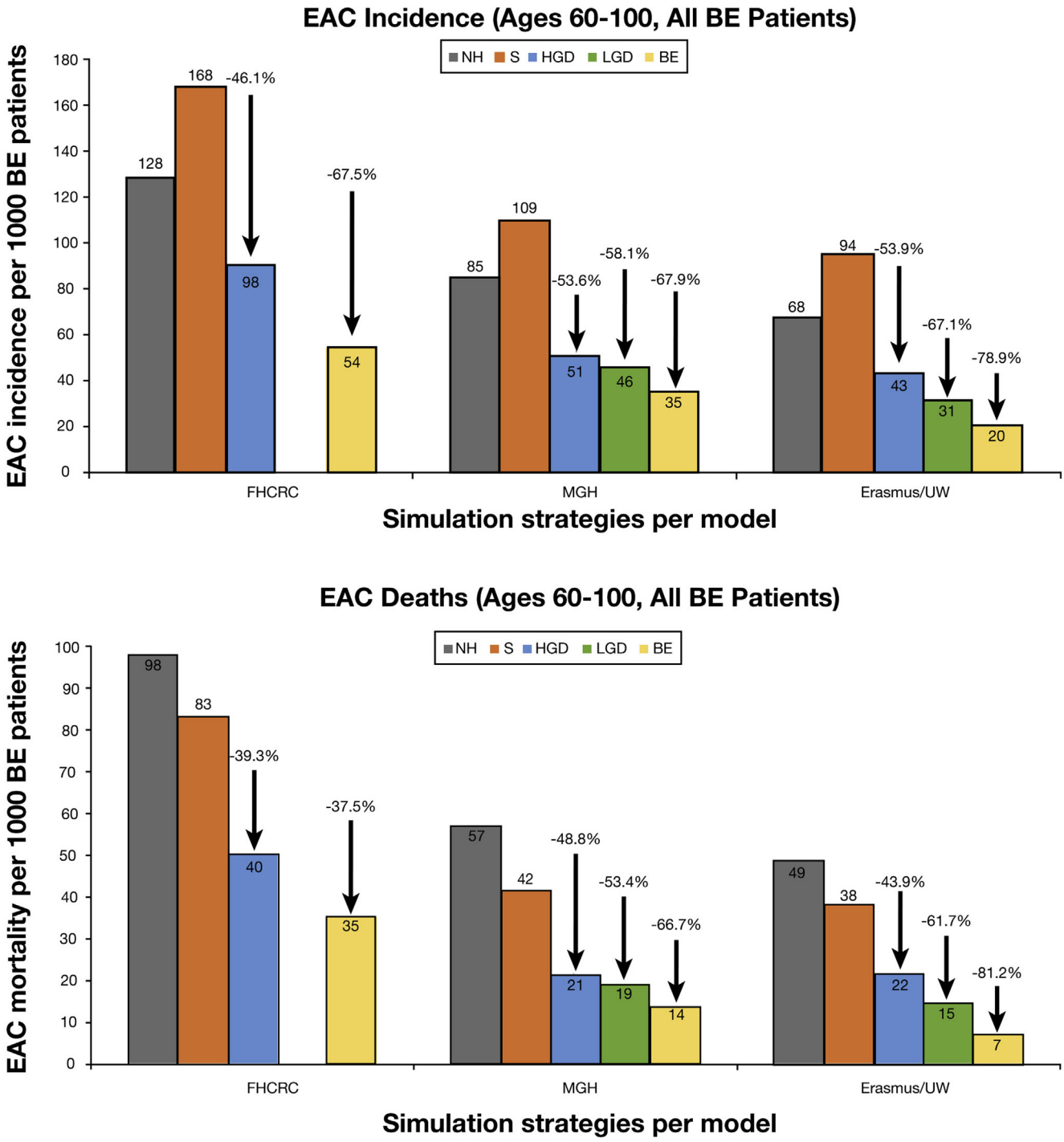

Figure 1. Upper part of figure shows EAC incidence per 1000 BE patients per model and strategy (no discounting). Lower part of figure shows EAC deaths per 1000 BE patients. EAC incidence and mortality reductions are shown for endoscopic eradicative treatment strategies compared with strategy including only surveillance and no endoscopic eradicative treatment. The range in model estimates reflects differences in model structures and assumptions on BE prevalence and time to development of malignancy. NH, natural history; S, Surveillance.

are predicted to be achieved for all BE endoscopic eradication strategies; however, the efficiency of eradication is substantially reduced if patients with LGD and no dysplasia are treated, and substantially more resources are required to avert a cancer death in these settings. These findings were consistent across all 3 CISNET esophageal cancer models and were robust to sensitivity analyses of RFA efficacy and durability. Our results add further support for endoscopic eradication therapy for BE 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.12.034.

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The authors disclose no conflicts.

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