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Identification of Prognostic Phenotypes of Esophageal Adenocarcinoma in 2 Independent Cohorts

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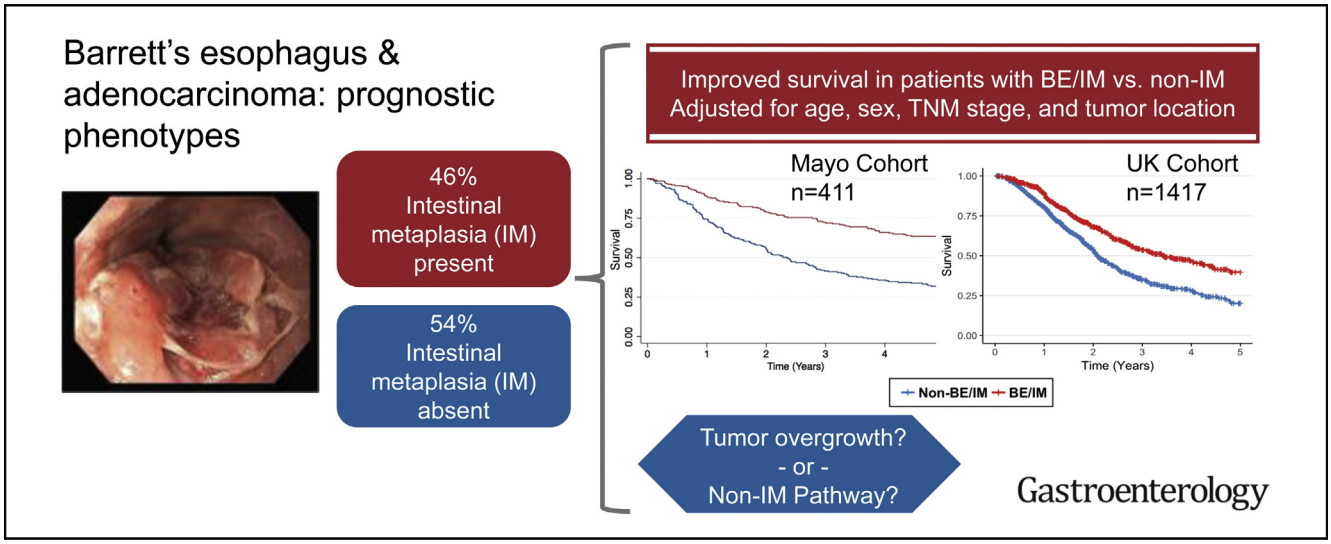
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e17. Learning Objective: Upon completion of this CME activity, successful learners will be able to discuss the possibility of 2 phenotypic presentations of adenocarcinoma that are dependent or independent of visible Barrett's epithelium and histologic intestinal metaplasia.



BACKGROUND & AIMS: Most patients with esophageal adenocarcinoma (EAC) present with de novo tumors. Although this could be due to inadequate screening strategies, the precise reason for this observation is not clear. We compared survival of patients with prevalent EAC with and without synchronous Barrett esophagus (BE) with intestinal metaplasia (IM) at the time of EAC diagnosis. **METHODS:** Clinical data were studied using Cox proportional hazards regression to evaluate the effect of synchronous BE-IM on EAC survival independent of age, sex, TNM stage, and tumor location. We analyzed data from a cohort of patients with EAC from the Mayo Clinic (n=411; 203 with BE and IM) and a multicenter cohort from the United Kingdom (n=1417; 638 with BE and IM). **RESULTS:** In the Mayo cohort, BE with IM had a reduced risk of death compared to patients without BE and IM (hazard ratio [HR] 0.44; 95% CI, 0.34–0.57; $P<.001$). In a multivariable analysis, BE with IM was associated with longer survival independent of patient age or sex, tumor stage or location, and BE length (adjusted HR, 0.66; 95% CI, 0.5–0.88; $P=.005$). In the United Kingdom cohort, patients BE and IM had a reduced risk of death compared with those without (HR, 0.59; 95% CI, 0.5–0.69; $P<.001$), with continued significance in multivariable analysis that included patient age and sex and tumor stage and tumor location (adjusted HR, 0.77; 95% CI, 0.64–0.93; $P=.006$). **CONCLUSION:** Two types of EAC can be characterized based on the presence or absence of BE. These findings could increase our understanding the etiology of EAC, and be used in management and prognosis of patients.

Keywords: Esophageal Adenocarcinoma; Barrett Esophagus; Survival; Esophagus.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Most patients with esophageal adenocarcinoma (EAC) present de novo suggesting either inadequate screening strategies or existence of a more rapid or independent Barrett's esophagus (BE) pathway.

NEW FINDINGS

Over half of EAC patients from two independent cohorts (one multicenter), comprising over 1800 cases, occurred without endoscopic or pathologic evidence of Barrett's esophagus/intestinal metaplasia. Patients with these cancers have a reduced overall survival compared to those with associated Barrett's.

LIMITATIONS

A poorer prognosis for EAC without IM may also result from poor response to therapy. Cancers of the esophago-gastric junction may also be confused with esophageal adenocarcinoma.

IMPACT

An association of esophageal adenocarcinoma without macroscopic or microscopic evidence of Barrett's esophagus alters prognosis and may have implications for screening and management strategies.

Esophageal adenocarcinoma (EAC) is a major public health concern because of rapidly increasing incidence rates and fewer than 20% patients surviving beyond 5 years. One of the most well-defined risk factors is the presence of the precursor lesion, Barrett esophagus (BE), which can occur in the background of heartburn symptoms or remain clinically silent. Therefore, there has been a concerted effort over several decades to identify and monitor patients with BE characterized by intestinal metaplasia (IM).[1] However, the overwhelming majority of patients who develop EAC present de novo[2] and therefore do not benefit from endoscopic surveillance programs.[3–5] Therefore, research efforts have focused on finding easily identifiable factors that might select an at-risk group for more systematic screening.[6–10] Similarly, researchers have been developing less expensive and easier to use screening devices and biomarker assays applied to biopsy and cytology specimens and blood samples.[11–13]

It has been assumed that the sequence of reflux-induced inflammation to cancer is similar across all patients who develop EAC such that identification of BE would provide years of surveillance to treat incident dysplasia or cancer before the development of incurable adenocarcinoma. However, in some patients who develop EAC, it has been observed that no BE is present at the time of surgical resection.[14] In these patients, it is assumed that the cancer grows over and/or replaces the previously extant metaplasia.

However, another quite distinct explanation could be possible. If a more rapidly evolving and/or aggressive form of EAC developed from a small and easily missed area of esophageal metaplastic epithelium or if the stage of intestinalization from inflammation to cancer was more ephemeral, less prominent, or absent,[14–16] attenuating identification with our current screening strategies, then a large proportion of prevalent EAC cases could be explained. In addition, there is some molecular evidence that catastrophic genomic events such as chromothripsis could lead to more rapid progression to cancer.[15,17]

Thus, we hypothesized that there might be a group of patients with EAC without coexisting BE-IM at the time of cancer diagnosis who have a more aggressive form of EAC that might lead to a poorer prognosis compared with those with prevalent BE-IM. To address this question, we compared the clinicopathologic characteristics and survival in 2 types of patients: those who present with EAC in the context of histologic and/or endoscopically identifiable IM of the esophagus vs those who present with adenocarcinoma without identifiable IM (non–BE-IM). This question was evaluated in 2 distinct but contemporaneous cohorts for whom we had high-quality pathologic and outcome data available.

Methods

Study Population

Two cohorts were independently collected and analyzed. At the Mayo Clinic (Rochester, MN), all patients with a diagnosis of EAC treated in 2011–2012 were included regardless of stage and treatment modality and a retrospective analysis was conducted. These years were selected to allow us to estimate 5-year mortality. The study was approved by the institutional review board of the Mayo Clinic (number 17-003675 on May 15, 2017). A prospective multicenter cohort was studied from the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) in the United Kingdom. The UK-based consortium was set up in 2010 to prospectively collect clinical and molecular data to inform patient management strategies and as the vehicle for whole-genome sequencing data as part of the International Cancer Genome Consortium. The study was registered (UKCRNID 8880) and approved by the relevant institutional ethics committees (REC 07/H0305/52 and 10/H0305/1) and all subjects provided individual informed consent. This analysis included all OCCAMS patients diagnosed with EAC from 2002 through 2017 from 25 sites across the United Kingdom, all stages of disease, all treatment modalities, and all locations as reported by Siewert classifications[18] and follow-up for all patients is up to 5 years.

Although these 2 cohorts were studied independently, the following common methodology was used. Patients were excluded for esophageal squamous cell carcinoma (Mayo Clinic, n = 75; OCCAMS, n = 122), nonprimary esophageal cancer (Mayo Clinic, n = 17; OCCAMS, n = 37), and absence of

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Abbreviations used in this paper: aHR, adjusted hazard ratio; BE, Barrett esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction; HR, hazard ratio; IM, intestinal metaplasia; IQR, interquartile range; OCCAMS, Oesophageal Cancer Clinical and Molecular Stratification.

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pathology specimens (Mayo Clinic, n = 12). For this study we were interested in all EAC cases presenting outside BE surveillance programs, because surveillance-detected cases are likely to be biased by being an earlier stage. Patients with EAC detected in a surveillance program more than 1 year after identification of BE were excluded from the Mayo Clinic cohort (n = 97). The OCCAMS cohort includes 135 patients who self-reported being in surveillance for BE because there was no information regarding the timeline for BE diagnosis and subsequent surveillance. These are evaluated for their effect on survival in the Results. All patients had BE-IM at the time of their cancer diagnosis.

Pathology Review

A strict expert pathology review was performed by 1 specialized gastrointestinal pathologist with more than 30 years of experience in the Mayo Clinic cohort (T.C.S.). In the OCCAMS cohort, pathology was reviewed by at least 2 pathologists for all cases: the upper gastrointestinal pathologist at the referring hospital followed by review performed by the OCCAMS central study upper gastrointestinal pathologist with more than 20 years of experience. The pathology reviews were abstracted from prior interpretation.

The TNM cancer stage was assigned in the 2 cohorts according to the American Joint Committee on Cancer seventh edition[19] using the available information in the medical record including clinical notes, endoscopic ultrasound, positron emission tomography, endoscopic mucosal resection, and histopathologic evaluation after surgical resection. In patients who underwent neoadjuvant therapy before surgical resection, the most advanced stage identified before treatment or at the time of surgical resection was used.

BE was defined by visual changes identified endoscopically in the prestaging evaluation with pathology demonstrating IM at time of surgical resection when reviewed by expert gastrointestinal pathologists in the recruiting hospitals. IM also was identified in cases without macroscopic evidence of BE upon expert review of the pathology specimen. In a small group of patients who were treated with chemoradiation therapy without endoscopic or surgical resection, BE-IM was ascertained using visual endoscopic appearance and endoscopic biopsy specimens from the tumor.

The reviewing pathologists followed a specific synoptic report proposed by the College of American Pathologists (www.cap.org/cancerprotocols) and the OCCAMS Consortium protocol that require thorough evaluation for BE in the proximal and distal resection margins and tumor. In addition, extensive sampling is performed for all tumor borders of the resected esophagus and tumor and the tumor bed, making sampling error less likely. The number of biopsy specimens varied based on tumor size.

Statistical Analysis

Baseline characteristics were compared between the 2 groups using χ^2 test for categorical variables and Student *t*-test for continuous ones. The primary outcome was overall survival. Survival in the Mayo Clinic cohort was ascertained from the date of diagnosis to death or the date of data collection (administrative censoring) using online death records from the U.S. Social Security Death Index. Survival time in the OCCAMS Consortium was evaluated from the date of diagnosis to the date the patient was last seen in clinic or the date of death. Survival was plotted using a Kaplan-Meier curve with statistical comparison between the 2 groups using the log-rank test. A Cox proportional hazard regression model was used to examine the impact of BE-IM on overall survival. Unadjusted and adjusted hazard ratios (HRs and aHRs) were calculated after adjusting for possible predefined confounders. In the 2 cohorts, age and sex were included.

Predefined subgroup analyses were performed to examine whether the survival effect of BE-IM was driven by the differential survival seen by stage, treatment, chemosensitivity, or location of the tumor (ie, IM being more likely to be involved because of cardia involvement). Each cohort was independently evaluated for these subgroups based on the specific data available. A 2-sided *P* value less than .05 was considered statistically significant. A final multivariable model included all significant subgroups, age, and sex in the 2 cohorts.

Missing value imputation was performed on the UK cohort to evaluate how these missing data might influence the survival effects. The missing values for variables (eg, TNM stages, Siewert class, age at diagnosis, and sex) were imputed using a multivariable chained equations method that applied random forest to categorical variables and used the distribution means for continuous variables.[20] Imputation was performed for 20 iterations with the Cox multivariable regression model evaluated at each iteration. We report on the mean values of the Cox regression model iterations. The imputed data were not used when reporting the primary or final Cox regression analyses. No imputation was performed on the Mayo Clinic cohort.

All analysis of the Mayo cohort was performed using STATA 14.0 (StataCorp, College Station, TX). All analysis of the OCCAMS cohort was performed using R 3.4.3 (R Foundation, Vienna, Austria), with the packages "survival" 2.41-3, "coxme" 2.2-7, "mice" 3.0.0, and "survminer" 0.4.

Results

Patient Characteristics

Retrospective Cohort: Mayo Clinic. There were 411 patients with prevalent EAC treated at the Mayo Clinic during 2011–2012 who met the inclusion criteria. Two hundred four patients (49.3%) had evidence of associated IM with or without a macroscopically visible BE segment, leaving 207 with no associated IM. The mean age was 64.0 ± 10.7 years (interquartile range [IQR] 57–72) without a meaningful clinical difference between the 2 groups (P = .06). The cohort showed a male predominance (85.2%) as expected for this disease. The BE-IM and non–BE-IM groups were similar for body mass index, family history of esophageal cancer, and smoking ($P > .05$; Table 1).

Prospective Multicenter Cohort: OCCAMS Consortium. In the UK multicenter cohort, 1417 patients who had recorded information on BE status, stage, chemotherapy, and survival were included. Six hundred thirty-four (45%) had BE adjacent to the tumor, whereas 783 (55%) did not. The mean age was 66 ± 9.5 years (IQR 60–73) without a meaningful clinical difference between groups ($P > .05$). The 2 groups were similar in male predominance (83%), history of smoking, and family history of EAC ($P > .05$), although patients with BE-IM had a slightly increased body mass index ($P < .001$; Table 1).

Table 1. Baseline Characteristics of Included Patients, Comparing Patients With Identified BE-IM With Those Without BE-IM in the Mayo Clinic and OCCAMS Cohorts

	Mayo Clinic				OCCAMS			
	BE-IM (n = 204)	Non–BE-IM (n = 207)	*P* value	Total (N = 411)	BE-IM (n = 634)	Non–BE-IM (n = 783)	*P* value	Total (N = 1417)
Age at diagnosis (*y*), mean (SD)	65 (10.4)	63 (11)	.02	64 (10.7)	67 (9)	66 (9.8)	.06	
Men, n (%)	172 (84)	178 (86)	.6	350 (85.2)	539 (85)	640 (81.7)	.1	1179 (83.2)
BMI (kg/m^2), mean (SD; IQR)	29.4 (5; 26–32)	29 (5.4; 25–33)	.6	29 (5.3; 25–32)	28 (5; 25–31)	27 (4.8; 24–29)	<.001	
Former or current smoker, n (%)	128 (63)	128 (62)	.2	256 (62.3)	362 (57.1)	456 (58.2)	.07	818 (57.7)
Family history of EAC, n (%)	9 (4.4)	11 (5.3)	.6	20 (5)	39 (6.2)	39 (5)	.662	78 (5.5)
TNM stage, n (%)			<.001				<.001	
I	62 (30.4)	10 (4.8)		72 (17.5)	53 (8.4)	17 (2.2)		70 (4.9)
II	55 (27)	37 (17.9)		92 (22.4)	323 (50.9)	339 (43.3)		662 (46.7)
III	61 (29.9)	93 (44.9)		154 (37.5)	195 (30.8)	285 (36.4)		480 (33.9)
IV	26 (12.7)	67 (32.4)		93 (22.6)	8 (1.3)	46 (5.9)		54 (3.8)
Missing	0	0		0	55 (8.7)	96 (12.3)		151 (10.7)
Tumor stage, n (%)			<.001				<.001	
T0	0	0		0	10 (1.6)	3 (0.4)		13 (0.9)
T1	66 (32.4)	11 (5.3)		77 (18.7)	70 (11)	21 (2.7)		91 (6.4)
T2	41 (20.1)	23 (11.1)		64 (15.6)	86 (13.6)	60 (7.7)		146 (10.3)
T3	46 (37.3)	107 (51.7)		183 (44.5)	380 (59.9)	511 (65.3)		891 (62.9)
T4	1 (0.5)	4 (1.9)		5 (1.2)	34 (5.4)	95 (12.1)		129 (9.1)
Missing	20 (9.8)	62 (30)		82 (20)	52 (8.2)	93 (11.9)		145 (10.2)
Nodal stage, n (%)			<.001				<.001	
N0	89 (43.6)	32 (15.5)		121 (29.4)	155 (24.4)	146 (18.6)		301 (21.2)
N1	77 (37.8)	84 (40.6)		161 (39.2)	205 (32.3)	230 (29.4)		435 (30.7)
N2	12 (5.9)	20 (9.7)		32 (7.8)	139 (21.9)	190 (24.3)		329 (23.2)
N3	5 (2.5)	8 (3.9)		13 (3.2)	76 (12)	139 (17.8)		215 (15.2)
Missing	21 (10.3)	63 (30.4)		84 (20.4)	53 (8.4)	78 (10)		131 (9.2)
Location (Siewert class), n (%)			.8				<.001	
I (distal; 1–5 cm above EGJ)	109 (53.4)	117 (56.5)		226 (55)	222 (35)	173 (22.1)		395 (27.9)
II (1 cm above + 2 cm below EGJ)	86 (42.2)	80 (38.6)		166 (40.4)	213 (33.6)	288 (36.8)		501 (35.4)
III (2–5 cm below EGJ)	—	—		—	50 (7.9)	125 (16)		175 (12.4)
Missing	4 (2)	6 (2.9)		10 (2.4)	149 (23.5)	197 (25.2)		346 (24.4)
Tubular esophagus > 5 cm	5 (2.4)	4 (2)		9 (2.2)	—	—		—
Treatment, n (%)			<.001				<.001	
Endoscopic therapy	37 (18.1)	2 (1)		39 (9.5)	—	—		—
Esophagectomy alone	31 (15.2)	10 (4.8)		41 (9.9)	137 (21.6)	114 (14.6)		251 (17.7)
Neoadjuvant chemotherapy + esophagectomy	93 (45.6)	91 (44)		184 (44.8)	416 (65.6)	518 (66.2)		934 (65.9)
Esophagectomy + adjuvant chemoradiation	5 (2.4)	4 (1.9)		9 (2.2)	—	—		—
Chemo- ± radiation therapy alone	29 (14.2)	79 (38.2)		108 (26.3)	25 (3.9)	76 (9.7)		101 (7.1)
Palliative	4 (2)	17 (8.2)		21 (5.1)	13 (2.1)	76 (9.7)		89 (6.3)
Missing	5 (2.4)	4 (1.9)		9 (2.2)	—	—		—

BMI, body mass index.

Lesion Features

Mayo Clinic. Most tumors (n = 226, 55%) occurred at the distal esophagus (Siewert type I; BE-IM group, n = 109, 54.3%; non–BE-IM group, n = 117, 56.5%). One hundred sixty-six patients had Siewert type II tumors spanning the esophagogastric junction (EGJ; BE-IM group, n = 86 patients, 42.2%; non–BE-IM group, n = 80 patients, 38.6%). Two percent of the tumors were in the middle of the esophagus, with the distal end of the tumor 5 cm above the EGJ.

Cancers were divided as stage I (n = 72, 17.5%), stage II (n = 92, 22.4%), stage III (n = 154, 37.5%), and stage IV (n = 93, 22.6%). Patients in the prevalent BE-IM group presented at earlier stages (30.4% with stage I, 27% with stage II, 29.9% with stage III, and 12.7% stage with IV) compared with more advanced stages in the non–BE-IM group (4.8%, 17.9%, 44.9%, and 32.4%, respectively; $P < .001$; Table 1). Tumor length overall was similar for the 2 groups when matched for stages I–III (Supplementary Table 1). Nevertheless, at stages I and IV and tumor lengths 3–6 cm and >6 cm, respectively, the non–BE-IM group trended toward an association with longer tumor length. The 2 groups were treated similarly with neoadjuvant chemoradiation therapy followed by esophagectomy (45.6% in BE-IM group and 44% in non–BE-IM group). Patients in the non–BE-IM group were more likely to undergo radiation and/or chemotherapy alone (n = 79, 38.2%) compared with the BE-IM group (n = 29 patients, 14.2%) in which there was a higher prevalence of stage IV disease. Endoscopic therapy was more common in the BE-IM group.

OCCAMS Consortium. Twenty-eight percent of tumors (n = 395) were in the distal esophagus (Siewert type I), with 35% of these occurring in the BE-IM group. Thirty-five percent (n = 501) of tumors were classified as spanning the EGJ (Siewert type II; BE-IM group, n = 213, 33%; non–BE-IM group, n = 288, 36%). Most patients received neoadjuvant chemotherapy and esophagectomy (66%, n = 934), with no difference between the 2 groups. The BE-IM group was more likely to receive esophagectomy only (22%, n = 137), whereas the non–BE-IM group was more likely to receive chemo- and/or radiotherapy as the only treatment (9.7%, n = 76). Most patients in the cohort had TNM stage II (47%, n = 662) or III (34%, n = 480). Patients with stage II were more likely to be in the BE-IM group (51%, n = 323), whereas patients with stage III were found more often in the non–BE-IM group (36%, n = 285). Patients with BE-IM tended to be more commonly associated with early stages (8.4% with TNM stage I); however, these accounted for only 5% (n = 70) of all cases (Table 1).

Survival

Mayo Clinic. The median overall survival for the entire cohort was 4 years (IQR 1.3–6.5). In the BE-IM group, the median survival was 5.8 years (IQR 2.5–7.2) compared with 2.3 years (IQR 0.9–5.6) in the non–BE-IM group ($P < .001$; Figure 1). The 5-year mortality was 219 of 411 (53.3%) in the entire cohort. This was significantly lower in the BE-IM group (75 of 203, 36.8%) compared with the non–BE-IM group (144 of 207, 69.6%; $P < .001$).

When comparing overall survival, the unadjusted model showed a significant survival benefit in the BE-IM group (HR 0.44, 95% confidence interval [CI] 0.34–0.57, $P < .001$; Figure 1). A multivariable Cox regression analysis including

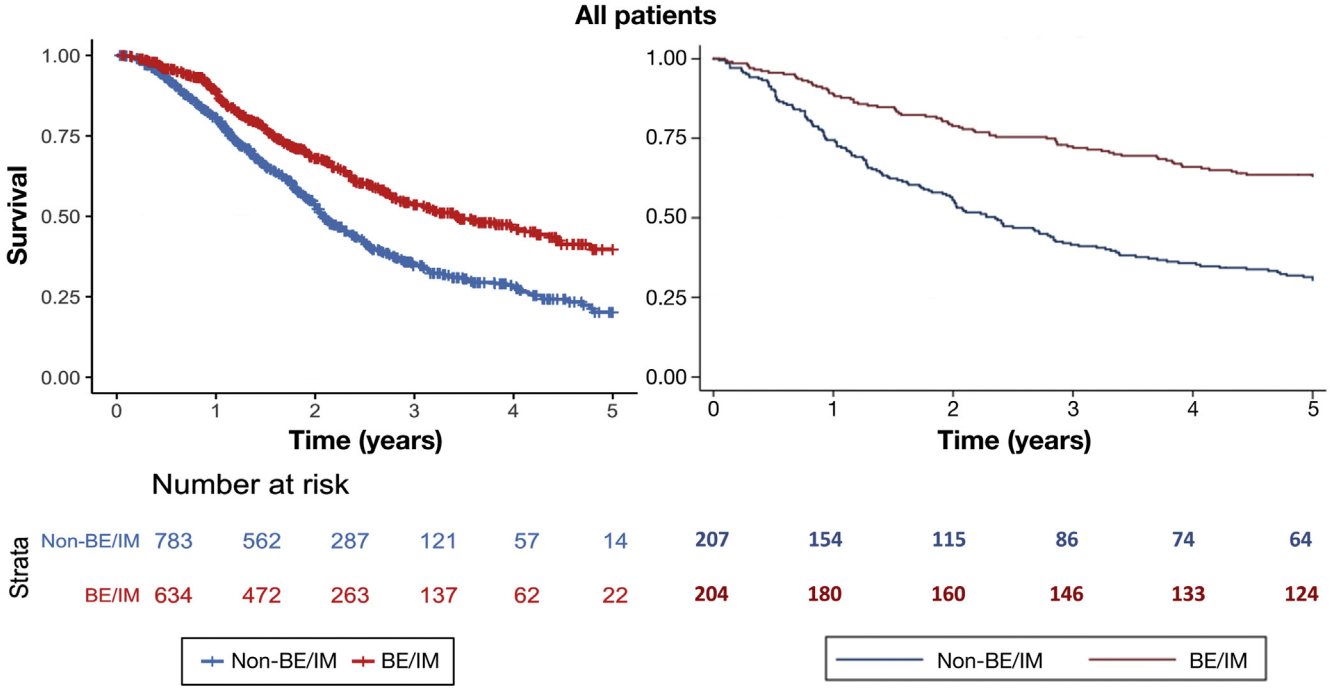

Figure 1. Overall survival time in years comparing esophageal adenocarcinoma with and without BE-IM in the (*right*) Mayo Clinic ($P < .001$) and (*left*) OCCAMS ($P < .001$) cohorts.

Table 2. Predictors for Survival in Patients With EAC presented as Hazard Ratios From Multivariate Cox Regression Model Including Barrett Phenotype, Sex, Age at Diagnosis, Siewert Classification, and TNM Stage in the Mayo Clinic and OCCAMS Cohorts and Tumor Length in the Mayo Clinic Cohort

	Mayo Clinic			OCCAMS		
	Total (N = 411)	Adjusted HR	95% CI	Total (N = 1417)	Adjusted HR	95% CI
BE						
Non–BE-IM	207	reference		783	reference	
BE-IM	204	0.66	0.5–0.88	634	0.77	0.64–0.93
Sex						
Male	350	reference		1179	1.1	0.84–1.43
Female	61	1.02	0.72–1.44	238	reference	
Age at diagnosis (*y*)	411	1.02	1.01–1.04	1417	1.01	1.0–1.02
Siewert classification						
I	226	reference		395	reference	
II	166	0.75	0.56–1	501	0.85	0.7–10.5
III	0			175	0.92	0.7–1.2
Tubular	9	1.24	0.56–2.74			
Missing	10	1.88	0.9–3.95			
TNM stage						
I	72	reference		70	reference	
II	92	2	1.22–3.44	662	3.25	1.44–7.33
III	154	3	1.8–5.1	480	6.25	2.77–14.13
IV	93	6.9	4–11.9	54	10.02	4.14–24.23
Missing	0					
Tumor length						
1–3 cm	161	reference				
3–≤6 cm	129	0.82	0.57–1.18			
>6 cm	69	1.1	0.7–1.63			
Missing	52	1.1	0.68–1.7			
Log-rank *P*	<.001			<.001		

age at diagnosis, sex, tumor location and length, and TNM stage resulted in an aHR of 0.66 (95% CI 0.5–0.88, P = .005), indicating better survival associated with the BE-IM phenotype independent of the factors listed earlier (Table 2).

OCCAMS Consortium. The median overall survival for the OCCAMS cohort was 1.6 years (IQR 0.9–2.6). For the BE-IM group, the median survival was 3.4 years (IQR 2.9–4.4) compared with 2.0 years (IQR 1.9–2.3) for the non–BE-IM group (P < .001). In the 864 patients who were diagnosed before 2014, 92% received curative treatment and the 5-year mortality was 444 of 864 (51%; BE-IM group, 42%, 164 of 386; non–BE-IM group, 58%, 280 of 478; P < .001). When comparing overall survival, the unadjusted model showed a significant difference between the 2 groups, with a survival benefit in the BE-IM group (HR 0.58, 95% CI 0.49–0.68, P < .001; Figure 1). A multivariable analysis including age at diagnosis, sex, tumor location, and TNM stage resulted in an aHR of 0.77 (95% CI 0.64–0.93, P = .006).

Subgroup Analysis

Mayo Clinic. In a multivariable Cox proportional hazards regression that included age at diagnosis and sex for all models, we performed predefined subgroup analyses to determine whether the survival difference was influenced by location (Siewert classification), TNM stage, or receiving neoadjuvant therapy (Table 2). In patients with tumors classed as Siewert type I (n = 226, HR 0.38, 95% CI 0.27–0.54, P < .001) or Siewert type II (n = 166, HR 0.5, 95% CI 0.33–0.77, P = .002), the BE-IM group showed better survival indicating that the effect of BE-IM is independent of esophageal location (Figure 2*A*).

In a subgroup analysis for each TNM stage, there was a benefit for the BE-IM group in TNM stages II (n = 92, HR 0.49, 95% CI 0.27–0.87, P = .01) and III (n = 154, HR 0.6, 95% CI 0.4–0.93, P = 0.02; Figure 2*B*). There was no difference in survival between the BE-IM and non–BE-IM groups for stages I (HR 0.59, 95%CI 0.2–1.8, P = .35) and IV (HR 0.99, 95% CI 0.6–1.6, P = .97).

In patients who underwent esophagectomy after neoadjuvant chemoradiation (n = 184, HR 0.6, 95% CI 0.38–0.97), a better survival for the BE-IM group persisted (Figure 2*C*). For the subgroup of patients receiving surgery without neoadjuvant therapy (n = 50), the HR was consistent with those of other subgroups and suggests that the benefit of BE-IM persists (HR 0.35, 95% CI 0.14–0.86, P = .02). We performed a subgroup analysis excluding patients who did not undergo surgical or endoscopic resection (ie, chemoradiation therapy alone or palliative therapy) to minimize the risk of tissue sampling error. BE-IM was associated with superior survival compared with non–BE-IM (HR 0.65, 95% CI 0.44–0.96, P = .03) after adjusting for age, sex, tumor location and length, and TNM stage.

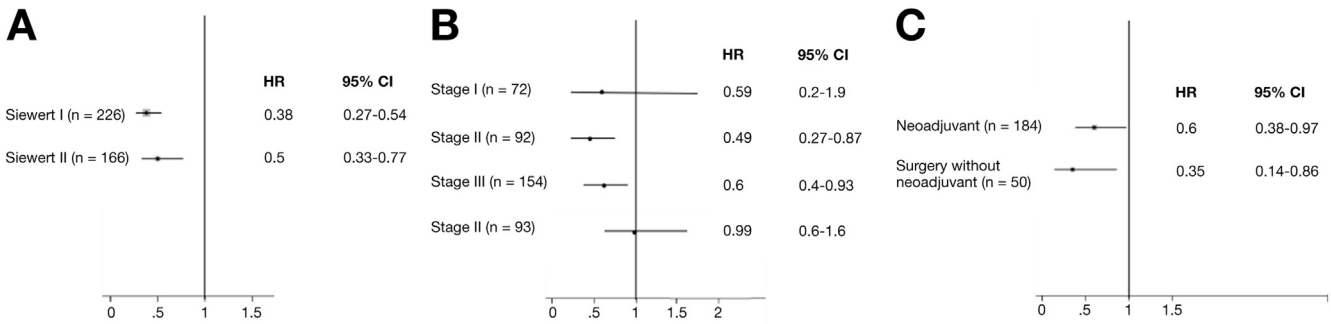

Figure 2. Forest plots for subgroup analysis HR in the Mayo Clinic cohort for BE-IM vs non–BE-IM adjusting for age and sex: (*A*) location based on Siewert classification, (*B*) TNM stage, and (*C*) surgery with and without neoadjuvant therapy.

OCCAMS Consortium. In a multivariable Cox proportional hazards regression that included age at diagnosis and sex, we performed subgroup analyses to determine whether other factors could be driving the survival difference observed in these patients (Table 2). Surveillance for BE, tumor location (ie, Siewert classification), TNM stage, tumor differentiation (ie, poor, moderate, or well), surgery with and without neoadjuvant chemotherapy, and response to chemotherapy (ie, change in tumor stage before to after surgery) were tested and had no effect (Supplementary Figures 1–5).

We also assessed whether the effect of BE-IM depends on stage, and how strong the dependence is. We added a random term for the interaction between BE-IM and TNM stage to the model. The estimated variance for this term was 1.52×10^{-5}, so the impact of TNM stage on the HR can be considered negligible.

We evaluated the impact of the missing data in each category by imputing the missing data points based on observed distributions and assessing the multivariable Cox regression from the full dataset. We performed 20 iterations of the imputation and a consistent improvement to the aHR of BE-IM resulted (mean aHR 0.64 ± 0.008, $P < .001$), indicating that the survival difference is robust to missing data.

Discussion

In this study we found an association between the presence of gross BE and/or histologic IM on EAC survival in 2 independent cohorts. In a retrospective single-center cohort from the United States we found that EAC in the background of BE-IM presented at earlier stages and had better survival even after adjusting for disease stage, tumor location and length, and neoadjuvant treatment. These findings were similar in the OCCAMS cohort, a larger cohort of patients with EAC collected from multiple hospitals in the United Kingdom.

Although the 2 cohorts demonstrated an improved survival when there was associated BE, there was a difference in median overall survival for the UK OCCAMS cohort (1.3 years, IQR 0.6–2.3) vs the Mayo Clinic cohort (4 years, IQR 1.3–6.5). It is noteworthy that the UK data reflect the typical 5-year survival for EAC of 12%–20%.[21,22] The Mayo Clinic is a tertiary referral center and there was a larger proportion of early-stage tumors (6% in OCCAMS vs 17% in Mayo Clinic) and the UK population was slightly older (OCCAMS, 66 ± 9.4 years; Mayo Clinic, 64.0 ± 10.7 years). In addition, in the 2 cohorts the survival benefit persisted with exclusion of neoadjuvant therapy exposure to cancers with pre-existing BE-IM. However, more aggressive use of neoadjuvant therapy at the Mayo Clinic could explain some of the overall improved survival differences.[23]

A key question is what it means from an etiologic perspective when BE and/or IM is not identified at the time of EAC resection or diagnosis. Several possibilities could be considered. First, IM was present but then eradicated by tumor growth and this scenario has been proposed previously[24,25]; however, in the Mayo Clinic cohort, a finding of BE-IM was overall similar for the 2 groups within cancer stages I–III, independent of the length of the tumor, making overgrowth of gross IM by a larger tumor a less likely explanation in the non-BE group. However, in specific subgroups of stage and tumor length, there appeared to be differences supporting the possibility of tumor overgrowth in some patients. Second, there is acquisition of sudden genomic instability that allows extant IM to progress rapidly to cancer that is no longer visible in the tumor.[16] Investigations into molecular mechanisms, including mutational signatures, copy number differences, or recurrent gene mutation analyses, that could explain these differences have so far been inconclusive. This is likely due to the complexity of the molecular profile of EAC.[26] Work is ongoing to examine the molecular characteristics in the subset of patients in the OCCAMS cohort with whole-genome sequencing data. Third, the cancer derives through a molecular sequence not involving IM.[27]

Although the initial study at the Mayo Clinic was limited due to the use of specimens from a single center, the demographics of these patients are representative of the typical patient who develops EAC—a middle-age to older white man with increased body mass index. This limitation has been addressed by the independent identification of similar findings in the OCCAMS cohort, which includes patients prospectively recruited from 25 different hospitals across the United Kingdom. A second concern might be the assuredness with which we propose

the existence of these 2 types of cancer based only on finding BE-IM at diagnosis and/or resection, with the possibility of missing a small focus of IM. Systematic pathology review for the presence of IM could help mitigate this limitation, and the prospective OCCAMS cohort addressed this because the presence of BE-IM is systematically assessed in all patient samples as part of the study protocol. Furthermore, in a small subset of OCCAMS patients, an independent review of their pathologic reports was undertaken, and the survival advantage remained for the BE-IM group.

One important finding that also argues for a different phenotype of esophageal cancer is that cancers without IM accounted for almost half the EACs from the years studied and were mostly distal EACs. This stands in contrast to data demonstrating that most EACs develop in a segment of BE mucosa.[28] As a result, these data further suggest the existence of a different phenotype of EAC rather than misclassifying the IM type that more likely would have arisen in the presence of long-segment BE mucosa. Another limitation might be in determining whether the poorer prognosis of EAC without IM results from poor response to therapy because most patients with stage II and III EAC receive chemotherapy and, in the United States, radiation therapy. Given the inaccuracy of endoscopic ultrasound and positron emission tomography with computed tomography for assessing lymph node involvement and tumor stage before therapy, it would be difficult to compare the response before and after treatment. However, analysis of patients with stage II cancer not treated with neoadjuvant therapy showed a persistent survival benefit of BE-IM cancers compared with non–BE-IM cancers, as did an analysis of response based on the differences between pre- and post-resection tumor staging. Furthermore, the advanced presentation of non–BE-IM adenocarcinoma before therapy suggests a more aggressive cancer. Another concern is whether we are confusing cancers of the EGJ with similarly true EACs, which can carry a different molecular signature and prognosis. However, in the 2 cohorts the survival advantage of BE-IM was present regardless of the location of the tumor. In our study, patients without BE and distal adenocarcinoma extending to EGJ but not Siewert type II adenocarcinoma had similar demographics to those with BE because all tumors extended >1 cm above the EGJ.[18] Furthermore, when we excluded all patients with extension of tumor into the cardia, there was a persistent decrease in overall survival when compared with BE-IM–related tumors.

In conclusion, this study suggests that there are phenotypically 2 types of EAC—one with grossly visible and/or histologically identifiable IM in the esophagus and one without. Furthermore, the presence or absence of these findings could influence the ability for early detection in this disease through screening for BE. It also could have ramifications for tumor behavior and/or response to therapy and therefore prognosis. Longitudinal and detailed molecular characterization studies are required to shed further light on the natural history of EAC that presents de novo to develop evidence-based screening and prevention strategies for this highly lethal malignancy on a population basis. Sequencing will be needed to determine ultimately whether this new phenotype is an IM-independent pathway.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.08.036.

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Conflicts of interest
David A. Katzka is involved in a pharmaceutical trial with Shire. John B. Kisiel and David A. Ahlquist are listed as inventors under an intellectual property development agreement between the Mayo Clinic and Exact Sciences (Madison, WI) under which royalties can be paid. Kenneth K. Wang receives research support from CSA Medical and C2 Therapeutics. Rebecca C. Fitzgerald is listed as an inventor on patents pertaining to Cytosponge and associated assays that have been licensed by the Medical Research Council to Medtronic. The other authors declare no conflicts of interest.

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Supplementary Material

Appendix. Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) Consortium

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Appendix. Continued

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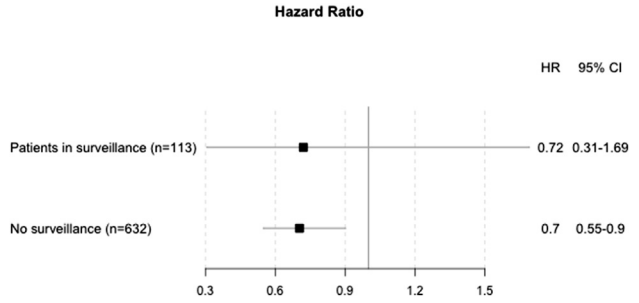
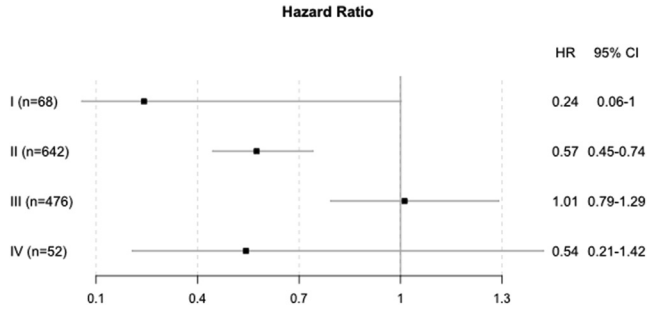
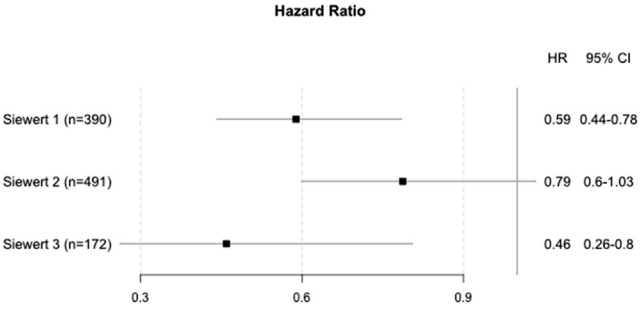
NOTE. In the OCCAMS cohort, we tested the following covariates to determine whether these drive the survival difference for patients with BE-IM: BE surveillance (Supplementary Figure 1), tumor location (Supplementary Figure 2), TNM stage (Supplementary Figure 3), treatment (Supplementary Figure 4), and response to neoadjuvant therapy (Supplementary Figure 5). All models controlled for age at diagnosis and sex. None of the subgroups altered the effect of BE-IM on survival.



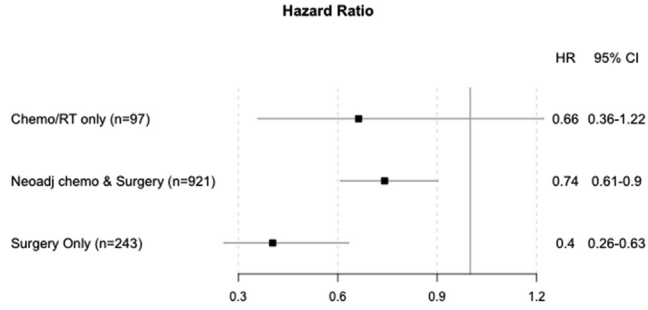
Supplementary Figure 1. BE surveillance in OCCAMS cohort.



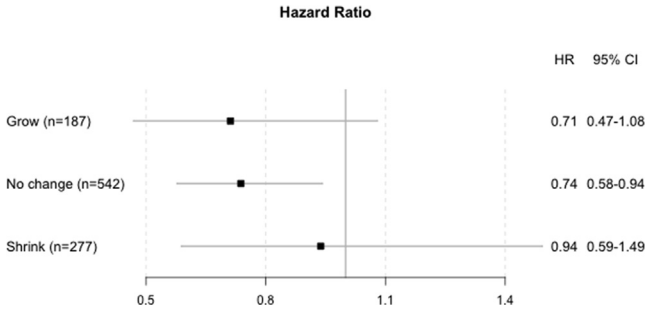
Supplementary Figure 3. TNM stages.



Supplementary Figure 2. Siewert classification.



Supplementary Figure 4. Treatment regimens. RT, radiation therapy.



Supplementary Figure 5. Tumor response to neoadjuvant therapy.

Supplementary Table 1. Tumor Length Comparison Between BE-IM and Non–BE-IM Based on Stages for the Mayo Clinic Cohort

	Length 1–3 cm		Length 3–≤6 cm		Length > 6 cm		Missing		
Stage	BE-IM, n (%)	Non–BE-IM, n (%)	BE-IM, n (%)	Non–BE-IM, n (%)	BE-IM, n (%)	Non–BE-IM, n (%)	BE-IM, n (%)	Non–BE-IM, n (%)	*P* value
I	53 (85.5)	6 (60)	4 (6.5)	3 (30)	0	0	5 (8)	1 (10)	.06
II	31 (56.4)	17 (46)	17 (30.9)	12 (32.4)	4 (7.3)	3 (8.1)	3 (5.4)	5 (13.5)	.54
III	15 (24.6)	25 (26.9)	26 (42.6)	39 (41.9)	16 (26.2)	22 (23.7)	4 (6.6)	7 (7.5)	.97
IV	8 (30.8)	6 (9)	10 (38.5)	18 (26.9)	3 (11.5)	21 (31.3)	5 (19.2)	22 (32.8)	.01