The Prognostic Value of Clinical and Pathologic Factors in Esophageal Adenocarcinoma: A Mayo Cohort of 796 Patients With Extended Follow-up After Surgical Resection

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OBJECTIVE: To identify and describe clinicopathologic prognostic factors in patients with esophageal adenocarcinoma who underwent surgical resection with curative intent.

PATIENTS AND METHODS: The study cohort consisted of 796 patients with adenocarcinoma of the esophagus, gastroesophageal junction, or gastric cardia who underwent complete tumor resection at Mayo Clinic from January 1, 1980, to December 31, 1997. We reviewed individual patient medical records and abstracted demographic, pathologic, perioperative, and cancer outcome data. Median follow-up for vital status and disease recurrence was 12.8 and 5.8 years, respectively.

RESULTS: Univariate analysis revealed the following factors to be statistically associated with worse 5-year disease-specific survival: higher N and T status, higher tumor grade, age older than 76 years, and the presence of extracapsular lymph node extension and signet ring cells. The following factors remained significantly linked with worse 5-year disease-specific survival on multivariate analysis: higher N and T status, grade, and age and the absence of preoperative chemotherapy or radiotherapy. Anatomic location of tumor was not associated with differential prognosis. Lymph node metastases were found in 25 (27%) of 93 T1b tumors, 397 (85%) of 468 T3 tumors, and 22 (67%) of 33 T4a tumors. Disease-specific survival was better in T3-4N0 than in T1bN1-3 carcinomas (hazard ratio, 0.50; 95% confidence interval, 0.28-0.89, adjusted for grade and age; $P=.02$).

CONCLUSION: Our results confirm the importance of T and N status and tumor grade and suggest that age may affect prognosis. In addition, we show that a significant proportion of superficial esophageal adenocarcinomas exhibit regional metastases and have worse prognosis than more invasive nonmetastatic tumors.

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AIC = Akaike information criterion; AJCC = American Joint Committee on Cancer; CI = confidence interval; DFS = disease-free survival; DSS = disease-specific survival; EAC = esophageal adenocarcinoma; ESCC = esophageal squamous cell carcinoma; GEJ = gastroesophageal junction; HR = hazard ratio; LN = lymph node; OS = overall survival

The increase in the incidence of adenocarcinoma of the esophagus, gastroesophageal junction (GEJ), and gastric cardia in recent decades has been among the highest for any cancer in Western countries.¹ This triad of adenocarcinomas (designated *esophageal adenocarcinoma* [EAC] in this article) has grown more than 400% in incidence in the past 40 years, paralleling the increase in obesity and gastroesophageal reflux.² It is lethal in most cases, yet its degree of aggressiveness also varies from person to person.³ These statistics signal a need for a better understanding of not only EAC

etiology, but its progression and long-term clinical behavior. Understanding and exploiting the heterogeneity in prognosis are critical to improving outcomes in EAC patients and require the study of large cohorts with well-described and robust follow-up. Because the emergence of EAC as a worsening public health burden is recent, our knowledge of its behavior has been limited by the small sample sizes of most studies and by the combining of heterogeneous diseases (glandular with squamous histologies, esophageal with distal stomach carcinomas) and therapies.

The main objective of our study was to assess which, and by what magnitude, clinicopathologic factors influence the long-term “natural” course in a homogeneous cohort of EAC patients who underwent surgical resection. To diminish (although not completely eliminate) the potential prognostic effects of systemic therapy, we focused on patients who underwent surgery before 1998. Perioperative therapy (typically involving preoperative chemotherapy and radiotherapy to patients with muscle-invasive or node-positive disease) was not commonly recommended until the late 1990s at Mayo Clinic and other centers.⁴ A postsurgical group remains clinically relevant in the contemporary trimodality era because surgical resection remains the foundation of curative-intent treatment.⁵

We also focused on adenocarcinoma histology, rather than esophageal squamous cell carcinoma (ESCC), because EAC and ESCC appear to be different clinical entities. Obesity and symptomatic gastroesophageal reflux disease clearly increase risk for EAC, with modest contributions from tobacco and a diet low in fruits and veg-

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etables, whereas ESCC is more heavily related to tobacco and alcohol exposure.^{6,7} When EAC recurs, the anatomic location of recurrence tends to be distant more often than in ESCC.^{8,9} Whereas EAC incidence has dramatically increased since 1975 in the United States, ESCC incidence has dropped by half over the same time period.¹⁰

This is one of the largest reported single-institution cohort studies¹¹⁻¹³ to describe long-term cancer outcomes for EAC in which patients underwent complete resection of all tumor mostly without perioperative chemotherapy or radiotherapy.

PATIENTS AND METHODS

We queried the Mayo Clinic Tumor Registry and Mayo Clinic Surgical Index for all patients with neoplasms of the esophagus, GEJ, or gastric cardia who received care at Mayo Clinic in Rochester, MN, from January 1, 1980, to December 31, 1997. The Surgical Index is a prospective database of all patients who undergo a surgical procedure at Mayo Clinic. Lists from both queries were consolidated, yielding 1591 patients. Individual patient medical records were reviewed in 2 phases by a multidisciplinary team consisting of specialists in medical oncology (H.H.Y., M.K., J.F.Q.), thoracic surgery (S.D.C.), and anatomic gastrointestinal pathology (T.-T.W.).

In the first phase (*screening for inclusion*), medical records of all 1591 patients were reviewed to assess whether patients met eligibility for the current study. To be included, patients had to have been older than 18 years at the time of surgery; have a tissue-confirmed adenocarcinoma of the esophagus, GEJ, or gastric cardia (ie, Siewert type I or II¹³); and have undergone surgical resection with curative intent at Mayo Clinic. Tumor location was determined through a combination of endoscopy, contrast radiography, histopathologic examination, and/or intraoperative findings. Preoperative cancer staging involved a combination of computed tomography of the chest and abdomen and, to a lesser degree, endoscopic ultrasonography, transabdominal ultrasonography, fluorodeoxyglucose–positron emission tomography, bone scan, and/or magnetic resonance imaging. By far the most common operation was a transthoracic (Ivor-Lewis type) esophagectomy,¹⁴ which, in brief, involves initial abdominal exploration through an upper midline laparotomy followed by en bloc esophageal resection and paraesophageal lymphadenectomy through a right posterolateral thoracotomy with a high intrathoracic anastomosis. Transhiatal (laparotomy, cervical incision), thoracoabdominal (left side of chest and oblique upper abdominal incision), and tri-incisional (McKeown type, ie, right thoracotomy, laparotomy, cervical approach) esophagectomies were also performed.

Patients with distant metastases on preoperative staging or poor general status that precluded a radical surgical resection were excluded. Also excluded were patients whose records were unavailable at the time of analysis or in whom curative-intent surgical resection was not performed (eg, exploratory laparotomy was performed without resection of tumor) or not performed at Mayo Clinic; histologic findings did not include adenocarcinoma (dysplasia-only cases were excluded); Siewert type III, surgical margins were microscopically or macroscopically incomplete (ie, R1 or R2 resections); surgery was performed for recurrent (rather than primary) disease; or second primary cancer (other than nonmelanoma skin cancer) was diagnosed within 3 months of index surgery (Figure 1). A total of 796 patients met all inclusion criteria and were included in the study cohort.

VARIABLES COLLECTED

In the second phase (*data extraction*), individual medical records of eligible patients were extensively reviewed. Variables collected included date of birth, sex, T status, total number and location of malignant and examined lymph nodes (LNs), histologic grade, the presence of signet ring cells or extension of tumor beyond the LN capsule, anatomic location of tumor, date and type of surgery, postoperative course, perioperative therapy (preoperative or postoperative chemoradiotherapy or chemotherapy or radiotherapy alone), tumor recurrence (date, location, method

FIGURE 1. Inclusion and exclusion criteria for the study. GEJ = gastroesophageal junction; R1 = microscopically incomplete resection; R2 = macroscopically incomplete resection.

of verification), vital status, and date and cause of death. The American Joint Committee on Cancer (AJCC) 2009 criteria were used for staging. About 10% of records were reviewed by one coinvestigator (P.A.B.) for accuracy of eligibility and data extraction. All data entries were reviewed for accuracy by research staff.

END POINTS

Our primary clinical outcome variable was disease-specific survival (DSS), defined as the time from surgery to death related to index cancer. Disease-specific survival was censored at the date of death due to postoperative complications or other nonmalignant causes. Secondary end points included disease-free survival (DFS) and overall survival (OS). Overall survival was defined as the time from surgery to death from any cause, and DFS was defined as the time from surgery to the first recurrence of index cancer or to all-cause death. For all end points, death beyond 5 years was censored because of the low likelihood, and difficulty of verifying, that such death was due to the index cancer.

STATISTICAL ANALYSES

Patient demographics and disease characteristics were summarized by frequencies and percentages for categorical variables and by mean $\pm$ SD for continuous variables. Kaplan-Meier methods were used to describe the time-to-event outcomes. The Wilcoxon rank sum test was used to compare continuous variables between groups. Cox proportional hazards regression models were used to examine univariate and multivariate associations between potential predictors and long-term outcomes.

For continuous and ordinal variables, the functional form and the strength of the association between individual variables and DSS were examined carefully. Specifically, likelihood ratio tests for comparing nested models and Akaike information criterion (AIC)¹⁵ for comparing competing models were used to determine a best form for continuous and ordinal variables. The candidate forms for continuous variables included a simple linear association with the hazard rates of DSS, a nonlinear association (quadratic or higher-order effect), and a categorized form. When higher-order effect was observed, the optimal cutoffs for categorizing variables were selected on the basis of graphic methods. The cumulative Martingale residuals¹⁶ against the covariate were plotted. The changing points observed on the cumulative Martingale residual process were used as cutoffs to categorize the continuous or ordinal variables. Backward elimination procedures (using $P < .05$) in conjunction with inspection of univariate association were implemented to identify the most important predictors of the hazard rate of disease-specific death. Hazard ratios (HRs) for unadjusted and adjusted association, along with 95% confidence intervals (CIs), were reported. All

analyses were conducted in SAS, version 9.1 (SAS Institute, Cary, NC), and the significance level of .05 was applied.

This study was approved by the Mayo Clinic Institutional Review Board.

RESULTS

Table 1 describes the baseline traits of the study cohort. Data were missing in a few cases for T status ($n=6$; 0.8%), LN status ($n=2$; 0.3%), grade ($n=11$; 1.4%), and whether postoperative chemotherapy or radiotherapy was delivered ($n=52$; 6.5%). Quartiles for age were 57.2, 65.0 (median), and 71.5 years. Among the 124 cases (16%) that were not transthoracic or transhiatal esophagectomies, 92 were thoracoabdominal and 32 were tri-incisional esophagectomies. Forty-five cases (6%) were T1a, 93 (12%) were T1b, 154 (19%) were T2, 468 (59%) were T3, and 30 (4%) were T4a. Because this cohort included only margin-free (R0) resections, no case was T4b by definition. Among the 543 patients (68%) with at least 1 metastatic LN, quartiles for the number of metastatic LNs were 2, 4 (median), and 6.

Preoperative chemotherapy with concurrent radiotherapy, chemotherapy alone, or radiotherapy alone was administered in 7 patients (0.9%), 1 patient (0.1%), and 1 patient (0.1%), respectively. Postoperative (adjuvant) chemotherapy with concurrent radiotherapy, chemotherapy alone, or radiotherapy alone was administered in 53 patients (7%), 28 patients (4%), and 26 patients (3%), respectively. Median follow-up for vital status (for surviving patients) and disease recurrence was 12.8 and 5.8 years, respectively. Nine patients (1.1%) died in the first 30 days and an additional 3 (0.4%) died after 30 days of postoperative complications. Twenty-five patients (3.1%) died 30 days to 60 months after surgery of nonoperative nonmalignant causes. The 1-, 3-, and 5-year OS rates were 77% (95% CI, 74%-80%), 42% (95% CI, 38%-45%), and 31% (95% CI, 28%-34%), respectively (544 all-cause deaths). The 1-, 3-, and 5-year DSS rates were 79% (95% CI, 76%-82%), 44% (95% CI, 41%-48%), and 33% (95% CI, 30%-37%), respectively (506 events). The 1-, 3-, and 5-year DFS rates were 61% (95% CI, 58%-64%), 35% (95% CI, 32%-39%), and 28% (95% CI, 25%-31%), respectively (567 events).

UNIVARIATE ANALYSIS

In univariate analysis, higher T status and grade, age older than 76 years, higher N status, and the presence of extracapsular LN extension and signet ring cells were associated with worse DSS and DFS (Table 1). Patients who received preoperative or postoperative chemotherapy or radiotherapy, compared with patients who did not receive perioperative therapy, trended toward improved DSS. The delivery of either preoperative or postoperative therapy

TABLE 1. **Univariate Associations Between Clinicopathologic Factors and 5-Year Outcomes^a**

Factor	No (%) of patients (N=796) ^c	Disease-specific survival ^b			Disease-free survival ^c			Overall survival ^d		
		No. of events	HR (95% CI) ^f	P value	No. of events	HR (95% CI) ^f	P value	No. of events	HR (95% CI) ^f	P value
Age at surgery (y)										
≤76	707 (89)	447	Reference		495	Reference		473	Reference	
>76	89 (11)	59	1.33 (1.01-1.74)	.04	72	1.34 (1.04-1.71)	.02	71	1.50 (1.17-1.92)	.002
Sex										
Male	705 (89)	454	Reference		511	Reference		489	Reference	
Female	91 (11)	52	0.84 (0.63-1.12)	.23	56	0.79 (0.60-1.05)	.10	55	0.82 (0.62-1.09)	.17
T status										
T1	138 (17)	36	Reference		39	Reference		38	Reference	
T2	154 (19)	91	3.02 (2.05-4.45)	<.001	108	3.54 (2.45-5.10)	<.001	102	3.20 (2.20-4.64)	<.001
T3 or T4	498 (63)	375	5.28 (3.74-7.44)	<.001	416	5.57 (4.00-7.75)	<.001	400	5.28 (3.78-7.38)	<.001
N status ^g										
N0	251 (32)	75	Reference		94	Reference		87	Reference	
N1 (1-2)	196 (25)	138	3.55 (2.68-4.71)	<.001	154	3.23 (2.50-4.19)	<.001	146	3.22 (2.46-4.21)	<.001
N2 (3-6)	217 (27)	178	6.16 (4.68-8.10)	<.001	194	5.50 (4.27-7.07)	<.001	191	5.62 (4.34-7.27)	<.001
N3 (≥7)	130 (16)	115	8.15 (6.06-11.0)	<.001	125	7.04 (5.35-9.27)	<.001	120	7.16 (5.40-9.50)	<.001
Tumor grade										
1 or 2	126 (16)	52	Reference		62	Reference		58	Reference	
3	351 (45)	230	1.99 (1.47-2.69)	<.001	258	1.90 (1.44-2.51)	<.001	244	1.89 (1.42-2.52)	<.001
4	308 (39)	224	2.72 (2.01-3.68)	<.001	247	2.49 (1.88-3.29)	<.001	242	2.61 (1.96-3.48)	<.001
Extracapsular LN extension										
Absent	754 (95)	469	Reference		528	Reference		505	Reference	
Present	42 (5)	37	2.09 (1.49-2.93)	<.001	39	1.97 (1.42-2.73)	<.001	39	2.03 (1.46-2.81)	<.001
Signet ring cells										
Absent	721 (91)	444	Reference		503	Reference		481	Reference	
Present	75 (9)	62	1.69 (1.29-2.21)	.001	64	1.49 (1.15-1.93)	.003	63	1.58 (1.21-2.05)	<.001
Tumor location										
Esophagus	379 (48)	244	Reference		271	Reference		260	Reference	
GEJ or gastric cardia only	417 (52)	262	0.98 (0.82-1.16)	.80	296	1.00 (0.85-1.18)	.97	284	0.99 (0.84-1.18)	.95
Surgery										
Ivor-Lewis	558 (70)	364	Reference		407	Reference		388	Reference	
Transhiatal	114 (14)	73	0.94 (0.73-1.21)	.17	75	0.87 (0.68-1.12)	.27	75	0.92 (0.73-1.17)	.45
Other	124 (16)	69	0.84 (0.65-1.08)	.65	85	0.89 (0.70-1.12)	.32	81	0.91 (0.71-1.17)	.50
Preop chemo or RT										
No	787 (99)	504	Reference		561	Reference		540	Reference	
Yes	9 (1)	2	0.27 (0.07-1.08)	.06	6	0.95 (0.43-2.12)	.90	4	0.50 (0.19-1.35)	.17
Postop chemo or RT										
No	638 (86)	386	Reference		440	Reference		420	Reference	
Yes	107 (14)	79	1.28 (1.00-1.63)	.05	84	1.16 (0.92-1.46)	.22	81	1.21 (0.95-1.53)	.12

^a chemo = chemotherapy; CI = confidence interval; GEJ = gastroesophageal junction; HR = hazard ratio; LN = lymph node; postop = postoperative; preop = preoperative; RT = radiotherapy.

^b The event is disease-specific death.

^c The event is all-cause death or tumor recurrence.

^d The event is all-cause death.

^e In calculating percentages, the denominator is the total number of patients for whom data are available; the total number of patients may not add up to 796.

^f Higher risk for the event is denoted by a HR value >1 and lower risk by a value <1.

^g Per American Joint Committee on Cancer 2009 criteria, the number of malignant lymph nodes is listed in parentheses.

was not associated with DFS. Anatomic location of tumor and surgery type were not associated with DSS or DFS. Figure 2 shows DSS curves for age, T status, N status, and grade. Median DSS was 21.0 months (95% CI, 17.3-36.0 months) for age older than 76 years and 30.2 months (95% CI, 25.6-33.3 months) for age 76 years or younger; not reached, 42.0 months (30.9-52.1 months), and 19.0 months (17.4-21.5 months) for T1, T2, and T3-4; not reached, 29.5 months (95% CI, 23.2-34.4 months), 16.5 months (15.3-

19.0 months), and 13.9 months (12.3-15.7 months) for N0, N1, N2, and N3; and not reached, 30.5 months (95% CI, 24.6-34.3), and 18.5 months (95% CI, 16.4-21.5 months) for grade 1-2, 3, and 4, respectively.

AGE

When we assessed the association between age in linear form and DSS in a Cox proportional hazards model, the cumulative Martingale residuals plot suggested a possible

FIGURE 2. Kaplan-Meier curves for disease-specific survival by (A) age, (B) T status, (C) N status, and (D) grade. (This illustration is in color online only.)

changing point at 76 years. Comparing models including age in linear vs dichotomous form (>76 vs ≤76 years), we found that the dichotomous form fit the data better than the linear form (AIC value of linear vs dichotomous form, 6260.5 vs 6256.7). Patients older than 76 years had worse DSS than patients 76 years or younger (HR, 1.33; 95% CI, 1.01-1.74; $P=.04$). This association became stronger (HR, 1.46; 95% CI, 1.10-1.93) after adjustment for T status, N status, and tumor grade (Figure 3).

OVERALL STAGE VS T STATUS, N STATUS, AND TUMOR GRADE

The AIC value (5907.9) of the Cox model including T status, N status, and tumor grade as individual variables was substantially lower than the AIC value (5919.6) of the Cox model including the composite variable of overall stage (2009 AJCC criteria). This suggested that the model with T status, N status, and grade as individual variables fit the data better than overall stage. (This analysis did not include M stage, because all eligible patients were M0.) Therefore,

FIGURE 3. Disease-specific survival, stratified by age ≤76 y or >76 y. CI = confidence interval; HR = hazard ratio.

we included T status, N status, and tumor grade as individual variables in further multivariate modeling.

MULTIVARIATE MODELING

Backward elimination in multivariate modeling revealed that only older age, higher T and N status, grade 4 differ-

entiation, and the absence of preoperative chemotherapy or radiotherapy were associated with worse DSS (Table 2). When these variables were included in a model evaluating OS, the associations were maintained, if not strengthened, in statistical significance and magnitude (Table 2).

TABLE 2. Multivariate Models Evaluating Clinicopathologic Factors and 5-Year Outcome^a

Factor	Disease-specific survival ^b		Disease-free survival ^c		Overall survival ^d	
	HR (95% CI) ^e	P value	HR (95% CI) ^e	P value	HR (95% CI) ^e	P value
Age (y)						
≤76	Reference		Reference		Reference	
>76	1.46 (1.10-1.93)	.008	1.39 (1.08-1.79)	.01	1.64 (1.27-2.12)	<.001
Tumor grade						
1 or 2	Reference		Reference		Reference	
3	1.32 (0.97-1.79)	.07	1.20 (0.90-1.59)	.21	1.26 (0.47-1.68)	.13
4	1.64 (1.20-2.24)	.002	1.41 (1.06-1.89)	.02	1.60 (1.19-2.16)	.002
T status						
T1	Reference		Reference		Reference	
T2	1.46 (0.97-2.20)	.05	1.90 (1.29-2.80)	.001	1.63 (1.10-2.43)	.02
T3 or T4	1.67 (1.13-2.47)	.01	2.07 (1.43-3.01)	.001	1.83 (1.25-2.66)	.002
N status ^f						
N0	Reference		Reference		Reference	
N1 (1-2)	2.78 (2.05-3.77)	<.001	2.39 (1.81-3.15)	<.001	2.48 (1.86-3.30)	<.001
N2 (3-6)	4.49 (3.30-6.09)	<.001	3.74 (2.83-4.94)	<.001	4.00 (3.00-5.32)	<.001
N3 (≥7)	5.94 (4.26-8.27)	<.001	4.75 (3.50-6.43)	<.001	5.08 (3.71-6.96)	<.001
Preop chemo or RT						
No	Reference		Reference		Reference	
Yes	0.17 (0.04-0.69)	.01	0.69 (0.31-1.56)	.37	0.32 (0.12-0.86)	.02

^a chemo = chemotherapy; CI = confidence interval; HR = hazard ratio; preop = preoperative; RT = radiotherapy.

^b The event is disease-specific death.

^c The event is all-cause death or tumor recurrence.

^d The event is all-cause death.

^e Higher risk for the event is denoted by a HR value >1 and lower risk by a value <1.

^f Per American Joint Committee on Cancer 2009 criteria, the number of malignant lymph nodes is listed in parentheses.

Because signet ring cells and extracapsular LN extension did not make it into the final DSS model, we evaluated their association with other covariates. Almost all 75 cases with signet ring cells were poorly differentiated tumors (69, 6, and 0 cases with signet ring cells were grade 4, 3, and 0, respectively; $P<.001$). The presence of signet ring cells was no longer associated with DSS after adjustment for grade (data not shown).

Likewise, extracapsular LN extension was associated with higher T status: 38 (90%) of 42 cases with extracapsular extension vs 460 (62%) of 748 cases without extracapsular extension were T3-4a tumors ($P<.001$). The presence of extracapsular LN extension was no longer associated with DSS after adjustment for T status (data not shown).

T status, N status, tumor grade, and age, but not preoperative chemotherapy or radiotherapy, were associated with DFS in a multivariate model (Table 2).

SUBGROUP ANALYSIS: EXPLORING LN-POSITIVE VS LN-NEGATIVE CASES

To explore the hypothesis that LN-positive tumors are distinct biological entities from LN-negative tumors regardless of primary tumor traits, we focused on the subgroup of patients at the extremes (T1N+ and T3-4aN0) of what would be expected to be good vs poor prognosis on the basis of only primary tumor pathology. Lymph node metastases were found in 0 of 43 T1a tumors, 25 (27%) of 93 T1b tumors, 397 (85%) of 468 T3 tumors, and 22 (67%) of 33 T4a tumors. As shown in Figure 4, DSS was better in T3-4aN0 compared with T1bN1-3 carcinomas (unadjusted HR, 0.55; 95% CI, 0.31-0.97; $P=.04$; HR adjusted

for grade and age, 0.50; 95% CI, 0.28-0.89; $P=.02$). There was no difference in the total number of LNs examined in T3-4aN0 vs T1bN1-3 resection specimens (T3-4aN0: median, 17 LNs; range, 4-39 LNs; T1bN1-3: median, 15 LNs; range, 3-59 LNs; $P=.76$).

DISCUSSION

In this large cohort with robust follow-up data from individual medical records, we had the statistical power to describe the influence of clinicopathologic factors on long-term outcome, including factors with low prevalence and modest impact. Other valuable studies of cancer prognosis in more than 500 EAC patients who underwent surgical resection have been reported.^{11-13,17} Our study fills a gap in this research field by using information verified by individual patient data,¹⁷ analyzing outcomes by incorporating cause of death or adjusting for potential confounders of prognosis,¹¹ evaluating patients in the United States,¹³ and examining the relative importance of clinicopathologic features.¹²

We confirmed that N status was by far the strongest prognostic factor, with the presence of metastatic LNs worsening DSS 3- to 6-fold.¹⁸ The other factors had less dramatic associations with outcome, worsening DSS by less than 2-fold. Next in prognostic strength were T status and tumor grade differentiation. Compared with T1 tumors, tumors confined within (T2) and extending beyond (T3-4a) the muscularis propria increased the relative risk for cancer-related death by 46% and 67%, respectively. We had too few T4a tumors to perform robust evaluation of this group separately from T3 tumors. Grade 4 differentiation increased the relative risk for DSS by 64% compared with grade 1-2, but grade 3 differentiation was not substantially worse than grade 1-2.

The presence of signet ring cells or extracapsular LN extension was each associated with poor outcome, but not after adjustment for tumor grade and T status, respectively. Few studies in EAC report a negative prognostic influence from these factors after adjustment for other important covariates. Two studies, one evaluating signet ring cells¹⁹ and another evaluating extracapsular LN extension,²⁰ involved reexamination of surgical specimens by a pathologist and found higher rates of each pathologic abnormality than found in our study. These higher rates, in turn, increased the power of their studies to detect prognostic differences. Those findings have yet to be validated. Another potential explanation of the difference between our study and the others is that signet ring cells and extracapsular LN extension may have modest effects on prognosis when tested across multiple populations.

We found that patients who received preoperative chemoradiotherapy had DSS substantially superior to that

FIGURE 4. Kaplan-Meier curves for disease-specific survival in the subgroups of T1b and T3-4a carcinomas. (This illustration is in color online only.)

of patients who did not receive preoperative chemoradiotherapy. These data should be viewed with caution, because the association between preoperative therapy and DFS was not significant. Furthermore, very few patients received preoperative therapy in our cohort. The superior outcome experienced by patients receiving all 3 modalities (chemotherapy and radiotherapy in addition to surgery) is likely heavily influenced by patient selection. Evidence from randomized clinical trials indicates that the survival benefit of adding preoperative chemoradiotherapy to surgery exists but is less pronounced.^{21,22}

We found that patients older than 76 years had modestly worse DSS and DFS than patients 76 years or younger. This finding is supported by HR point estimates trending toward worse DSS consistently within a particular stratification level of T or N status or tumor grade. Limited sample size likely impaired the substratification associations from reaching statistical significance. Our results are consistent with a recent report of 600 esophagectomies for cancer patients, which found that age greater than 70 years was linked to higher surgical complications and worse OS (even when postoperative death was excluded) than age less than 70 years, regardless of whether preoperative systemic therapy was delivered.¹² Our results are also supported by an international collaboration involving 4627 esophagectomies (performed at 13 institutions, including Mayo Clinic), which found that higher age (>70 vs <60 or 60-70 years) was modestly linked to worse all-cause mortality.¹¹ In contrast, 4 earlier studies of patients with esophageal cancer who underwent resection failed to show that age had prognostic impact.²³⁻²⁶ The smaller size of these studies (<550 patients) may have reduced their capacity to detect such an effect. In addition, those studies used a lower age cut point (50-70 years) than ours, which may be too low to consistently show a difference in outcome across multiple cohorts. Although the precise influence of age is unresolved, our data support the incorporation of advanced age in risk assessments for curative esophageal surgery and signal the need for further evaluation.

Our subgroup analysis of T1bN1-3 and T3N0 carcinomas showed worse prognosis in the former subgroup. It is intriguing that one-fourth of T1b tumors had LN metastases, half of which had 3 or more malignant nodes. These findings cannot be explained by less intense LN evaluation in T3N0 than in T1bN+ resection specimens, because the total number of LNs examined was equivalent in both groups. In addition, T status was assessed using microscopically uninvolved resection (not biopsy) tissue, sharply reducing the possibility that areas of more invasive tumor were missed. Moreover, tumor differentiation cannot explain this finding, because LN metastases portended worse

outcome in T1b than in T3N0 tumors after adjustment for tumor grade.

To our knowledge, our study is the largest reported sample evaluating T1b EAC (n=93) and long-term cancer-specific outcome. The prognostic role of LN metastases in T1b tumors is not well-described. According to AJCC 2009 staging criteria, the same stage (ie, IIB) is assigned to T3N0 and T1-2N1 adenocarcinomas and a worse stage (ie, IIIA) to T1-2N2 tumors. The AJCC criteria are based largely on the international collaboration described earlier, which included 2775 EACs.²⁷ Although the collaboration did not report prognostic data specific to T1 status in EACs, our findings are consistent with theirs. In light of our purpose of identifying cancer-specific prognostic features, one advantage of our approach over that of the international collaboration is our use of DSS as the primary end point, whereas the collaboration used OS. An additional limitation of the collaboration is that each contributing institution had its own template for data collection and for intensity and completeness of patient follow-up, and not all institutions provided the same data fields. Other smaller studies evaluated T1b EACs,²⁸⁻³⁵ but only two^{29,34} examined more than 50 cases of T1b EAC. Both studies reported the same rate of LN metastases (27%) in T1b tumors as in our study. Neither study compared prognosis between T1bN+ and more invasive tumors. A study of 41 T1b carcinomas, using recursive partitioning analysis (which prioritizes factors on the basis of their relative influence on outcome), was unable to find a significant prognostic difference between T1bN+ and T3N0 carcinomas.³⁰ Other studies examined 30 or fewer T1b cases and therefore had limited capacity to address this question. In all, our study underscores the prognostic importance of nodal metastases even in superficial EAC.

That superficial EAC tumors disseminate to regional LNs may be due to the presence of rich lymphatic channels in the esophageal submucosa, which penetrate even to lamina propria.^{29,36,37} As first described by Rice et al,³⁶ even a "shallow" T1a tumor that has penetrated through the basement membrane into the lamina propria is at some risk of lymphatic spread. This possibility underscores the importance of early detection in improving outcomes.

However, a substantial proportion of more invasive (T2-4a) tumors (21% in our cohort), which presumably have similar or greater access to lymphatic vessels than T1b tumors, nonetheless failed to spread to regional LNs. Why some tumors spread to LNs and others do not may require further explanation beyond the presence of rich lymphatics in superficial esophageal tissue. Another explanation may be that EAC, like other carcinomas,³⁸ is heterogeneous in biology and contains molecular subtypes that spread distantly before invasion, independent of lymphatic vessel involvement. Our conventional understanding of oncologic

development and progression is that tumors progress by proceeding through a series of steps (acquiring constitutive mitogenic signals, resisting growth-inhibiting signals, avoiding programmed cell death) that confer selective advantage before metastatic spread. However, an emerging paradigm is that some deadly tumors begin metastatic spread early in their course.³⁸ Death is almost always due to metastases, and early detection of the primary tumor may have limited impact in these cases. Characterizing these biologic/molecular subtypes may identify targets for therapy and represents an additional approach to improving outcomes in this highly fatal disease.

We did not find a prognostic difference between distal esophageal (Siewert I) vs GEJ/cardia (Siewert II) EACs, consistent with findings of other large studies.^{13,27} A Surveillance, Epidemiology, and End Results analysis of esophageal cancers found that tumors with only local-regional spread of the lower one-third or abdominal esophagus had higher risk of death compared with more proximal tumors.¹⁷ However, the location of tumor was not verified by review of individual patient records, and an explanation for the differential outcome has not been provided. We did not find the type of surgery to be associated with differential outcomes, consistent with the results of randomized controlled trials failing to show differential outcomes in transthoracic vs transhiatal esophagectomies.³⁹⁻⁴¹

Although strengths of our study include its size, robust and long-term follow-up, and homogeneous population, caution should be used in attempting to generalize our findings. First, the outcomes of a single high-volume institution may not extend to lower-volume centers. Second, our cohort (by design) did not generally undergo perioperative therapy; as a result, our prognostic associations based on surgical pathology may not extend to patients who have received neoadjuvant therapy. Even so, the influence of T status, N status, tumor grade, and possibly age likely remains important in the trimodality setting.^{12,18} Third, the exclusion of R1-2 resections and the limited availability of preoperative staging advances (eg, fluorodeoxyglucose-positron emission tomography) in our cohort may have variably affected our cancer outcomes. Our outcomes are similar to those of R0 resections reported in large prospective clinical trials.^{42,43} In addition, the intensity of follow-up surveillance may have varied by individual in our (retrospective) study, more so than in a prospective study. This variability may particularly affect DFS, which is one reason we designated DSS as our main end point.

CONCLUSION

This study describes the importance of N status relative to T status and tumor grade in the cancer survival of patients

with EAC. Our data suggest that age greater than 76 years modestly worsens outcome, although this observation requires further evaluation. Moreover, we show that a significant subset of patients exhibit regional dissemination with only minimal tumor invasion and have worse prognosis than patients with substantially invasive nonmetastatic tumors.

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