Title
Incidence of Esophageal Adenocarcinoma and Causes of Mortality After Radiofrequency Ablation of Barrett's Esophagus

Journal
Gastroenterology, 149(7)

ISSN
0016-5085

Authors
Wolf, W Asher
Pasricha, Sarina
Cotton, Cary
et al.

Publication Date
2015-12-01

DOI
10.1053/j.gastro.2015.08.048

Peer reviewed

HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Gastroenterology. 2015 December ; 149(7): 1752–1761.e1. doi:10.1053/j.gastro.2015.08.048.

Incidence of Esophageal Adenocarcinoma and Causes of Mortality in Barrett's Esophagus after Radiofrequency Ablation

W. Asher Wolf[1], **Sarina Pasricha**[1], **Cary Cotton**[1], **Nan Li**[1], **George Triadafilopoulos**[2], **V. Raman Muthusamy**[3], **Gary W. Chmielewski**[4], **F. Scott Corbett**[5], **Daniel S. Camara**[6], **Charles J. Lightdale**[7], **Herbert Wolfsen**[8], **Kenneth J. Chang**[9], **Bergein F. Overholt**[10], **Ron E. Pruitt**[11], **Atilla Ertan**[12], **Srinadh Komanduri**[13], **Anthony Infantolino**[14], **Richard I. Rothstein**[15], and **Nicholas J. Shaheen**[1]

[1]From the University of North Carolina at Chapel Hill, Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, Chapel Hill, NC

[2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine

[3]Division of Digestive Diseases, David Geffen School of Medicine at UCLA

[4]Thoracic and Cardiac Surgery, Rush University Medical Center

[5]Gastroenterology Associates of Sarasota, Sarasota, FL, Florida Digestive Health Specialists

[6]Digestive Health Physicians, Cheektowaga, NY

Corresponding Author: Nicholas J. Shaheen, MD, MPH, Professor of Medicine and Epidemiology, Director, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, CB#7080, Chapel Hill, NC 27599-7080, Phone: (919) 966-2513, Fax: (919) 843-2508.

Author Contributions: WAW: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis
SP: drafting of the manuscript, critical revision of the manuscript for important intellectual content
NL: analysis and interpretation of data, statistical analysis
CCC: analysis and interpretation of data, critical revision of the manuscript for important intellectual content
GT: study concept and design, critical revision of the manuscript for important intellectual content
VRM: study concept and design, critical revision of the manuscript for important intellectual content GWC: study concept and design, critical revision of the manuscript for important intellectual content
FSC: study concept and design, critical revision of the manuscript for important intellectual content
DSC: study concept and design, critical revision of the manuscript for important intellectual content
CJL: study concept and design, critical revision of the manuscript for important intellectual content
HW: study concept and design, critical revision of the manuscript for important intellectual content
KJC: study concept and design, critical revision of the manuscript for important intellectual content
BFO: study concept and design, critical revision of the manuscript for important intellectual content
REP: study concept and design, critical revision of the manuscript for important intellectual content
AE: study concept and design, critical revision of the manuscript for important intellectual content
SK: study concept and design, critical revision of the manuscript for important intellectual content
AI: study concept and design, critical revision of the manuscript for important intellectual content
RIR: study concept and design, critical revision of the manuscript for important intellectual content
NJS: study concept and design, analysis and interpretation of data, drafting of the manuscript, study supervision

[7]Division of Digestive and Liver Diseases, Columbia University

[8]Gastroenterology and Hepatology, Mayo Clinic

[9]Division of Gastroenterology, University of California, Irvine

[10]Gastrointestinal Associates, Knoxville, TN

[11]Nashville Gastrointestinal Associates, Nashville, TN

[12]Department of Medicine, University of Texas Health Medical School

[13]Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine

[14]Gastroenterology and Hepatology, Thomas Jefferson University Hospital

[15]Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center

Abstract

Background & Aims—Radiofrequency ablation (RFA) is commonly used to treat Barrett's esophagus (BE). We assessed the incidence of esophageal adenocarcinoma (EAC) after RFA, predictors of EAC, and EAC-specific and all-cause mortality rates.

Methods—We assessed outcomes in a multicenter study of RFA for BE. Kaplan-Meier curves of EAC incidence were stratified by baseline histology. Crude EAC incidence and mortality (both all-cause and EAC-specific) rates were calculated, and adjusted all-cause mortality rates were assessed. Logistic regression models were constructed to assess predictors of EAC and all-cause mortality.

Results—Among 4982 patients, 100 (2%) developed EAC (7.8/1000 person-years (PY)), and 9 (0.2%) died of EAC (0.7/1000 PY) in a mean 2.7 ± 1.6 years. The incidence of EAC in non-dysplastic BE (NDBE) was 0.5/1000 PY. Overall, 157 (3%) patients died during follow-up (all-cause mortality 11.2/1000 PY). On multivariate logistic regression, baseline BE length (OR 1.1 per cm) and baseline histology (ORs of 5.8 and 50.3 for low grade dysplasia and high grade dysplasia (HGD) respectively) predicted EAC incidence. Among 9 EAC deaths, 6 (67%) had baseline HGD and 3 (33%) had baseline intramucosal EAC. The most common causes of death were cardiovascular (15%) and extra-esophageal cancers (15%). No deaths were associated with RFA.

Conclusion—In this multicenter registry of RFA for BE, death from EAC was rare. The incidence of EAC was markedly lower than natural history studies, with the greatest absolute benefit seen in HGD.

Keywords

Keywords: Barrett's esophagus; radiofrequency ablation; incidence; esophageal adenocarcinoma; mortality

Introduction

Barrett's esophagus (BE) is defined as esophageal metaplasia in which normal squamous epithelium is replaced by intestinal metaplasia (IM). BE is associated with an increased risk

of esophageal adenocarcinoma (EAC), a cancer with a rapidly increasing incidence over the last four decades.[1-5] Radiofrequency ablation (RFA) is an endoscopic treatment shown to be safe and effective in inducing reversion to squamous epithelium.[6]

RFA is performed with the goal of preventing the development of EAC by eliminating intestinal metaplasia and dysplasia.[7] Endoscopic treatment has been associated with decreased rates of progression to EAC in the setting of dysplasia.[6,8-10] However, few studies have assessed the risk of development of EAC and the risk of death from EAC after RFA. Also, no study has had adequate power to assess the risk of EAC following RFA for non-dysplastic BE (NDBE). All cause-mortality in untreated BE may be increased, but due to non-neoplastic events, compared to the general population.[11-17] However, little is known about all-cause mortality in patients after endoscopic treatment for BE.

The aims of this study were 1) to assess the incidence of EAC in patients with varying grades of dysplasia treated with RFA in a large multicenter sample, 2) to assess the mortality from EAC in patients receiving RFA, 3) to identify the predictors of EAC incidence in patients receiving RFA, and 4) to evaluate all-cause mortality in patients undergoing RFA.

Methods

U.S. RFA Patient Registry

The U.S. RFA Patient Registry is a multi-center study reporting processes and outcomes of care after treatment with RFA for BE at 148 institutions (113 community-based, 35 academic-affiliated). The registry was developed as a research tool to assess clinical outcomes after RFA using the HALO Ablation Systems (Covidien, GI Solutions, Sunnyvale, CA), and was funded by Covidien. The registry did not mandate protocols for care, but provided a suggested protocol for treatment and follow-up of patients with BE. All physicians (n=320) used either Western institutional review board (IRB) approval, or obtained IRB approval through their respective institutions.

Registry Patient Eligibility

Patients were enrolled from July, 2007 to July, 2011, and followed intil July, 2014. Patients were eligible for inclusion if: (1) they had endoscopic evidence of columnar metaplasia in the tubular esophagus with accompanying biopsies from the esophagus demonstrating intestinal metaplasia, and (2) received circumferential and/or focal RFA treatment for BE. Subjects were classified using standardized histological grading, including non-dysplastic BE (NDBE), indefinite for dysplasia (IND), low-grade dysplasia (LGD), high-grade dysplasia (HGD), or esophageal adenocarcinoma (EAC), subclassified as intramucosal carcinoma (IMC), and invasive esophageal adenocarcinoma .[18,19] Patients who had received one or more RFA treatments prior to enrollment had collection of retrospective data, with subsequent prospective collection for ensuing treatments. Patients who had not yet undergone treatment were prospectively enrolled in the study.

Data Collection and Record Retention

Information collected in the registry included demographic data, baseline histology, endoscopic findings, number of treatment sessions, ablation outcomes, and complications. Data on mortality were prospectively collected, with cause of death reported by the enrolling center. All data were recorded on standardized case report forms. Data were collated into a central electronic database, with real-time monitoring for logic checks and consistency. Data were analyzed by investigators in the clinical epidemiology program at UNC (T32 DK07634), who had complete access to the data.

Treatment Protocol

We provided a suggested treatment protocol to physician investigators, as previously described.[20] This standardized protocol included medical therapy with twice-daily PPIs to minimize any baseline inflammatory changes of the mucosa and decrease acid reflux prior to and throughout RFA treatment, unless there was a documented history of antireflux surgery. Recommended treatment was based on previously published data,[6] and called for a follow-up endoscopy 2-3 months after initial RFA. At this endoscopy, additional circumferential or focal RFA treatment was performed for any visible residual columnar epithelium in the tubular esophagus, depending on the extent of the disease. If no visible columnar epithelium was observed, four-quadrant biopsies every cm were recommended throughout the length of the pre-treatment BE. If these biopsies were clear of BE on pathologic review, the patients entered the surveillance phase. Initial surveillance was recommended at 3 months for HGD or 6 months for NDBE, IND, or LGD. If follow-up biopsies revealed IM, dysplasia, or intramucosal EAC, recurrent treatment with RFA was recommended, unless mucosal nodularity was detected, in which case endoscopic mucosal resection was suggested. For invasive EAC, patients without contraindication were referred for consideration for esophagectomy or multimodality therapy as appropriate.

Adverse events were reported using standardized forms and terminology. Each site also complied with reporting guidelines for their institution regarding reporting adverse events to their IRB and FDA under the MDR reporting regulation in 21 C.F.R. Part 803.

Statistical Analysis

Statistical analysis was performed using Stata version 12.0 and SAS version 9.3. All patients completing at least one biopsy session after study enrollment were included. Additionally, in order to generate the most conservative estimates of mortality, any patient dying after the initial treatment but prior to the first biopsy session was also included in mortality calculations. There were no further exclusion criteria. For all-cause mortality and EAC-specific mortality calculations, person-years (PY) were calculated as the difference between the date of the first RFA and the date of the last visit or death, whichever came first. For the EAC incidence calculation, the population was limited to patients who were EAC-free at baseline, had not undergone esophagectomy prior to study enrollment, and completed at least one biopsy session after enrollment. To provide the most conservative estimate of EAC incidence following RFA, for our primary analysis, any EAC detected at any time after the initial RFA treatment session was considered incident EAC. To assess the possible effect of

miscategorization of prevalent EAC as incident EAC, we also provide an estimate excluding the first year after RFA.

Bivariate analyses were performed with chi-square testing for categorical variables. For continuous variables with non-normal distributions, the Wilcoxon two-tailed t approximation (rank-sum) was used. Comparison of rates in the present study to historical controls was performed assuming Wald confidence limits and degrees of freedom of one less than the N for the smaller study or subgroup. Logistic regression models were constructed by including all variables significant at the $p<0.2$ level on bivariate testing and then reducing until all factors were significant at the $p<0.05$ level. Main effects multivariate odds ratios (ORs) were generated from the reduced model, and adjusted multivariate odds ratios were generated by adding known clinical predictors of EAC to the model. Kaplan-Meier curves were generated by baseline histology. Crude incidence and mortality (all-cause and EAC-specific) rates were calculated, and age- and sex-adjusted all-cause mortality rates were calculated using the 2010 US population aged ≥45 years as reference.[21] For odds ratios with empty strata and incidence rates of zero exact methods were applied.

Results

Of 5521 patients who enrolled in the U.S. RFA Patient Registry, 4982 (90%) met inclusion criteria. The remaining 539 (10%) did not undergo a biopsy session following initial treatment, and therefore were not at risk for a cancer diagnosis. These subjects were excluded from the risk analysis. The subjects were predominantly white (95%), male (74%), and had a mean age of 62 years (Table 1). At presentation, the mean BE segment was 4.1 cm, and 2346 (47%) patients had NDBE, 368 (7%) had IND, 1020 (20%) had LGD, 990 (20%) had HGD, 195 (4%) had intramucosal EAC, and 63 (1%) had invasive EAC. Compared to the subjects undergoing at least one biopsy session, those who were unbiopsied and therefore excluded were younger (mean 60 years vs 62 years, $p<0.0001$), and more likely to be non-white (8% vs 5%, $p=0.0006$) and female (30% vs 26%, $p=0.03$). These unbiopsied patients also had BE of lower histologic grade at baseline (61% NDBE vs 47%, $p<0.0001$).

The average time in study was 2.7 ± 1.6 years, producing a total of 13,835 PY of follow up, and patients underwent a mean of 2.9 ± 1.8 RFA treatments. Eighty-four percent of patients achieved complete eradication of intestinal metaplasia (CEIM). During the study period, 100 (2%) incident cases of EAC developed and 9 (0.2%) patients died from EAC, among 157 (3%) total deaths.

EAC Incidence

Among 4,982 patients in the study, 4,698 (94%) were included in the EAC incidence calculation. Over 12,804 PY, 100 (2%) patients developed EAC, an incidence rate of 7.8 per 1000 PY (Table 2). Excluding the first year after RFA, 54 patients (1%) developed EAC over 8,924 PY, an incidence rate of 6.1 per 1,000 PY. Among all registry participants, the majority of incident EAC (n=83) occurred in patients with HGD (30.3 per 1000 PY) while an additional 12 occurred in patients with LGD (4.3 per 1000 PY), 2 occurred in patients with IND (2.1 per 1000 PY), and the remaining 3 cases occurred in patients with NDBE (0.5

per 1000 PY) (Figure 1). All three patients with NDBE who progressed to cancer had long segment disease (7, 10, and 11cm). The cancer incidence among NDBE with long segment disease (> 3 cm) was 1.5 per 1,000 person-years (95% CI 0.4-3.8) compared to 0.0 per 1,000 person-years (95% CI 0.0-0.9) for short segment.

Of the 100 incident cases of EAC, 46 were invasive and 54 were IMC. Among the invasive cancers, 39 (85%) occurred in patients who never achieved CEIM while the remaining 7 (15%) occurred after CEIM. Of 54 IMC, 24 (44%) never reached CEIM. An additional 16 (30%) developed EAC, but were successfully treated to CEIM. The remaining 14 (26%) developed IMC after CEIM. Of those 14, 11 (79%) were treated back to CEIM. Thus, 27 (50%) of the patients developing IMC concluded treatment with CEIM. Thirty-five patients with incident cancer underwent esophagectomy (21 invasive EAC, 14 IMC).

Compared to patients who did not develop EAC, patients with incident EAC were older (mean 66 years vs 61, $p<0.0001$) and more likely to be male (82% vs 73, $p = 0.04$) (Table 1). They had longer BE segments at presentation (7 cm vs 4, $p<0.0001$), and higher pathologic grade (3% NDBE at presentation vs 51%, $p<0.0001$). Patients who developed EAC were more likely to have undergone gastric bypass prior to study enrollment (3% vs 0.4%, $p<0.0001$). EAC incidence was not impacted by treatment in an academic vs a community center (13.9 per 1,000 person-years vs 5.7 per 1,000 person-years, RR adjusted for baseline histologic grade 0.92 [95% CI 0.62-1.38]).

Subsquamous BE was identified in a small number of patients (n = 136, 3%), but those patients more frequently went on to develop cancer (49.6 per 1,000 person-years vs. 7.1 per 1,000 person-year, $p < 0.0001$; univariate OR 6.0 [95% CI 3.3-10.8]). The majority of subsquamous pathology was NDBE (n=94, 69%), while IND occurred in 3 (2%) patients, LGD in 14 (10%) and HGD in 19 (14%). Six cases of subsquamous adenocarcinomas were identified, 4 intramucosal cancers (3%) and 2 invasive cancers (1.5%). All subsquamous EAC occurred prior to CEIM. Following CEIM, subsquamous pathology was much less common, found in 31 of 3983 (0.8%) patients. There were 26 visits with subsquamous NDBE, 3 with indefinite for dysplasia, 3 with LGD, 6 with HGD and no cases of EAC.

Increasing BE length also appeared to be associated with EAC incidence. Among patients with LGD, incidence rates of cancer were higher among long (>3cm) segment BE (6.3 per 1000 PY, 95% CI 2.4 - 10.2) than short segment (1.6 per 1000 PY, 95% CI 0.0 - 3.9). Among patients with HGD, incidence rates of cancer were also higher among long segment BE (37.9 per 1000 PY, 95% CI 28.6 - 47.1) than short segment BE (18.2 per 1000 PY, 95% CI 10.0 - 26.4).

On multivariate logistic regression, BE length, baseline histologic grade, and development of subsquamous pathology at any time during the study were associated with development of EAC. After adjustment for age, race, gender, and time in the study, each 1 cm increase in the length of the BE carried an OR of EAC development of 1.2 (95% CI 1.1-1.2) (Table 3). The odds of developing EAC increased with increasing histologic grade, with an adjusted OR of 3.6 for IND (95% CI 0.6-21.7), 5.9 for LGD (95% CI 1.6-21.5), and 48.44 for HGD

(95% CI 14.9-157.0) (Figure 2). Subsquamous pathology increased the odds of developing EAC (OR 2.7 95% CI [1.4-5.3]) as did prior gastric bypass (OR 9.4, 95% CI [1.1-78.7]).

A separate logistic regression model for invasive EAC again resulted in the same three factors—BE segment length, histologic grade, and subsquamous pathology at any time during the study—as the only significant factors predicting invasive EAC. Each 1 cm increase in the length of the BE segment carried an OR of EAC development of 1.1 (95% CI 1.02-1.2). The OR for invasive EAC among patients with subsquamous pathology at any time was 2.6 (95% CI 1.02-6.4). The OR for IND was 2.8 (95% CI 0.3-31.2), for LGD it was 2.7 (0.5-16.6), and for HGD it was 32.5 (95% CI 7.5-140.7) (Table 3).

Comparison of EAC Risk to Historical Controls

The cancer incidence for each grade of dysplasia among treated patients in the registry was lower than that reported in past natural history studies. Historical incidence rates are reported in Supplemental table 1, along with significance testing against currently reported EAC incidence rates. Rates in treatment-naïve populations without dysplasia range from 1.0 to 5.0 per 1000 PY compared to our rate of 0.5 per 1000 PY.[22-24] In treatment-naïve populations with LGD the rates of progression range from 5.1 to 9.2 per 1000 PY compared to our rate of 4.3 per 1000 PY.[23-25] A meta-analysis of treatment-naïve patients with HGD estimated the rate of progression to adenocarcinoma at 65.8 per 1000 PY compared to our rate of 30.3 per 1000 PY.[2]

EAC Mortality

Of 4,982 patients, 9 (0.2%) died from EAC over 13,835 PY, a rate of 0.7 per 1000 PY (Table 2). Six (67%) of the deaths occurred in patients who had HGD at baseline, a rate of 2 per 1000 PY. The remaining 3 (33%) cases occurred in patients who presented with intramucosal EAC, a rate of 5.4 per 1000 PY. Compared to patients who did not die of EAC, those who died were older (mean 74 years vs 62, p=0.004) and had higher grade pathology at baseline (0% NDBE vs 47%, p<0.0001) (Table 1). EAC mortality was not impacted by treatment in a community vs. academic setting.

All-Cause Mortality

Of 4,982 patients, 157 (3%) died over 13,835 PY of follow up, an age- and sex-adjusted[21] rate of 11.7 per 1000 PY (Table 2). The mortality rate ratio for patients undergoing RFA for BE is 0.62 [95% CI 0.52-0.74]. Compared to those who did not die, those who died were older (mean 72 years vs 61, p<0.0001), had longer BE segments at baseline (mean 4.7cm vs 4.1, p=0.01), and had higher pathologic grade at baseline (23% NDBE vs 48%, p<0.0001) (Table 1). Survival correlated with baseline histologic grade, with patients with NDBE least likely to die and patients with invasive EAC most likely to die (Figure 3). The adjusted mortality rate was 6.4 per 1000 PY for patients entering the registry with NDBE, 10.6 for IND, 6.8 for LGD, 24.8 for HGD, 27.1 for intramucosal EAC and 43.3 for invasive. The most common causes of death were cardiac (n=24, 15%), non-EAC cancers (n=24, 15%), and natural causes (n=21, 13%) (Table 4). EAC was the 5th leading cause of death (n=9, 6%). There were no deaths related to RFA.

A logistic regression model was constructed to evaluate factors associated with mortality. On multivariate analysis after adjustment for race, gender, and time in study, the odds of dying during the study increased with increasing age (OR 1.1 per year, 95% CI [1.1-1.1]), and with increasing histologic grade (OR for IND 1.6 [0.8-3.3], LGD 1.3 [0.7-2.2], HGD 2.7 [1.7-4.4], intramucosal EAC 2.1 [1.0-4.6], and invasive EAC 12.0 [5.4-26.7]). Achieving CEIM was protective with an OR of 0.4 [0.3-0.6] (Table 3).

Discussion

Though the relationship of BE and EAC is well established, the impact of endoscopic therapy for BE on EAC incidence and mortality is not well described. Given that these therapies are performed in an effort to decrease death from cancer, such data are vital. The U.S. RFA Registry was designed to assess rates of EAC incidence and EAC-specific and overall death in a large, primarily community practice-based cohort. In this largest reported cohort of patients treated with RFA for BE, the rate of cancer incidence was low (7.8 per 1000 PY). For each baseline grade of dysplasia, cancer incidence was markedly decreased compared to natural history estimates from previous studies. This suggests that endoscopic therapy of BE, when applied outside tertiary care centers and randomized controlled trials, is associated with a low rate of EAC incidence.

Increasing BE segment length, subsquamous BE, and higher baseline pathologic grade were associated with an increased risk of EAC, with the greatest risk coming in the setting of baseline HGD. Subsquamous BE was uncommon, and no subsquamous cancers occurred after CEIM. In this large cohort, we did not find evidence of the occurrence of *de novo* subsquamous cancer, since any patient with a biopsy containing submucosal cancer also had residual visible columnar tissue. Interestingly, however, the finding of subsquamous BE prior to CEIM was a strong risk factor for subsequent incident EAC. Whether this finding marks a group with a more aggressive disease state, is a chance finding due to the relatively low numbers of subsquamous BE patients who later developed EAC, or is due to another explanation, is unclear. During almost 14,000 PY of follow up, 9 patients died from EAC, a rate of 0.7 per 1000 PY. Among 157 total deaths, EAC tied for fifth behind causes typically associated with the 6^{th} and 7^{th} decades of life in the US population: cardiovascular disease, malignancy at sites outside the esophagus, “natural causes,” and multi-organ system failure.

This work is the first to provide a robust estimate of EAC incidence after endoscopic treatment for NDBE. It joins a small body of literature addressing the risk of development of EAC after RFA, though no prior research for this purpose has been composed primarily of patients treated outside of tertiary centers. Compared to results from a previous meta-analysis evaluating the natural history of BE, RFA reduced the incidence of EAC from 6 per 1000 PY to 0.5 per 1000 PY in NDBE, from 17 per 1000 PY to 4 per 1000 PY for LGD, and from 66 per 1000 PY to 30 per 1000 PY in HGD.[26] Even when compared to the lowest estimates of risk available in NDBE, the currently reported risk is less than half, suggesting a protective effect.[24] While care must be taken when comparing the current results to those from meta-analyses and previous cohort data due to the potential for heterogeneity of the compared patients and the possibility of a “healthy patient effect” in those treated with RFA, given the present data and past studies, RFA appears effective for reducing the incidence of

EAC after BE, regardless of histologic grade. The greatest benefit, in terms of absolute risk reduction compared to historical estimates, was seen in patients with HGD.

Unlike some previous analyses, which have assessed rates of progression and EAC after the achievement of CEIM,[27] the present analysis assessed EAC risk after the first treatment with RFA. Requiring successful RFA prior to inclusion in this analysis would have excluded 63 of the 100 incident cancers we report, as those cancers occurred in patients who never reached CEIM. However, the clinically relevant question to the patient considering RFA therapy is the cancer risk after initiation of therapy, not the risk after achieving CEIM. In calling any EAC occurring after initiation of therapy an incident EAC, we have likely miscategorized a proportion of prevalent EAC as incident EAC and consequently inflated our risk estimates by some degree. In order to avoid this miscategorization, some previous natural history studies have excluded EAC occurring within the first 6-12 months from calculations of cancer incidence.[28] Such an approach would have decreased the EAC rates we report. However, we sought to generate the most conservative estimate of EAC risk we could, and the appropriate period of time necessary to exclude a cancer as prevalent is unknown.

Our findings that BE segment length and higher baseline pathologic grade increase the risk of EAC are corraborated by previous studies.[24,26] To date, only baseline pathologic grade has been used in the determination of surveillance intervals after RFA. These data may be useful in further tailoring endoscopic surveillance following RFA to patient risk for EAC.

Previous studies have examined the mortality rate in patients with BE with inconsistent results. Several population-based studies have shown an increase in mortality rates in people with BE compared to the general population[11,13,15,29] while several other studies have shown that the overall mortality rate excluding esophageal and gastric cancers was comparable to the general population.[12,30] Our findings demonstrate a significant decrease in all-cause mortality among patients undergoing RFA for BE. This is likely due to a “healthy patient effect,” analogous to the healthy worker effect, wherein the patients selected for RFA would have been selected in part for generally good health and an expectation that the procedure would be well tolerated. The all-cause mortality rate in our population was more than 15 times higher than the EAC mortality rate. Patients treated with RFA for their BE were far more likely to die from cardiac disease or cancer at sites outside the esophagus than from esophageal cancer, which is consistent with previous research.[29,30]

Interestingly, almost half of this study population had NDBE. This finding suggests that in real-world practice, treatment of NDBE with RFA is common. Societal guidelines are divided on this issue, with AGA guidelines suggesting that RFA should be an option in the treatment of select individuals with NDBE and for those with confirmed LGD, while the British Society of Gastroenterology (BSG) stands against the use of ablative therapy in those with LGD or NDBE.[31-33] As the BSG guidelines note, recently available level one evidence regarding the efficacy of RFA in the treatment of LGD may impact future recommendations.[10] As to the impact of a large number of NDBE patients in the present study, it might lead to under-estimation of cancer risk in the overall cohort compared to other RFA cohorts with larger proportions of dysplastic patients, but it would not impact the

rates when stratified by degree of baseline dysplasia. As we seek to better understand the role of ablative therapy in the BE disease spectrum, precise estimates of cancer risk following ablation of patients with varying degrees of histologic disease severity are essential to understand the value of the intervention. Currently, policy makers and decision analysts rely on expert opinion for these estimates. The current data allow a more evidence-based approach to utilization decisions for ablation in BE.

Our study has several limitations that must be considered. Our data are derived from an observational study where care paradigms including surveillance and biopsy intervals were recommended but not mandated. Given the size of this study, local pathology labs were used for the assessment of histology. While this is consistent with care of BE patients in the U.S., it likely introduces a higher degree of misclassification than would a single expert pathologist. Additionally, when comparing our data to historical estimates of cancer risk, there may be selection bias toward a healthier patient population in the present study since patients were only included if they were healthy enough to tolerate RFA treatment sessions. Due to this potential for selection bias, we suggest caution in the interpretation of the comparisons between these data and incidence rates from natural history studies. Also, approximately 10% of our patients did not undergo at least one biopsy session, and therefore were not included in our analyses. These patients tended to be younger with lower grade disease at baseline, making it less likely that differential progression in these patients would increase our estimates of EAC risk or death. However, we cannot exclude the possibility that patients who did not complete at least one biopsy session could have experienced EAC at a rate higher than the remainder of the cohort. Finally, our study suffers from the limitations which hamper any research evaluating cause of death: presumed causes of death are demonstrably inconsistent with autopsy findings,[34] and, while most Americans do not undergo autopsy, the lack of autopsy data may under- or over-estimate specific causes. While the lack of post-mortem results increases the possibility that EAC mortality could be underestimated, given the frequent endoscopies in this cohort and their known diagnosis of BE, we suspect that the rate of undiagnosed EAC leading to mortality would be low.

There are several important strengths to this study. First, we report the largest cohort of patients treated with RFA for BE. Additionally, our study utilized 320 physician participants from 148 community-based and academic-affiliated institutions. The diversity of practice settings and variety of procedural volumes improves the generalizability of our results. All study definitions were a priori, and data were collected in a standardized fashion. We applied the most conservative possible conventions to assessing cancer and mortality rates.

In conclusion, after initiating treatment with RFA, the risk of incident EAC or death from EAC is small. EAC incidence rates are lower than estimates derived from natural history studies when stratified by baseline histology, including a 3 to 10-fold decrease in the rate of progression from NDBE to EAC and an at least 50% decrease in the rate of HGD to EAC. However, comparisons between these estimates and historical controls are susceptible to selection bias. We have also found the risk of death to be similar in patients treated with RFA compared to the broader US population. Baseline histologic grade is the most important predictor not only of cancer development, but also of death from cancer and from non-cancer causes. EAC accounts for only a small portion of deaths in patients with BE, in

both treated cohorts as well as in past reports of untreated cohorts. The leading causes of death of BE patients are heart disease and cancers outside the esophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Relevant Personal and Financial Disclosures: Dr. Shaheen receives research funding from Covidien Medical, CSA Medical, NeoGenomics, Takeda Pharmaceuticals, Interpace Diagnostics, and CDx Medical. He is a consultant for Oncoscope. Drs. Triadafilopoulos, Muthusamy, Chmielewski, Corbett, Camara, Lightdale, Wolfsen, Chang, Overholt, Pruitt, Ertan, Komanduri, Infantolino, and Rothstein have received research funding from Covidien Medical. Dr. Wolf has received funding to attend educational events sponsored by Nestlé. The other authors have no conflicts to declare.

This research was funded by T32 DK07634 and P30 DK034987 from the National Institutes of Health and GI Solutions, a subsidiary of Covidien.

References

1. Ronkainen J, Aro P, Storskrubb T, et al. Prevalence of Barrett's esophagus in the general population: an endoscopic study. Gastroenterology. 2005; 129:1825–1831. [PubMed: 16344051]
2. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc. 2008; 67:394–398. [PubMed: 18045592]
3. Zagari RM, Fuccio L, Wallander MA, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. 2008; 57:1354–1359.
4. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005; 97:142–146. [PubMed: 15657344]
5. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. Am J Gastroenterol. 2008; 103:2694–2699. [PubMed: 18853967]
6. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med. 2009; 360:2277–2288. [PubMed: 19474425]
7. Bulsiewicz WJ, Shaheen NJ. The role of radiofrequency ablation in the management of Barrett's esophagus. Gastrointest Endosc Clin N Am. 2011; 21:95–109. [PubMed: 21112500]
8. Lyday WD, Corbett FS, Kuperman DA, et al. Radiofrequency ablation of Barrett's esophagus: outcomes of 429 patients from a multicenter community practice registry. Endoscopy. 2010; 42:272–278. [PubMed: 20146164]
9. Sharma VK, Jae Kim H, Das A, Wells CD, Nguyen CC, Fleischer DE. Circumferential and focal ablation of Barrett's esophagus containing dysplasia. Am J Gastroenterol. 2009; 104:310–317. [PubMed: 19174783]
10. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA. 2014; 311:1209–1217. [PubMed: 24668102]
11. Cook MB, Wild CP, Everett SM, et al. Risk of mortality and cancer incidence in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2007; 16:2090–2096. [PubMed: 17890521]
12. Schouten LJ, Steevens J, Huysentruyt CJ, et al. Total cancer incidence and overall mortality are not increased among patients with Barrett's esophagus. Clinical Gastroenterology and Hepatology. 2011; 9:754–761. [PubMed: 21570484]
13. Solaymani-Dodaran M, Logan RF, West J, Card T. Mortality associated with Barrett's esophagus and gastroesophageal reflux disease diagnoses-a population-based cohort study. Am J Gastroenterol. 2005; 100:2616–2621. [PubMed: 16393209]

14. Eckardt VF, Kanzler G, Bernhard G. Life expectancy and cancer risk in patients with Barrett's esophagus: a prospective controlled investigation. Am J Med. 2001; 111:33–37. [PubMed: 11448658]
15. Moayyedi P, Burch N, Akhtar-Danesh N, et al. Mortality rates in patients with Barrett's oesophagus. Aliment Pharmacol Ther. 2008; 27:316–320. [PubMed: 18062791]
16. van der Burgh A, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut. 1996; 39:5–8. [PubMed: 8881798]
17. Sikkema M, De Jonge PJ, Steyerberg EW, Kuipers EJ. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. Clinical gastroenterology and hepatology. 2010; 8:235–244. [PubMed: 19850156]
18. Wang KK, Sampliner RE. Practice Parameters Committee of the American College of Gastroenterology Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol. 2008; 103:788–797. [PubMed: 18341497]
19. Voltaggio L, Montgomery EA, Lam-Himlin D. A clinical and histopathologic focus on Barrett esophagus and Barrett-related dysplasia. Arch Pathol Lab Med. 2011; 135:1249–1260. [PubMed: 21970480]
20. Shaheen NJ, Kim HP, Bulsiewicz WJ, et al. Prior fundoplication does not improve safety or efficacy outcomes of radiofrequency ablation: results from the U.S. RFA Registry J Gastrointest Surg. 2013; 17:21–8. discussion p.28-9. [PubMed: 22965650]
21. Centers for Disease Control and Prevention. [Accessed Oct. 29, 2014] National Center for Health Statistics. Underlying Cause of Death, 1999-2011. The Centers for Disease Control and Prevention. Available at: http://wonder.cdc.gov/controller/datarequest/D76
22. Desai TK, Krishnan K, Samala N, et al. The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. Gut. 2012; 61:970–976. [PubMed: 21997553]
23. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2011; 103:1049–1057. [PubMed: 21680910]
24. Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med. 2011; 365:1375–1383. [PubMed: 21995385]
25. Singh S, Manickam P, Amin AV, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014; 79:897–909.e4. 983.e1–983.e3. quiz. [PubMed: 24556051]
26. Wani S, Puli SR, Shaheen NJ, et al. Esophageal adenocarcinoma in Barrett's esophagus after endoscopic ablative therapy: a meta-analysis and systematic review. Am J Gastroenterol. 2009; 104:502–513. [PubMed: 19174812]
27. Shaheen NJ, Overholt BF, Sampliner RE, et al. Durability of radiofrequency ablation in Barrett's esophagus with dysplasia. Gastroenterology. 2011; 141:460–468. [PubMed: 21679712]
28. Sharma P, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2006; 4:566–572. [PubMed: 16630761]
29. Solaymani-Dodaran M, Card TR, West J. Cause-specific mortality of people with Barrett's esophagus compared with the general population: a population-based cohort study. Gastroenterology. 2013; 144:1375–83. 1383.e1. [PubMed: 23583429]
30. Anderson LA, Murray LJ, Murphy SJ, et al. Mortality in Barrett's oesophagus: results from a population based study. Gut. 2003; 52:1081–1084. [PubMed: 12865262]
31. Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ, Association AG. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. Gastroenterology. 2011; 140:1084–1091. [PubMed: 21376940]
32. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2006; 63:570–580. [PubMed: 16564854]
33. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut. 2014; 63:7–42. [PubMed: 24165758]

34. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. N Engl J Med. 1985; 313:1263–1269. [PubMed: 4058507]

Abbreviations

BE	Barrett's esophagus
CEIM	complete eradication of intestinal metaplasia
CI	confidence interval
EMR	endoscopic mucosal resection
EAC	esophageal adenocarcinoma
HGD	high grade dysplasia
IND	indefinite for dysplasia
LGD	low grade dysplasia
NDBE	non-dysplastic Barrett's esophagus
OR	odds ratio
PY	person-years
RFA	radiofrequency ablation

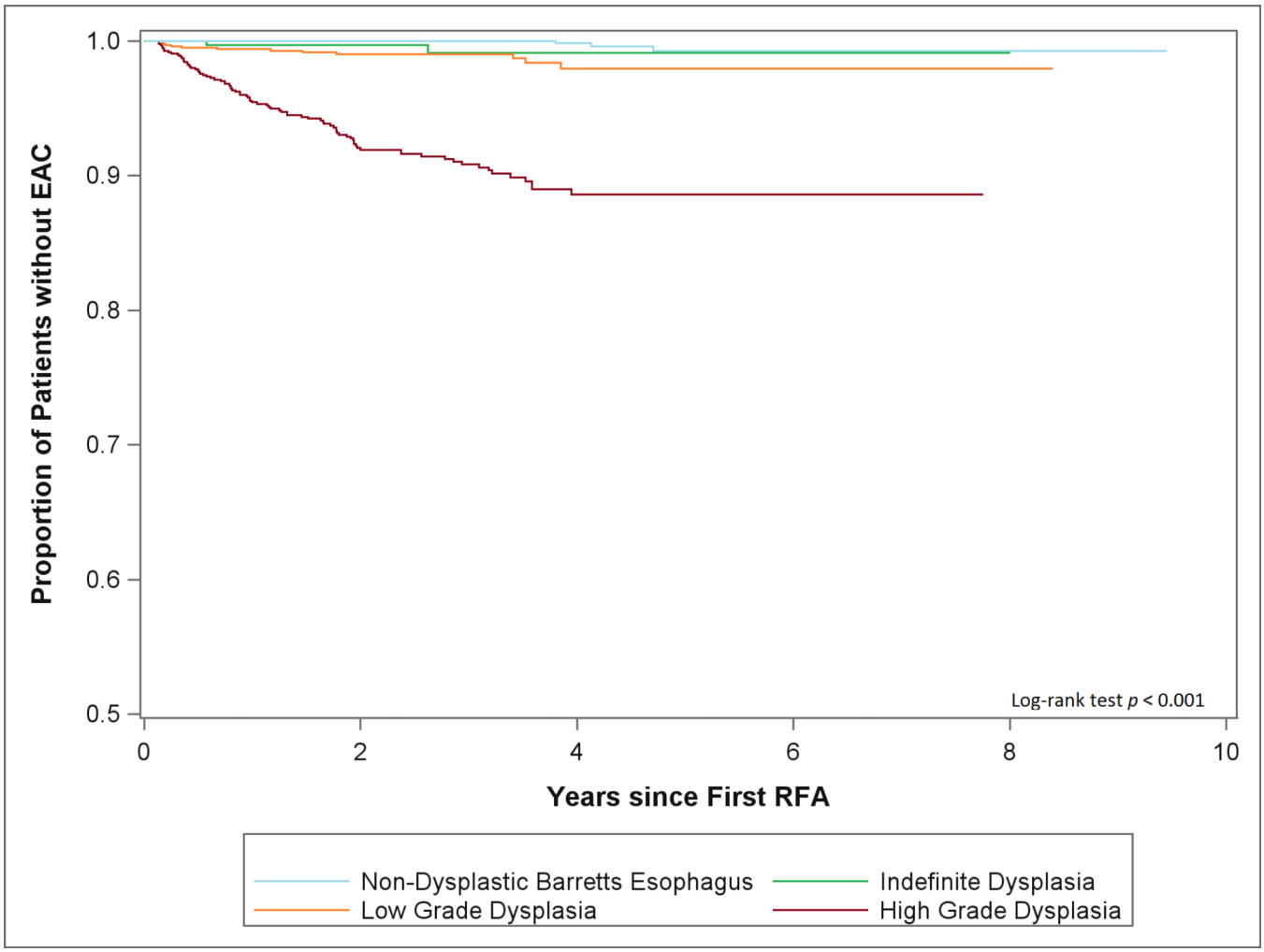

Figure 1. Kaplan-Meier Curves of EAC Incidence by Baseline Pathology

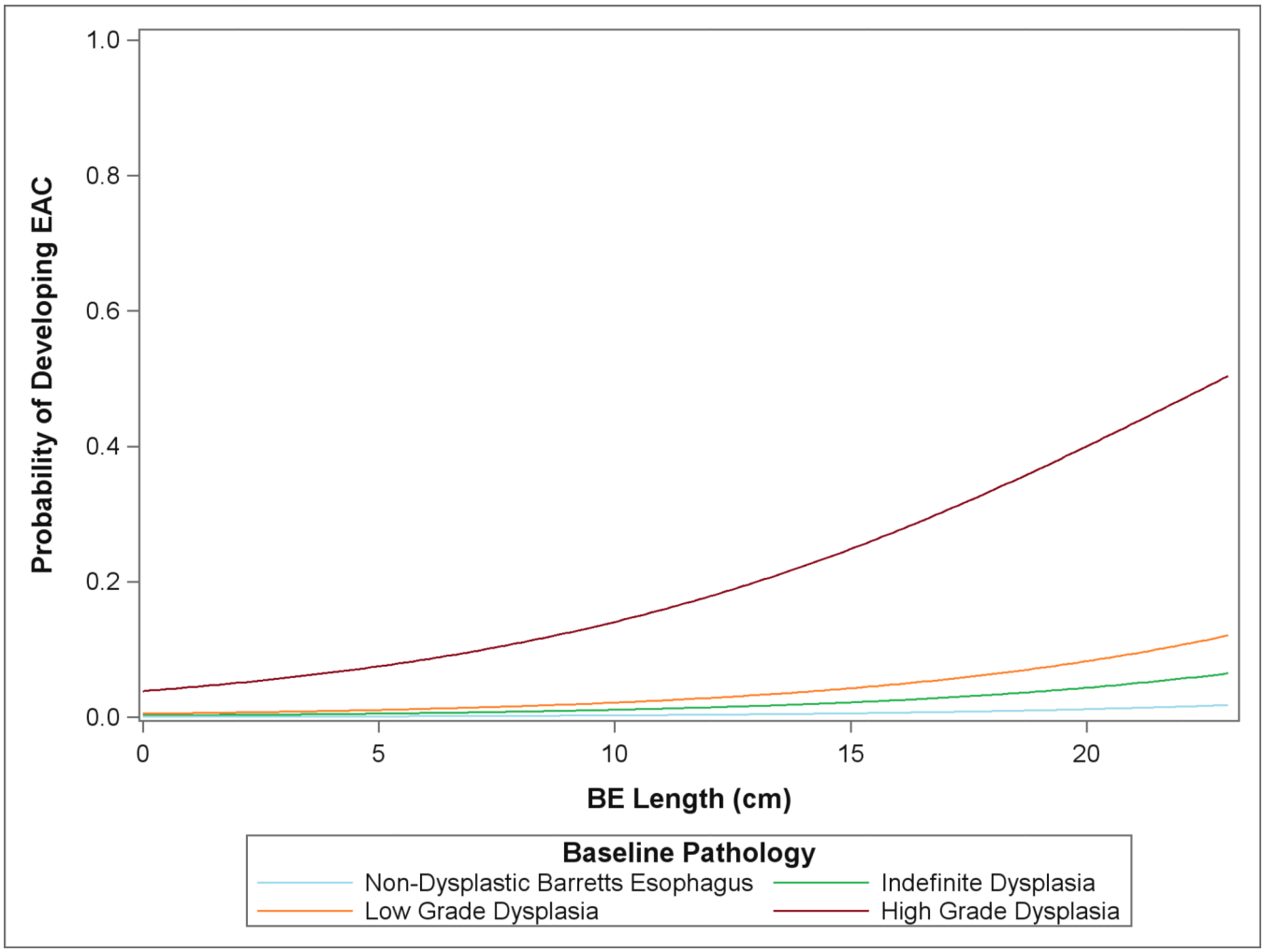

Figure 2. Probability of Developing EAC Based on Baseline Pathology and BE Segment Length. Derived via Multivariate Logistic Regression

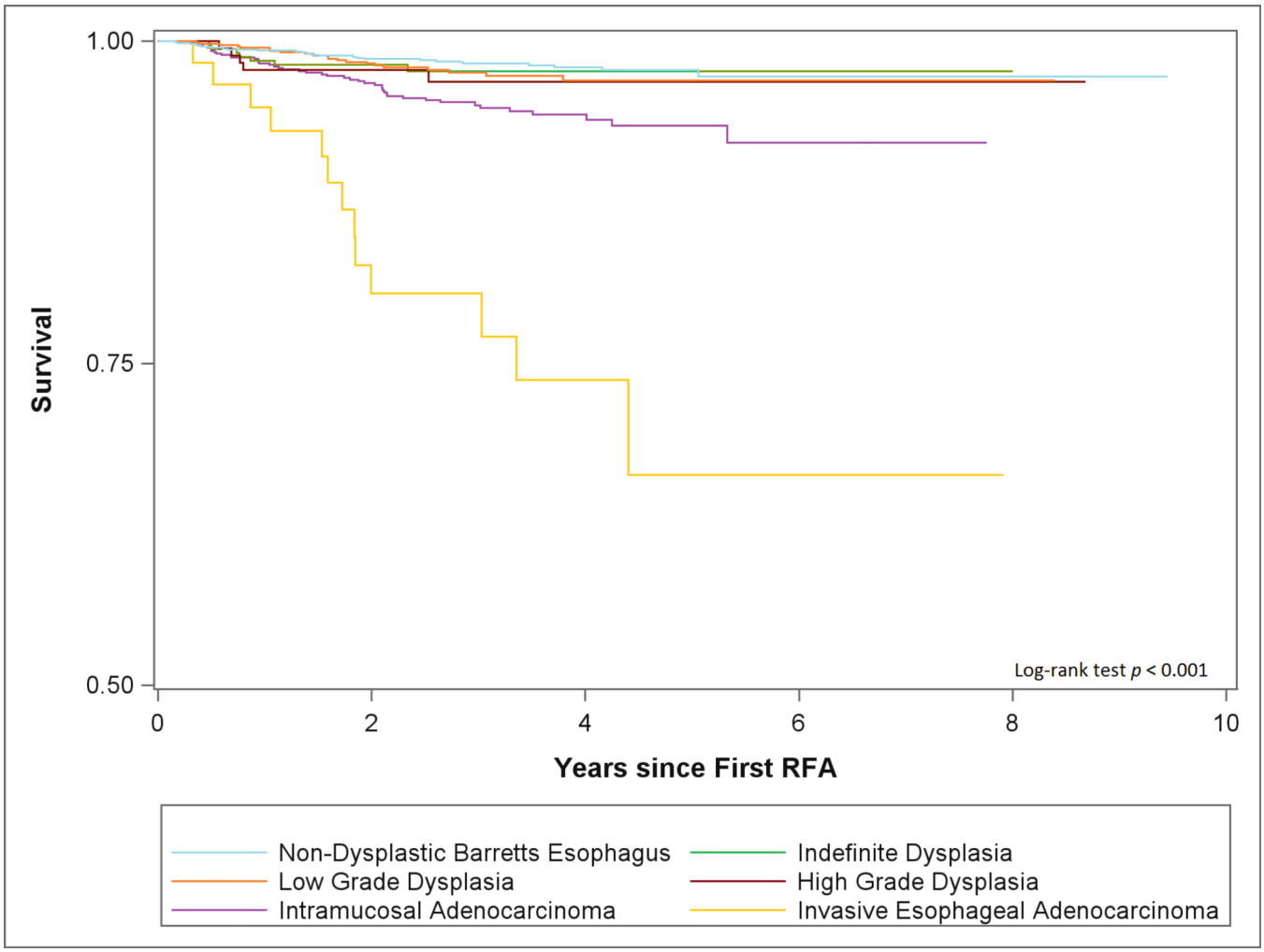

Figure 3. Kaplan-Meier Survival Curves by Baseline Histology

Table 1

Demographics and Baseline Characteristics

		Incident EAC†			EAC Mortality			All-Cause Mortality		
	All Subjects (n = 4982)	**Incident EAC (n = 100)**	**No EAC (n = 4598)**	**p-value**	**EAC Death (n = 9)**	**No EAC Death (n = 4973)**	**p-value**	**Death (n = 157)**	**No Death (n = 4825)**	**p-value**
Age, years (mean ± SD)	62 ± 11	66 ± 10	61 ± 11	<0.0001	74 ± 12	62 ± 11	0.004	72 ± 9	61 ± 11	<0.0001
White Race, n (%)	4634 (95)	95 (99)	4264 (95)	0.07	9 (100)	4625 (95)	0.50	149 (96)	4485 (95)	0.55
Male Gender, n (%)	3677 (74)	82 (82)	3349 (73)	0.04	6 (67)	3671 (74)	0.63	122 (78)	3555 (74)	0.26
Esophagectomy, n (%)	17 (0.3)	0 (0)	0 (0)	--	0 (0)	17 (0.3)	0.86	0 (0)	17 (0.4)	0.46
Fundoplication, n (%)	271 (5)	3 (3)	260 (6)	0.25	0 (0)	271 (5)	0.47	5 (3)	266 (6)	0.21
Gastric Bypass, n (%)	20 (0.4)	3 (3)	17 (0.4)	<0.0001	0 (0)	20 (0.4)	0.85	0 (0)	20 (0.4)	0.42
BE length, cm (mean ± SD)	4.1 ± 3.3	7.0 ± 3.8	4.0 ± 3.2	<0.0001	5.3 ± 4.7	4.1 ± 3.3	0.53	4.7 ± 3.5	4.1 ± 3.3	0.01
Stricture, n (%)	187 (4)	4 (4)	159 (3)	0.94	1 (11)	186 (4)	0.38	9 (6)	178 (4)	0.57
Baseline Pathology				<0.0001			<0.0001			<0.0001
NDBE, n (%)	2346 (47)	3 (3)	2341 (51)		0 (0)	2346 (47)		36 (23)	2310 (48)	
IND, n (%)	368 (7)	2 (2)	363 (8)		0 (0)	368 (7)		10 (6)	358 (7)	
LGD, n (%)	1020 (20)	12 (12)	1003 (22)		0 (0)	1020 (21)		26 (17)	994 (21)	
HGD, n (%)	990 (20)	83 (83)	891 (19)		6 (67)	984 (20)		60 (38)	930 (19)	
Intramucosal EAC, n (%)	195 (4)	--	--		3 (33)	192 (4)		11 (7)	184 (4)	
Invasive EAC, n (%)	63 (1)	--	--		0 (0)	63 (1)		14 (9)	49 (1)	

†This excludes 22 patients who died before undergoing a biopsy (3 with baseline intramucosal and 1 with baseline invasive EAC), 192 patients with baseline intramucosal EAC (4 with esophagectomy), 62 with baseline invasive EAC (5 with esophagectomy), and 8 who did not have EAC but had previously undergone esophagectomy.

Table 2

Incidence and Mortality of EAC after RFA in Patients with BE, by Baseline Histology

Baseline Histology	Patients n (%)	Patient-Years of Follow-up	Incident EAC Cases n	EAC Incidence per 1000 PY [95% CI]	Deaths from EAC n	EAC Mortality per 1000 PY [95% CI]	All-Cause Mortality n	All-Cause Mortality per 1000 PY [95% CI]	
								Unadjusted	Adjusted‡
NDBE	2346 (47)	6348	3	0.5[0.1-1.4]	0	0 [0-0.6]	36	5.7 [4.0-7.9]	6.4 [4.0-8.8]
IND	368(7)	967	2	2.1[0.3-7.6]	0	0 [0-3.8]	10	10.3 [5.0-19.0]	10.6 [1.9-19.4]
LGD	1020(21)	2852	12	4.3[2.2-7.5]	0	0 [0-1.3]	26	9.1 [6.0-13.4]	6.8 [3.4-10.1]
HGD	990(20)	2928	83	30.3[24.2-37.6]	6	2.0 [0.8-4.5]	60	20.5 [15.6-26.4]	24.8[12.1-37.4]
Total, non-malignant	4724(95)	13095	100	7.8[6.4-9.5]	6	0.5 [0.2-1.0]	132	10.1 [8.4-12.0]	11.5 [8.3-14.6]
Intramucosal EAC	195(4)	560	--	--	3	5.4[1.1-15.7]	11	19.6 [9.8-35.2]	27.1 [0.0-69.2]
Invasive EAC	63(1)	180	--	--	0	0 [0-20.5]	14	77.9 [42.6-130.8]	43.3[1.4-85.2]
Total	4982	13835	--	--	9	0.7[0.3-1.2]	157	11.3 [9.6-13.3]	11.7 [9.0-14.5]

‡Age- and sex-adjusted to the 2010 US population age 45 and older.

Table 3
Multivariate Logistic Regression Results for Predictors of EAC and Mortality

	Multivariate Main Effect Odds Ratio [95% CI]	Adjusted‡ Multivariate Odds Ratio [95% CI]
Predictors of Incident EAC		
BE Length (per cm)	1.1 [1.1, 1.2]	1.2 [1.1, 1.2]
Subsquamous BE	2.9 [1.5, 5.4]	2.7 [1.4, 5.2]
Histology (reference = NDBE)		
IND	3.6 [0.6, 21.7]	3.6 [0.6, 21.7]
LGD	7.4 [2.1, 26.3]	5.9 [1.6, 21.5]
HGD	51.8 [16.2, 165.2]	48.4 [14.9, 157.0]
Predictors of Invasive EAC		
BE Length (per cm)	1.1 [1.01, 1.2]	1.1 [1.02, 1.2]
Subsquamous BE	3.0 [1.3, 7.1]	2.6 [1.02, 6.4]
Histology (reference = NDBE)		
IND	2.8 [0.3, 31.6]	2.8 [0.3, 31.2]
LGD	4.9 [1.0, 25.6]	2.7 [0.5, 16.6]
HGD	36.5 [8.7, 153.4]	32.5 [7.5, 140.7]
Predictors of All-Cause Mortality		
Age (per year)	1.1 [1.1, 1.1]	1.1 [1.1, 1.1]
Achieved CEIM	0.2 [0.1, 0.3]	0.4 [0.3, 0.6]
Histology (reference = NDBE)		
IND	1.5 [0.7, 3.0]	1.6 [0.8, 3.3]
LGD	1.1 [0.6, 1.9]	1.3 [0.7, 2.2]
HGD	2.2 [1.4, 3.4]	2.7 [1.7, 4.4]
Intramucosal EAC	1.6 [0.8, 3.4]	2.1 [1.0, 4.6]
Invasive EAC	8.6 [4.1, 18.2]	12.0 [5.4, 26.7]

‡Predictors of EAC model adjusted for age, race, gender, and time in study. Predictors of all-cause mortality model adjusted for race, gender, and time in study.

Table 4

Causes of Death by Worst Histology

	ND, n	IND, n	LGD, n	HGD, n	IMC, n	EAC, n	Total, n (%)
Cardiac	7	0	4	9	3	1	**24 (15)**
Non-EAC cancer	5	1	4	10	2	2	**24 (15)**
Natural Causes	7	2	5	5	0	2	**21 (13)**
Multi-Organ System Dysfunction	1	3	2	4	0	0	**10 (6)**
Neurologic	3	0	0	4	0	2	**9 (6)**
EAC	0	0	0	6	3	0	**9 (6)**
Pulmonary	1	0	4	2	0	1	**8 (5)**
Infection	0	0	0	3	0	1	**4 (3)**
Renal disease	1	0	0	2	0	0	**3 (2)**
Accident/trauma	0	0	0	3	0	0	**3 (2)**
Liver disease	0	0	1	0	0	1	**2 (1)**
Other[§]	5	1	3	0	0	1	**10 (6)**
Not Specified	6	3	3	12	3	3	**30 (19)**
Total, n (%)	**36 (23)**	**10 (6)**	**26 (17)**	**60 (38)**	**11 (7)**	**14 (9)**	**157 (100)**

[§]Includes post-surgical complications, heat stroke, hypovolemic shock due to bleeding, ischemic bowel disease, severe deconditioning, and suicide.