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Journal

Foregut, 2(4)

Authors

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Publication Date

2022-12-01

DOI

10.1177/26345161211033277

Peer reviewed

Published in final edited form as:

Foregut (Thousand Oaks). 2022 December ; 2(4): 356–364. doi:10.1177/26345161211033277.

Prognostic Impact of the Presence of Barrett's Esophagus and Intestinal Metaplasia on Esophageal Adenocarcinoma Survival

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Abstract

Background/Aims: Barrett's esophagus (BE), defined by the presence of intestinal metaplasia (IM) on histology, is thought to be the only identifiable precursor lesion for esophageal adenocarcinoma (EAC). Recent studies have suggested the possibility of an alternate, non-IM associated EAC that is a more aggressive form of EAC with worse survival. Among EAC patients, we aimed to compare survival of patients with and without IM at the time of diagnosis.

Methods: This was a retrospective cohort study of all patients with histologic confirmed EAC evaluated at a tertiary care center from 2013 to 2019. Cases were categorized according to the presence or absence of IM on histologic specimens (Group I—IM-EAC and Group II—non-IM-EAC). We compared demographic characteristics, clinical stage, therapy, and survival between the 2 groups using the Chi-square and ANOVA tests (for categorical and continuous variables, respectively). We used Cox proportional hazards regression to determine the association of IM with overall survival, adjusting for sex, age at diagnosis, tumor location, histologic grade, and clinical stage.

Results: A total of 475 patients were included in this analysis (mean age 64.8 years [SD 10.8], 89% white) and 109 (23.0%) had no evidence of IM. Compared with IM-EAC (Group I), individuals in the non-IM-EAC group were younger ($P = .01$) and had a greater proportion of patients diagnosed with advanced disease (49.5 vs 20.2% for stage 4, $P < .001$). These patients were less likely to undergo endoscopic therapy alone (0.92% vs 29.78%, $P < .001$) or surgery alone (0 vs 9.84%, $P = .001$). On multivariable analysis, the presence of IM-EAC was associated with improved overall survival compared to non-IM-EAC (HR 0.69, 95% CI 0.49–0.96). Additional factors associated with poor survival was increasing stage of diagnosis (HR 6.49: 95% CI 3.77–11.15 for stage 4, HR 2.19: 95% CI 1.25–3.84 for stage 3, HR 2.04: 95% CI

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Author Contributions

Conceptualization: JMK, SW, Formal Analysis: JMK, Investigation: JMK, CF, SW, Methodology: JMK, FIS, SW, Project Administration: SW, Resources: CF, AG, Supervision: SW, Writing: JMK, SW, and Reviewing and Editing: JMK, CF, CF, SH, MM, MM, FIS, JK, CHL, AG, DAK, SW.

Results of this study were presented at Digestive Disease Week 2020 and the American Foregut Society Annual Meeting 2020.

0.98–4.25 for stage 2 compared to stage 1) and more advanced histologic stage (HR 2.00, 95% CI 1.26–3.19) for poorly/undifferentiated compared to well differentiated).

Conclusions: EAC without the presence of IM on histology was associated with worse survival compared to those with IM. Future prospective studies with detailed molecular sequencing are required to clarify if 2 separate phenotypes of EAC exist (IM-EAC and non-IM-EAC). If confirmed, this may have significant implications for screening and management strategies.

Keywords

esophageal adenocarcinoma; Barrett's esophagus; intestinal metaplasia

Introduction

Esophageal adenocarcinoma (EAC) is a highly lethal cancer with an incidence of 3.3 per 100 000 person-years that typically presents with late stage disease and is associated with poor prognosis.[1] EAC affected approximately 85 000 individuals worldwide in 2018, with the largest burden in Eastern Asia (35%) followed by 18% of cases in the United States (US). The American Cancer Society estimates 18 440 new cases and 16 170 deaths due to esophageal cancer in the US in 2020 of which adenocarcinoma is the predominant histologic subtype.[2,3] Five year survival rates are dismal for late stage III (17.6%) and IV disease (2.1%).[2]

Barrett's esophagus (BE), defined by the presence of intestinal metaplasia (IM) on histology, is the only identifiable precursor lesion for esophageal adenocarcinoma (EAC). BE affects up to 5% of the general population.[4] It results from chronic reflux to the distal esophagus which leads to IM and progresses in a well described stepwise fashion from non-dysplastic to low grade then high grade dysplasia to intramucosal carcinoma and finally invasive EAC. This sequence provides the opportunity to intervene through BE screening programs that focus on the performance of an upper endoscopy in an at-risk population,[5] and surveillance programs that potentially allow for early detection and treatment of BE-related dysplasia and early EAC[6] with the ultimate goal of reducing morbidity and mortality. However, the effectiveness of these programs is limited: >90% of EAC have no prior BE diagnosis. Overall, we have made little progress in improving EAC outcomes.[7,8]

Sawas, Killcoyne, and colleagues have suggested the possibility of an alternate, non-BE/IM phenotype of EAC that is associated with more aggressive disease and worse survival. In 2 separate cohorts they identified an approximately 50% reduced risk of death in EAC with IM compared to without IM independent of age, sex, tumor stage, tumor location, and length of BE.[9] They hypothesized an IM variant with the occurrence of a genomic catastrophe where all IM rapidly progressed to cancer and tumor overgrowth may preclude identification of IM, or the potential existence of a non-IM pathway to EAC. If confirmed, this would have significant implications for our approach to identifying at risk individuals for screening for BE and EAC and our overall understanding of the epidemiology of this disease. We sought to evaluate if these findings were reproducible in a second US-based cohort of individuals with EAC. The aims of this study were to (1) analyze EAC survival according to the presence of BE/IM and (2) determine predictors of EAC survival.

Methods

Study Cohort

This was a retrospective cohort study of patients with EAC evaluated at the University of Colorado Hospital which is a large tertiary care center from 2013 to 2019. Eligible patients were identified through a prospective database maintained by the medical and surgical multidisciplinary team. Tumors were included if they were Siewert I (adenocarcinoma of the lower esophagus with the center located within 1–5 cm above the anatomic gastroesophageal junction) or Siewert II (tumor of the cardia with the center located 1 cm above or 2 cm below the gastroesophageal junction).[10] All Siewert III tumors (tumor center 2–5 cm below the gastroesophageal junction) were excluded. EAC stage 0 disease, indicating BE with high grade dysplasia, was excluded from the analysis. All patients underwent additional diagnostic testing for staging, which typically included cross sectional imaging (CT or PET) and/or endoscopic ultrasound.

Study Variables

Data on patient related factors and history were recorded including age, sex, race, history of alcohol use or smoking, family history, and comorbidities. The presence of Barrett's esophagus was determined according to endoscopy reports and histology reports from endoscopic and surgical specimens. Tumor characteristics such as Siewert classification, histologic grade, stage, (AJCC eighth edition clinical stage, collapsed into 1, 2, 3, 4),[11] were recorded as well as cancer treatment.

Study Classification

All biopsies, endoscopic resection specimens, and final surgical specimens were reviewed by at least 2 expert gastrointestinal pathologists as part of the multidisciplinary evaluation of EAC cases. All cases were categorized according to the presence or absence of IM on histopathology specimens (Group I—IM-EAC and Group II—non-IM-EAC). Patients assigned to Group 1 (IM related) had to meet one of the following criteria: (1) the presence of IM on the EAC biopsy specimen, or (2) endoscopic report documenting EAC in the setting of BE (columnar lined esophagus), or (3) any history of BE in the medical record or on previous endoscopies. For example, if a patient had EAC without obvious IM, but a documented history of BE prior to the EAC diagnosis, this individual was assigned to group I. In cases where the pathology report did not indicate the presence or absence of IM, when possible, the slides were re-reviewed by an expert gastrointestinal pathologist.

Study Outcomes and Statistical Analysis

We compared demographic and cancer characteristics between the 2 groups using the Chi-square for categorical and ANOVA tests for continuous variables. The primary outcome was overall survival for IM-EAC compared to non-IM-EAC patients. Survival was determined from the date of diagnosis to the date of last clinical evaluation or death. We used Kaplan Meier curves to examine the association between the presence of IM and overall survival using the log rank test. Cox proportional hazards regression was performed adjusting for sex, age at diagnosis, tumor location, clinical stage, and histologic grade. Only those variables

that were significant in univariable analysis ($P < .1$) were included in the model. Variables that were significant on univariable analysis but were not included in the multivariate analysis were PPI use (not included due to inherent flaws in recorded medication use), and treatment. A sensitivity analysis was performed using the multivariable model for survival to assess the impact of excluding Siewert II tumors to ensure no unintentional gastric cancers were included in the cohort. Approval for this study was obtained by the Colorado Multiple Institutional Review Board.

Results

A total of 475 patients were included in this analysis (mean age at diagnosis 64.8 ± 10.8 years, 88.6% white) of whom 366 (77.1%) had evidence of intestinal metaplasia (Table 1; Figure 1). The majority (57.3%) of EAC cases were Siewert I. Compared with IM-EAC, individuals with non-IM-EAC were diagnosed younger and had a greater proportion of patients diagnosed with advanced disease (49.5 vs 20.2% for stage 4, $P < .001$) (Figure 2). As a result, these patients were less likely to undergo endoscopic therapy alone (0.92% vs 29.78%, $P < .001$) or surgery alone (0.0% vs 9.84%, $P = .001$) and more likely to undergo chemotherapy +/− radiation (alone or adjuvant or both) (42.20% vs 18.03%, $P < .001$). Compared with IM-EAC, individuals with non-IM-EAC were more likely to have poorly/undifferentiated tumors ($P < .001$) (Figure 3).

Survival Analysis and Predictors of Survival

Median overall survival for the entire cohort was 593 days (IQR 254–1210) (Table 1). On unadjusted analyses, the presence of IM-EAC was associated with improved overall survival compared to non-IM-EAC (HR 0.44, 95% CI 0.32–0.59) (Figure 3). On univariable analysis, treatment with endoscopic therapy (HR 0.17, 95% CI 0.09–0.29) and surgery alone were associated with improved survival compared to chemotherapy +/− radiation (HR 4.29, 95% CI 3.18–5.78). On multivariable analysis after adjusting for age at diagnosis, sex, tumor location, clinical stage, and histologic grade individuals with IM-EAC had a survival advantage (HR 0.69, 95% CI 0.49–0.96) (Table 2; Figure 4). Additional factors associated with poor survival was increasing stage of diagnosis (HR 6.49: 95% CI 3.77–11.15 for stage 4, HR 2.19: 95% CI 1.25–3.84 for stage 3, HR 2.04: 95% CI 0.98–4.25 for stage 2 compared to stage 1) and histologic grade (HR 2.54, 95% CI 1.17–5.50 for poorly/undifferentiated compared to well differentiated). Age at diagnosis, sex, and location of tumor were not associated with overall survival. A sensitivity analysis excluding Siewert II tumors did not significantly impact findings (Table 3).

Stage Specific Survival

IM was identified in nearly all of the stage I (124/125) and stage II (30/31) EACs, precluding analysis of stage specific survival. For stage III EAC, the presence of IM was not associated with overall survival on univariable (HR 0.90, 95% CI 0.53–1.55) or adjusted analyses (HR 0.97, 95% CI 0.54–1.91). For stage IV, IM-EAC had better survival compared to non-IM-EAC on univariable analysis (HR 0.60, 95% CI 0.39–0.92) and after adjusting for age at diagnosis, sex, tumor location, and histologic grade (HR 0.50, 95% CI 0.31–0.81).

Additional Subgroup Analysis

Since the non-IM-EAC group had higher stage, worse histologic grade, greater comorbidities, more tubular esophagus and Siewert II, and in order to control for confounding, a repeat multivariable analysis was performed in a subgroup of only stage III/IV tumors in the tubular esophagus or Siewert I, adjusting for age, sex, charlson deyo score, tumor location, stage, histological grade, and receipt of chemoradiation (Table 4). Results were overall similar although the upper limit of the CI was 1.00 for the presence of BE/IM.

Discussion

In a cohort of 475 patients with EAC, 23% of cases did not have a history of BE or evidence of BE/IM at the time of cancer diagnosis. These non-IM-EAC patients were younger and presented with more advanced stage disease with worse histologic grade compared to IM-EAC patients. The presence of IM was associated with improved overall survival, findings that are consistent with the recent study by Sawas et al.[9] Additionally, we identified increasing stage of disease and poor histologic grade as predictors of worse survival.

It has long been accepted and well understood that Barrett's esophagus progresses through a well-defined pathway from squamous epithelium to intestinal metaplasia (resulting from reflux induced inflammation) and dysplasia and ultimately invasive adenocarcinoma. Screening and surveillance programs to date have focused on identifying and surveying BE, as this likely provides the opportunity to interrupt this sequence and detect EAC at earlier stages, a critical intervention since stage at diagnosis is related to outcomes. While the benefits of surveillance continue to be debated in the absence of data from randomized controlled trials, results from observational studies suggest that EAC mortality is improved with regular BE surveillance (RR 0.60, 95% CI 0.50–0.71) and with EAC detected during surveillance, as opposed to EAC diagnosed due to symptomatic presentation (RR 0.73, 95% CI 0.57–0.94).[12] Therefore, identifying a novel non IM pathway to EAC would have significant implications for screening and management strategies, as it would circumvent existing efforts. Prior research by Sawas et al[9] indicated that about half of patients had non-IM EAC and a consistent proportion was identified in a separately analyzed historical cohort (1996–1997).[13] In our study, only 1 quarter of EAC patients did not have demonstrable BE/IM. Larger population-based analyses are needed to determine the true incidence of non-IM EAC and any unique molecular features of this pathway.

There are several potential etiologies for a diagnosis of EAC in the absence of IM. In very aggressive EACs, the dysplastic and neoplastic areas have features similar to non-intestinalized columnar lined esophagus which raises the question of whether this can be derived without the intermediate step of IM. It is plausible that widespread dysplasia can overgrow the IM as EAC develops and progresses, resulting in cases where complete tumor overgrowth precludes identification of IM on histologic evaluation.[14,15] In these scenarios, it is possible that the conversion of intestinalized metaplastic cells to cancer is rapid and complete. This would therefore still represent a BE/IM pathway consistent with our current understanding of IM as the only known precursor to EAC, however with a possible uniquely aggressive phenotype. We hypothesize that if this were to occur it would likely be the

poorly differentiated tumors that exhibit dramatic tumor overgrowth and rapid transition and may spread below the surface in the submucosa. The other proposed theories for this finding include acquisition of sudden genomic instability allowing IM to progress rapidly to cancer and finally that EAC develops through a molecular sequence that does not involve IM.[16] The concept of having more than 1 pathway to carcinoma is not unique and has been demonstrated in colorectal cancer (adenomatous and serrated pathway),[17] head and neck, cervical, and other cancers. More work is required to understand the subtypes of EAC.[16,18,19] Finally, sampling error and misclassification bias may pay a role.

The strengths of this study are that we had a large cohort of EAC who all underwent comprehensive evaluation by a multidisciplinary team consisting of gastroenterologists, surgeons, medical oncologists, radiation oncologists, and pathologists which strengthens the quality and completeness of data. Our results demonstrated poor survival associated with later stage disease and worse histologic grade, consistent with prior studies. This study has several limitations. These results are based on a retrospective study design and thus require validation in a large prospective cohort of EAC cases. Although categorization of the 2 cohorts was based on strict definitions and expert gastrointestinal pathologist review, and all surgically resected EAC had extensive and complete sampling of the tumor area to assess for residual EAC after neoadjuvant treatment, the possibility of the endoscopist sampling the cancer rather than the surrounding tissue and missing a small focus of IM cannot be excluded and this sampling error thus introducing the potential for misclassification bias. We also included a past medical history of known BE as part of the exposure definition. The cause of death was unavailable due to more recent restrictions on reporting to the Social Security Death Index SSDI so we were unable to analyze disease specific survival.

In conclusion, our results indicate that almost 1 quarter of patients with EAC do not have a history of BE or findings of IM at the time of cancer diagnosis. Individuals with BE/IM have improved overall survival compared to non-IM-EAC, however survival is still dismal and the majority of patients still present with advanced stage disease. Future studies should focus on the molecular phenotypes of a possible pathway to EAC that is, either independent of BE/IM or that develops through IM but progressed rapidly and completely to EAC.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jennifer M. Kolb: Received funding from National Institutes of Health (NIH) T32-DK007038, Frank I. Scott: Received research funding from the National Institute of Health/NIDDK (K08-DK095951), Crohn's and Colitis Foundation, and investigator-initiated grants from Takeda Pharmaceuticals USA and Janssen Pharmaceuticals. He has received consulting fees from PRIME Incorporated, Janssen Pharmaceuticals, Takeda Pharmaceuticals, and Merck Pharmaceuticals, Christopher Lieu: Consultant and advisory board member for Foundation Medicine, David A. Katzka: Advisory board member of Celgene and Shire, and Sachin Wani: Received funding from the University of Colorado Department of Medicine Outstanding Early Scholars Award, Consultant for Medtronic, Boston Scientific, Cernostics and Interpace.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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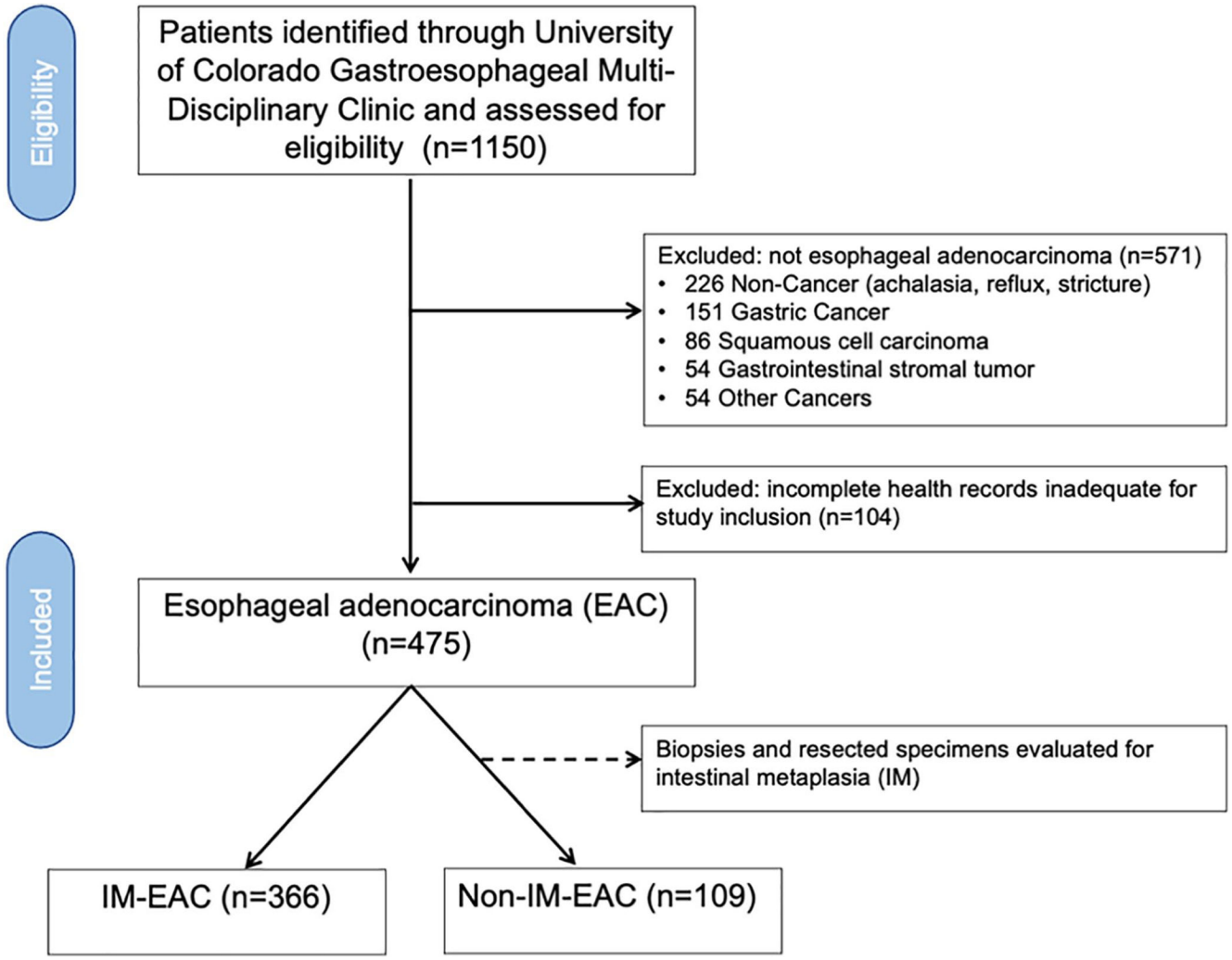

Figure 1.
Consort diagram outlining study population.

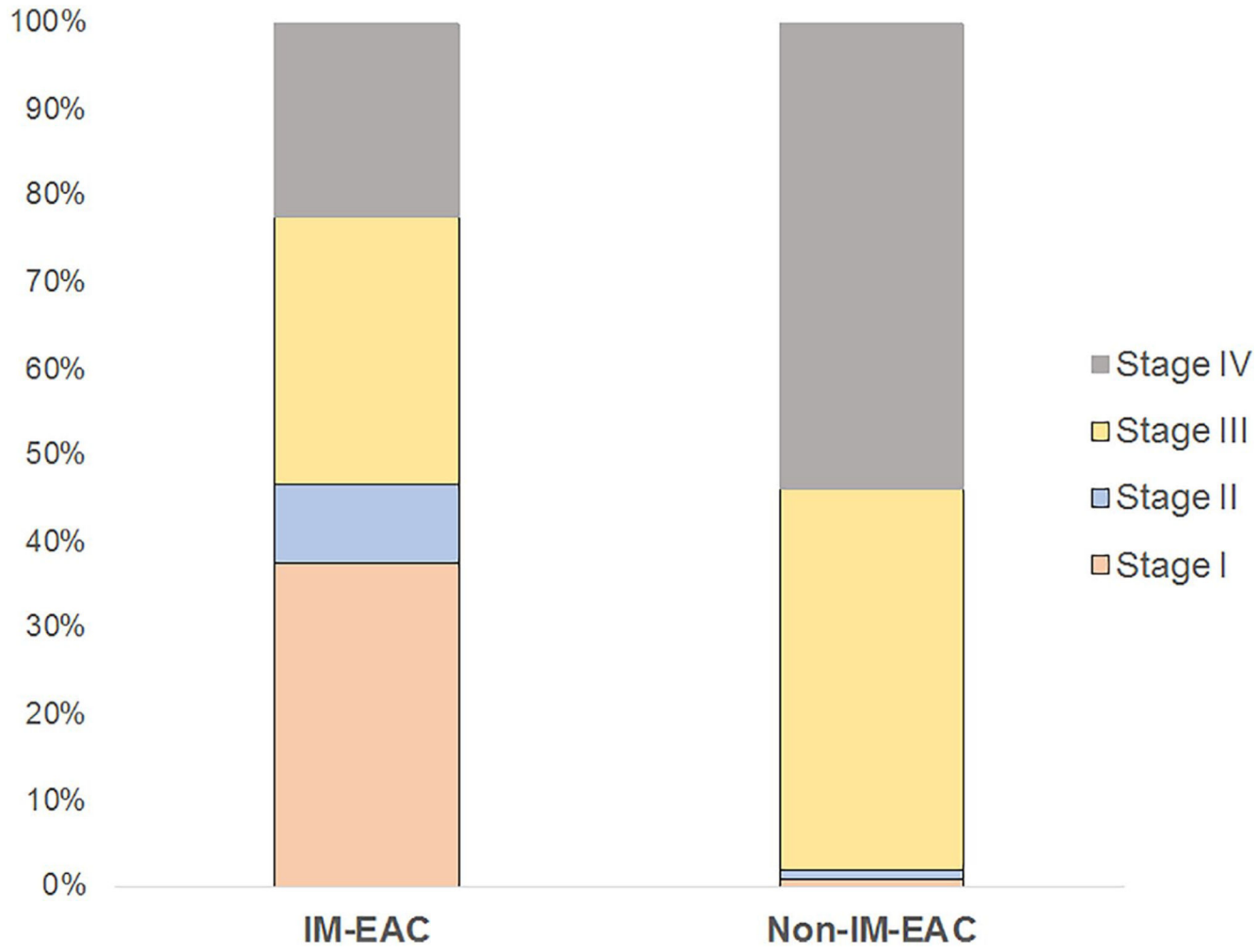

Figure 2.
Stage distribution among patients with IM-EAC versus non-IM-EAC.

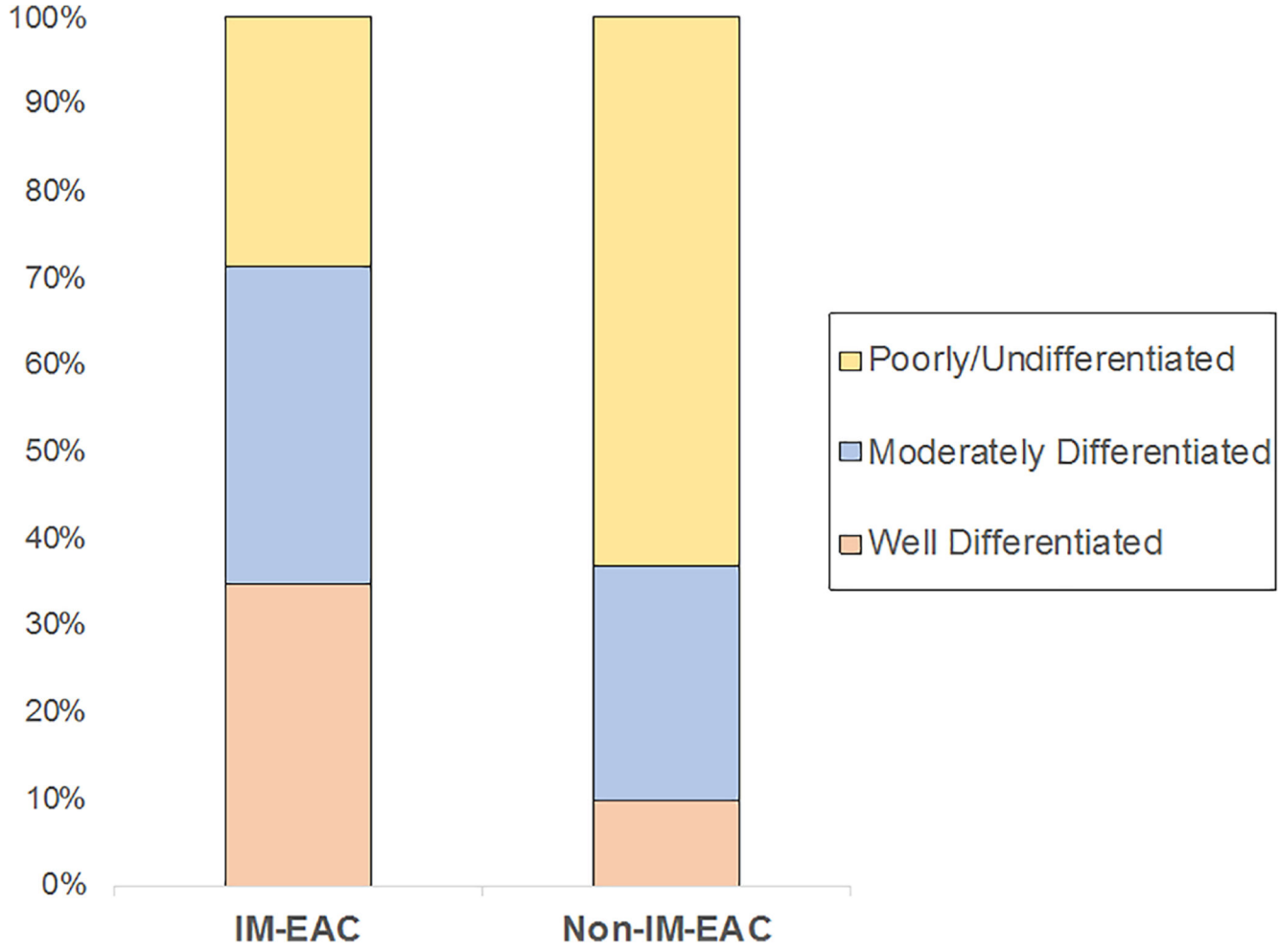

Figure 3.
Histologic grade distribution among patients with IM-EAC versus non-IM-EAC.

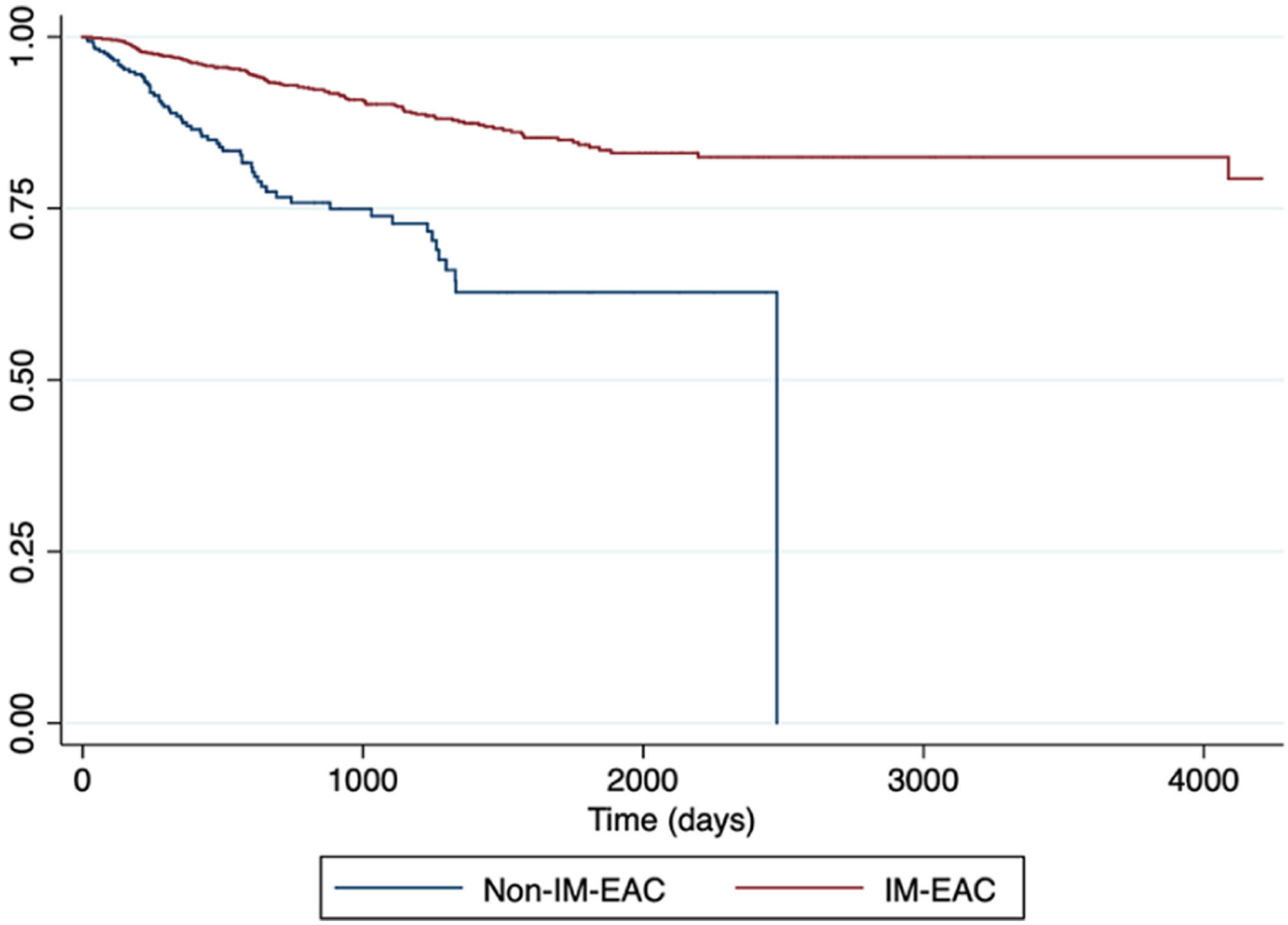

Figure 4.
Overall survival of individuals with IM-EAC versus non-IM-EAC, adjusted for age, sex, tumor location, stage, and histologic grade.

Table 1.

Characteristics of individuals with and without intestinal metaplasia

Characteristic	Total N=475	IM-EAC N=366 (77.05%)	Non-IM-EAC N= 109 (22.95%)	P value*
Survival, days, median (IQR)	593 (254–1210)	649 (287–1277)	420 (218–857)	<0.001
Age at diagnosis, mean ± SD	64.76 ± 10.78	65.46 ± 10.52	62.44 ± 11.33	0.010
BMI, kg/m^2, mean ± SD	27.96 ± 5.51	28.39 ± 5.52	26.66 ± 5.29	0.892
	N (%)	N (%)	N (%)	P value**
Gender				0.772
Male	422 (88.84)	326 (89.07)	96 (88.07)	
Female	53 (11.16)	40 (10.93)	13 (11.93)	
Race				0.807
White	421 (88.63)	323 (88.25)	98 (89.91)	
Black	2 (0.42)	2 (0.55)	0 (0)	
Asian	1 (0.21)	1 (0.27)	0 (0)	
Unknown	51 (10.74)	40 (10.93)	11 (10.09)	
Smoker				0.576
Non-smoker	164 (34.53)	127 (34.70)	37 (33.94)	
Former/Current	295 (62.11)	225 (61.48)	70 (64.22)	
Unknown	16 (3.37)	14 (3.83)	2 (1.83)	
Ethanol use				0.710
None	390 (82.11)	302 (82.51)	88 (80.73)	
Former/Current	64 (13.47)	47 (12.84)	17 (15.6)	
Unknown	21 (4.42)	17 (4.64)	4 (3.67)	
Family history EAC	20 (4.38)	15 (4.27)	5 (4.72)	0.895
Charlson Deyo Score				0.034
0	313 (65.89)	230 (62.84)	83 (76.15)	
1	97 (20.42)	78 (21.31)	19 (17.43)	
2	28 (5.89)	26 (7.10)	2 (1.83)	
3+	37 (7.79)	32 (8.74)	5 (4.59)	
PPI Use	264 (57.27)	227 (63.76)	37 (35.24)	<0.001
Insurance Type				0.707
Private	131 (27.58)	103 (28.14)	28 (25.69)	
Government	147 (30.95)	110 (30.05)	37 (33.94)	
Medicare & Private	136 (28.63)	108 (29.51)	28 (25.69)	
Unknown/Not reported/Other	61 (12.84)	45 (12.30)	16 (14.68)	
Cancer Location				<0.001
Tubular esophagus	203 (42.74)	180 (49.18)	23 (21.10)	
Siewert I	69 (14.53)	52 (14.21)	17 (15.60)	
Siewert II	181 (38.12)	116 (31.69)	65 (59.63)	

Characteristic	Total N=475	IM-EAC N=366 (77.05%)	Non-IM-EAC N= 109 (22.95%)	P value*
Unknown	22 (4.63)	18 (4.92)	4 (3.67)	
Histologic Grade				<0.001
Well differentiated	127 (26.74%)	117 (31.97%)	10 (9.17%)	
Moderately differentiated	150 (31.58%)	122 (33.33%)	28 (25.69%)	
Poorly/Undifferentiated	161 (33.895)	96 (26.23%)	65 (59.63%)	
Unknown	37 (7.79%)	31 (8.47%)	6 (5.50%)	
Clinical Stage				<0.001
1	125 (26.32)	124 (33.88)	1 (0.92)	
2A	6 (1.26)	6 (1.64)	0 (0)	
2B	25 (5.26)	24 (6.56)	1 (0.92)	
3	146 (30.74)	102 (27.87)	44 (40.37)	
4A	45 (9.47)	30 (8.20)	15 (13.76)	
4B	83 (17.47)	44 (12.02)	39 (35.78)	
Unknown	45 (9.47)	36 (9.84)	9 (8.26)	
Her2 status				<0.01
Positive	58 (12.21%)	42 (11.48%)	16 (14.68%)	
Negative	202 (42.53%)	138 (37.7%)	64 (58.72%)	
Unknown	215 (45.26%)	186 (50.82%)	29 (26.61%)	
Mismatch Repair Deficiency				0.066
Yes	43 (9.05%)	4 (1.09%)	1 (0.92%)	
No	5 (1.05%)	27 (7.38%)	16 (14.68%)	
Unknown	427 (89.89%)	335 (91.53%)	92 (84.40%)	
PDL1 expression				0.013
Yes	4 (0.84%)	1 (0.27%)	3 (2.75%)	
No	9 (1.89%)	5 (1.37%)	4 (3.67%)	
Unknown	462 (97.26%)	360 (98.36%)	102 (93.58%)	
Endoscopic therapy alone	110 (23.16)	109 (29.78)	1 (0.92)	<0.001
Surgery alone	36 (7.58)	36 (9.84)	0 (0)	0.001
Neoadjuvant + surgery	151 (31.79)	108 (29.51)	43 (39.45)	0.050
Chemotherapy +/− radiation	112 (23.58)	66 (18.03)	46 (42.20)	<0.001

*ANOVA test was used to assess differences among groups for continuous variables.

**Chi-square test was used to assess differences among groups for categorical variables.

Table 2.

Univariable and Multivariable Survival Analysis.

	Univariable Analysis	Multivariable Analysis
Characteristic	**Hazard Ratio [95% CI]**	**Adjusted Hazard Ratio [95% CI]**
Smoker (ref: non)		--
Former/ Current	0.95 (0.70–1.27)	
Unknown	0.84 (0.40–1.75)	
Ethanol use (ref: none)		--
Former/ Current	1.48 (0.98–2.25)	
Unknown	1.25 (0.70–2.25)	
Family hx esophageal cancer	1.10 (0.56–2.01)	--
Race (ref: white)		--
Black	0.99 (0.14–7.02)	
Asian	5.25 (0.73–37.82)	
Unknown	1.33 (0.83–2.14)	
Charlson Deyo Score (ref: 0)		--
1	1.38 (0.97–1.97)	
2	1.89 (1.11–3.07)	
3+	1.44 (0.87–2.40)	
Endoscopic Therapy alone	0.17 (0.10–0.30)	--
Surgery alone	0.31 (0.15–0.67)	--
Neoadjuvant + surgery	0.71 (0.52–0.96)	--
Chemo +/− radiation	4.34 (3.24–5.83)	--
No treatment	150.40 (37.98–595.59)	--
PPI Use (ref: no)	0.52 (0.9–0.70)	--
Her2 status		--
Positive	0.77 (0.49 – 1.21)	
Unknown	0.47 (0.24 – 0.64)	
Age at diagnosis	1.01 (0.99–1.02)	1.03 (1.01–1.04)
Male Sex	1.41 (0.87–2.29)	1.31 (0.80–2.14)
Presence of BE/IM	0.44 (0.32–0.59)	0.69 (0.49–0.96)
Location (ref: esophageal)		
Siewert Class I	1.98 (1.32–2.96)	1.49 (0.98–2.25)
Siewert Class II	1.55 (1.12–2.14)	1.07 (0.75–1.51)
Unknown	1.35 (0.69–2.63)	1.67 (0.84–3.33)
Clinical Stage (ref: 1)		
2	2.96 (1.46–6.02)	2.04 (0.98–4.25)
3	3.53 (2.14–5.82)	2.19 (1.25–3.84)
4	9.10 (5.59–14.83)	6.49 (3.77–11.15)
Unknown	2.41 (1.27–4.57)	1.81 (0.93–3.53)

	Univariable Analysis	Multivariable Analysis
Characteristic	**Hazard Ratio [95% CI]**	**Adjusted Hazard Ratio [95% CI]**
Histologic Grade (ref: well diff.)		
Moderately differentiated	3.02 (1.95–4.67)	2.02 (1.26–3.26)
Poorly/Undifferentiated	3.71 (2.43–5.67)	2.00 (1.26–3.19)
Unknown	1.62 (0.85 – 3.08)	1.04 (0.54–2.01)

Table 3.

Sensitivity Analysis for survival excluding Siewert II tumors

	Multivariable Analysis
Characteristic	**Adjusted Hazard Ratio [95% CI]**
Age at diagnosis	1.03 (1.01–1.06)
Male Sex	1.03 (0.57–1.87)
Presence of BE/IM	0.57 (0.35–0.93)
Clinical Stage (ref: 1)	
2	2.91 (1.11–7.57)
3	2.09 (0.98–4.47)
4	8.71 (4.17–18.20)
Unknown	1.42 (0.54–3.74)
Histologic Grade (ref: well diff.)	
Moderately differentiated	2.83 (1.48–5.41)
Poorly/Undifferentiated	2.66 (1.41–5.00)
Unknown	1.34 (0.54–3.32)

Table 4.

Multivariable Survival Analysis for Subgroup of EAC (Stage III/IV, Tubular Esophagus/Siewert I) and Adjusted for Age, Sex, Charlson Score, Tumor Location, Histological Grade, Stage, and Treatment.

	Multivariable Analysis
Characteristic	**Adjusted Hazard Ratio [95% CI]**
Charlson Deyo Score (ref: 0)	
1	1.77 (0.94–3.32)
2	0.79 (0.25–2.48)
3+	1.91 (0.72–5.09)
Neoadjuvant + surgery	0.22 (0.10–0.50)
Chemo +/− radiation	0.55 (0.27–1.11)
Age at diagnosis	1.01 (0.99–1.04)
Male Sex	1.47 (0.67–3.25)
Presence of BE/IM	0.59 (0.34–1.00)
Location (ref: esophageal)	
Siewert Class I	1.44 (0.88–2.34)
Clinical Stage (ref: 3)	
4	3.58 (1.86–6.88)
Histologic Grade (ref: well diff.)	
Moderately differentiated	4.11 (1.50–11.28)
Poorly/Undifferentiated	4.94 (1.91–12.74)
Unknown	1.18 (0.27–5.13)