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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Specific Tumor Characteristics Predict Upstaging in Early-Stage Esophageal Cancer

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ABSTRACT

Background. Early-stage esophageal cancer (stages 0–1) has been shown to have relatively good outcomes after local endoscopic or surgical resection. For this reason, neoadjuvant chemoradiation usually is reserved for higher-stage disease. Some early tumors, however, are found after resection to be more advanced than predicted based on initial clinical staging, termed pathologic upstaging. Such tumors may have benefited from alternate treatment models had their true stage been known preoperatively. This study aimed to identify high-risk features in early esophageal cancers that might predict tumor upstaging and guide more individualized treatment algorithms.

Methods. Through retrospective review of a single-institution foregut disease registry, we evaluated patients who underwent esophagectomy for high-grade dysplasia (Tis) or stage 1 esophageal cancer, searching for factors associated with pathologic upstaging.

Results. The review included 110 patients (88% male, median age at diagnosis, 64.5 years) treated between January 2000 and June 2016. Upstaging occurred for 20.9% of the patients, and was more common for patients with angiolymphatic invasion (odds ratio [OR], 11.07; 95% confidence interval [CI], 2.96–41.44; $P < 0.001$) or signet-ring features (OR, 23.9; 95% CI, 2.6–216.8; $P = 0.005$). In the absence of other predictors, upstaging was associated with decreased overall survival ($P = 0.006$).

Conclusions. Approximately 20% of patients with early-stage esophageal cancer may be upstaged at resection. Angiolymphatic invasion and signet-ring features may predict tumors likely to be upstaged, resulting in decreased overall survival.

Even when diagnosed early, esophageal cancer is a challenging disease, with 5-year survival rates lower than 50% and a high incidence of treatment-related morbidity.[1,2] Because the outcomes for early-stage esophageal cancer are improving with aggressive application of endoscopic resection (stage 1A) and surgical monotherapy (stage 1B).[3,4] the addition of neoadjuvant chemoradiation usually is reserved for stages 2 and 3 disease.[5–8] However, there remains a subset of early-stage esophageal tumors whose biologic behaviors are more aggressive in terms of growth, spread, and mortality than would have been predicted based solely on their clinical stage.[9]

Pathologic upstaging occurs when a higher T, N, or M stage is found at the time of resection than was identified by clinical staging, which occurs in 10% to 20% of cases.[10,11] Although it remains unclear whether this is a result of disease progression between diagnosis and surgery or of inaccurate clinical staging at the time of initial diagnosis, a patient moving from having early, localized disease (stages 0–1) into the realm of locally advanced

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(stages 2–3) or metastatic (stage 4) cancer has significant repercussions in terms of treatment options and expected mortality.[1]

Given the potentially high clinical cost of upstaging and its possible reflection of a more aggressive underlying tumor, this research aimed to identify pathologic features of early esophageal cancers that might predict which tumors are likely to be upstaged. This may allow us to identify patients that could benefit from alternate or more aggressive treatment models despite their apparent early clinical stage.

MATERIALS AND METHODS

Selection and Description of Participants

We performed a retrospective review of an esophageal diseases database at a single, tertiary-care, university medical center. The Esophageal Cancer and Related Diseases (ECRD) Registry is prospectively maintained under local institutional review board (IRB) approval (IRB 1759). It tracks clinical and surgical data for consecutively presenting patients with esophageal cancer who are referred for esophagectomy.

From this registry, we selected patients with early-stage esophageal cancer (stages 0–1) based on the seventh edition of the American Joint Committee on Cancer (AJCC) guidelines.[12]

We analyzed patients between January 2000 and June 2016 who had completed esophagectomy for definitive treatment of their cancer. We excluded those patients who underwent surgery for benign disease, such as achalasia, esophageal strictures, perforation, or dysmotility. The surgical approach was left to the discretion of the attending surgeon. The majority of the cases were transhiatal (69.1%), with 72.3% of these managed using minimally invasive techniques. The remainder of the cases involved either an Ivor-Lewis (16.4%) or a three-field approach (14.5%), with 22.2% of the Ivor-Lewis cases and 56.2% of the three-field cases being minimally invasive.

All the patients with clinical stage 2 or higher disease at the time of clinical staging and those who had received neoadjuvant chemotherapy or radiation were excluded from the dataset. We were unable to include patients whose cancers were treated successfully with endoscopic mucosal resection (EMR) because these patients are treated by our gastroenterology colleagues and are not captured in our surgical database.

Patient demographics, as well as their clinical and operative variables, were extracted from the ECRD registry, and missing data points that could be collected from the patient's electronic medical record were entered separately. Those patients whose clinical or pathologic stage could not be determined based on chart review (n = 11) were excluded from the final cohort because we could not accurately evaluate them for upstaging.

Staging and Upstaging

Clinical tumor-node-metastasis (TNM) staging in our registry is established in accordance with the seventh-edition American Joint Committee on Cancer (AJCC) guidelines.[12] This entails a combination of endoscopic ultrasound (EUS), biopsy, and positron emission tomography (PET)/computed tomography (CT). Pathologic TNM staging is determined through analysis of the surgically removed esophageal specimen and associated nodal tissue performed by a board-certified pathologist.

For the purposes of our evaluation, upstaging was defined as a binary variable. We considered a patient to have been upstaged if the patient's final pathologic stage was higher than his or her initial clinical stage to a point that would have affected a change in the recommended treatment had the higher stage been determined preoperatively. We simplified this to mean that stages 0 to 1A tumors were most likely to be treated endoscopically, that stage 1B tumors were most likely to be treated with surgical resection, and that stage 2 and higher tumors would have been indicated for trimodal therapy using neoadjuvant chemoradiation (nCRT) followed by surgery. Thus, a progression from stage 0 to stage 1A was not considered upstaging because this would not have changed the clinical management. Conversely, upstaging did include those patients who progressed from stage 0 or 1A to stage 1B because this would potentially have indicated the patient for surgical resection rather than endoscopic eradication, a clear change in management. Upstaging also included any patient who progressed to stage 2 or higher disease, including any patient with nodal (N1–3) or metastatic (M1) disease discovered at resection.

Statistical Analysis

Patient demographics and clinical characteristics were examined and compared across groups of patients who were upstaged versus those who were not. These comparisons were analyzed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. A P value lower than 0.05 was considered significant.

The primary outcomes for the study included rates of upstaging, rates of node-positivity, and overall survival (OS). For each outcome of interest, the demographic and clinical variables were considered as candidate predictors in uni- and multivariable settings.

Univariable modeling, with each candidate predictor evaluated separately, was performed with logistic regression for the two binary outcomes and with Cox proportional hazards regression for OS. The reported survival rates are nonparametric Kaplan–Meier estimates. Candidate predictors with univariable Wald-test (for logistic regression) or score-test (for Cox PH regression) P values lower than 0.20 were chosen for entry into a stepwise variable selection procedure, which produced a final model for each outcome consisting of predictors with Wald P values lower than 0.05. The final multivariable logistic regression models yielded adjusted odds ratio estimates and predicted probabilities of the event of interest for select subgroups. The final multivariable Cox regression model for survival yielded adjusted hazard ratio estimates. All statistics were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Of the 569 patients in our registry at the time of the query, 110 esophageal cancer patients with stages 0 to 1 disease met the inclusion criteria. The patients then were stratified into groups based on whether they were upstaged at the final pathology or not, with 23 patients (20.9%) meeting our definition of upstaging. Demographic and clinical characteristics stratified according to these two groups are summarized in Table 1. The groups were noted to be similar in terms of age, gender, American Society of Anesthesiology (ASA) class, ethnicity, smoking status, and length of time between diagnosis and surgery. In terms of tumor characteristics, clinical grade differed significantly between the upstaged and non-upstaged groups ($P = 0.026$), with more poorly differentiated tumors in the upstaged group. In addition, the upstaged group had a higher proportion of patients with angiolymphatic invasion (34.8% vs 4.6%; $P < 0.001$) and with signet ring features (21.7% vs 1.1%; $P = 0.001$) than the non-upstaged group.

Tumor Upstaging

Overall, 20.9% (95% confidence interval [CI], 13.7–29.7%) of the population was upstaged at the time of resection. In the univariable analysis, whereas histologic subtype ($P = 0.086$), clinical T stage ($P = 0.086$), and clinical grade ($P = 0.051$) had borderline significance, only angiolymphatic invasion (odds ratio [OR], 11.1; 95% CI, 3.0–41.4; $P < 0.001$) and signet ring features (OR, 23.9; 95% CI, 2.6–216.8; $P = 0.005$) were significantly associated with a higher likelihood of pathologic upstaging (Table 2a). These tumor features were the only variables retained in the multivariable model for this outcome. After adjustment for each other, a significant relationship with upstaging persisted for both angiolymphatic invasion (OR, 8.5; 95% CI, 2.1–34.6; $P = 0.003$) and signet ring features (OR, 15.8; 95% CI, 1.5–162.9; $P = 0.020$) (Table 2b).

Node-Positivity

Nine patients, all of whom were clinically node-negative at the time of diagnosis (per inclusion criteria), were found to have node-positivity after resection (8.2%). Clinical T stage was significantly predictive of nodal disease in the univariable analysis ($P = 0.014$), as was a wait of at least 84 days between the time of diagnosis and surgical resection ($P = 0.040$). Node-positivity also was found to be more frequent among patients with angiolymphatic invasion (OR, 9.3; 95% CI, 2.1–41.7; $P = 0.004$) or signet ring features (OR, 16.3; 95% CI, 2.7–98.8; $P = 0.002$) (Table 3a). When control was used for other variables that were significant during the univariable analysis, angiolymphatic invasion and time between diagnosis and surgery lost statistical significance. Clinical T stage, however, remained a significant predictor of nodal disease, with T2 lesions having an OR of 19.5 (95% CI, 1.8–217.3; $P = 0.017$), compared with Tis. Signet ring features also remained a significant predictor of nodal disease in the multivariable setting (OR, 32.4; 95% CI, 2.5–426.1; $P = 0.008$) (Table 3b).

Survival

The median follow-up time for the patients in this cohort was 3.4 years, with 14.6 years as the longest follow-up period. In the univariable analysis, age of 65 years or older ($P = 0.007$), smoking status ($P = 0.047$), and upstaging of disease ($P = 0.006$) all were significant predictors of OS (Table 4a). Pathologic staging, including the T stage ($P = 0.011$), N stage ($P = 0.001$), and overall stage ($P < 0.001$) each were significant predictors of mortality as well. Assuming that death rates are proportional over time, upstaged patients had about three times the risk of dying than non-upstaged patients (hazard ratio [HR], 2.96; 95% CI, 1.31–6.68; $P = 0.006$) (Fig. 1). Using Kaplan–Meier estimated survival curves for the upstaging groups, increased mortality was seen in the patients upstaged at the final pathology (HR, 2.96; 95% CI, 1.31–6.68; $P = 0.006$) (Fig. 1).

In the multivariable context, only age ($P = 0.030$) and pathologic stage ($P = 0.008$) remained significant predictors of mortality (Table 4b). When forced into the multivariable model as a predictor alongside age and pathologic stage, neither upstaging (HR, 1.27; 95% CI,

TABLE 1 Demographic and clinical variables by upstaged status

Clinical variable	Subgroup (or summary stat)	Upstaged (n = 23) n (%)	Not upstaged (n = 87) n (%)	P value
Age at diagnosis (years)	Range	45.1–78.2	37.9–80.6	0.722
	Median	64.8	64.0	
Gender	Female	1 (4.3)	12 (13.8)	0.294
	Male	22 (95.7)	75 (86.2)	
Ethnicity	Caucasian	23 (100)	86 (98.9)	1.000
	Other	0 (0.0)	1 (1.1)	
Histologic subtype (preoperative)	HGD	3 (13.0)	34 (39.1)	0.044
	Adenocarcinoma	19 (82.6)	50 (57.5)	
	SCC	1 (4.3)	3 (3.4)	
ASA class	1	0 (0.0)	0 (0.0)	0.443[a]
	2	9 (39.1)	42 (48.3)	
	3	11 (47.8)	26 (29.9)	
	4	0 (0.0)	1 (1.1)	
	Unknown	3 (13.0)	18 (20.7)	
Smoking status	Never	6 (26.1)	26 (29.9)	0.708
	Former	16 (69.6)	49 (56.3)	
	Current	1 (4.3)	10 (11.5)	
	Unknown	0 (0.0)	2 (2.3)	
Days from diagnosis to surgery	Range	19–206	10–1724	0.105
	Median	54	85	
Clinical T stage	Tis	4 (17.4)	35 (40.2)	0.057
	T1a	10 (43.5)	22 (25.3)	
	T1b	5 (21.7)	24 (27.6)	
	T2	4 (17.4)	6 (6.9)	
Clinical N stage	N0	23 (100)	84 (96.6)	1.000
	Nx	0 (0.0)	3 (3.4)	
Clinical grade (differentiation)	HGD	3 (13.0)	34 (39.1)	0.026
	Well	2 (8.7)	12 (13.8)	
	Moderate	9 (39.1)	24 (27.6)	
	Poor	7 (30.4)	8 (9.2)	
	Unknown	2 (8.7)	9 (10.3)	
Angiolymphatic invasion	No	15 (65.2)	83 (95.4)	< 0.001
	Yes	8 (34.8)	4 (4.6)	
Signet ring features	No	18 (78.3)	86 (98.9)	0.001
	Yes	5 (21.7)	1 (1.1)	

HGD high-grade dysplasia, *SCC* squamous cell carcinoma, *ASA* American Society of Anesthesiology, *Nx* unknown nodal status

[a]ASA P = 0.377 for collapsed ASA variable with categories 1/2, 3/4, and unknown

0.30–5.40; P = 0.744) nor node-positivity (HR, 2.10; 95% CI, 0.45–9.91; P = 0.347) had a significant effect on OS.

DISCUSSION

This study demonstrated that pathologic upstaging or having more advanced disease at the time of surgical resection than expected based on clinical staging occurs for a relatively high proportion of patients with early-stage esophageal cancer. Furthermore, our findings show a positive correlation between the presence of certain tumor characteristics (specifically, signet ring features and angiolymphatic invasion) and the risk for pathologic upstaging, with a negative correlation between upstaging and overall survival. These findings may signify a subpopulation of esophageal tumors whose biologic behavior is more aggressive than their clinical stage would suggest and who merit special attention.

TABLE 2 Uni- and multivariable analysis of upstaging

Predictor	Subgroups	Sample size (upstaged)	Estimated OR (95% CI) for predictor	*P* Value (Wald)
a Univariable analysis of upstaging				
Age	< 65 years[a]	58 (12)	N/A	0.952
	≥ 65 years	52 (11)	1.03 (0.41–2.58)	
Gender	Female[a]	13 (1)	N/A	0.239
	Male	97 (22)	3.52 (0.43–28.59)	
ASA class	1/2[a]	51 (9)	N/A	0.315
	3/4	38 (11)	1.90 (0.70–5.19)	
	Unknown	21 (3)	0.78 (0.19–3.21)	
Smoking status	Never[a]	32 (6)	N/A	0.698
	Former	65 (16)	1.42 (0.49–4.05)	
	Current	11 (1)	0.43 (0.05–4.07)	
	Unknown	2 (0)	N/A	
Histologic subtype (preoperative)	HGD[a]	37 (3)	N/A	0.086
	Adenocarcinoma	69 (19)	4.31 (1.18–15.70)	
	SCC	4 (1)	3.78 (0.29–48.51)	
Clinical T stage	Tis[a]	39 (4)	N/A	0.086
	T1a	32 (10)	3.98 (1.11–14.25)	
	T1b	29 (5)	1.82 (0.44–7.49)	
	T2	10 (4)	5.83 (1.14–29.90)	
Clinical grade (differentiation)	HGD[a]	37 (3)	N/A	0.051
	Well	14 (2)	1.89 (0.28–12.71)	
	Moderate	33 (9)	4.25 (1.04–17.36)	
	Poor	15 (7)	9.92 (2.09–47.02)	
	Unknown	11 (2)	2.52 (0.36–17.42)	
Angiolymphatic invasion	No[a]	98 (15)	N/A	< 0.001
	Yes	12 (8)	11.07 (2.96–41.44)	
Signet ring features	No[a]	104 (18)	N/A	0.005
	Yes	6 (5)	23.88 (2.63–216.83)	
Days from diagnosis to surgery	< 84[a]	55 (14)	N/A	0.244
	≥ 84	55 (9)	0.57 (0.22–1.46)	
b Multivariable analysis of upstaging				
Angiolymphatic invasion	No[a]	98 (15)	8.49 (2.08–34.58)	0.003
	Yes	12 (8)		
Signet ring features	No[a]	104 (18)	15.80 (1.53–162.85)	0.020
	Yes	6 (5)		

OR odds ratio, *CI* confidence interval, *N/A* not applicable, *ASA* American Society of Anesthesiology, *HGD* high-grade dysplasia, *SCC* squamous cell carcinoma

[a]Reference

Our current treatment systems for esophageal cancer rely on accurate clinical staging and the assumption that such cancers are unlikely to spread while in their early stages. Unfortunately, EUS, the mainstay of clinical staging, is notoriously unreliable when examining early esophageal lesions (T1a/T1b)0.[13] Even when EUS is used in combination with additional staging methods, such as CT and PET, our clinical staging systems had limitations in their diagnostic accuracy.[14,15] As a result, these cancers can easily be understaged at diagnosis.[11] This is clinically problematic because larger tumors with increasing depth of invasion (i.e., higher T stage) are associated with a much higher risk of regional lymph node metastases and a concomitant lower survival rate.[16–19] Because patients with deeper tumors or nodal disease (stage 2 or 3) clearly benefit from the inclusion of neoadjuvant chemoradiation, it is important that we do everything possible to identify understaged lesions preoperatively.

TABLE 3 Uni- and multivariable analysis of node-positivity

Predictor	Subgroups	Sample size (LN +)	Estimated OR (95% CI) for predictor	*P* value (Wald)
a Univariable analysis of node-positivity				
Age	< 65 years[a]	58 (4)	N/A	0.605
	≥ 65 years	52 (5)	1.44 (0.36–5.66)	
Gender	Female[a]	13 (0)	N/A	0.963
	Male	97 (9)	Unknown	
ASA class	1/2[a]	51 (5)	N/A	0.781
	3/4	38 (3)	0.79 (0.18–3.53)	
	Unknown	21 (1)	0.46 (0.05–4.19)	
Smoking status	Never[a]	32 (1)	N/A	0.691
	Former	65 (7)	3.74 (0.44–31.81)	
	Current	11 (1)	3.10 (0.18–54.24)	
	Unknown	2 (0)	N/A	
Histologic subtype (preoperative)	HGD[a]	37 (1)	N/A	0.357
	Adenocarcinoma	69 (8)	4.72 (0.57–39.31)	
	SCC	4 (0)	N/A	
Clinical T stage	Tis[a]	39 (1)	N/A	0.014
	T1a	32 (3)	3.93 (0.39–39.77)	
	T1b	29 (1)	1.36 (0.08–22.64)	
	T2	10 (4)	25.33 (2.41–266.80)	
Clinical grade (differentiation)	HGD[a]	37 (1)	N/A	0.462
	Well	14 (1)	2.77 (0.16–47.56)	
	Moderate	33 (4)	4.97 (0.53–46.89)	
	Poor	15 (3)	9.00 (0.85–94.90)	
	Unknown	11 (0)	N/A	
Angiolymphatic invasion	No[a]	98 (5)	N/A	0.004
	Yes	12 (4)	9.30 (2.08–41.68)	
Signet ring features	No[a]	104 (6)	N/A	0.002
	Yes	6 (3)	16.33 (2.70–98.82)	
Days from diagnosis to surgery	< 84[a]	55 (8)	N/A	0.040
	≥ 84	55 (1)	0.11 (0.01–0.90)	
b Multivariable analysis of node-positivity				
Signet ring features	No[a]	104 (6)	N/A	0.008
	Yes	6 (3)	32.41 (2.47–426.13)	
Clinical T stage	Tis[a]	39 (1)	N/A	0.017
	T1a	32 (3)	2.26 (0.19–26.97)	
	T1b	29 (1)	0.38 (0.01–11.85)	
	T2	10 (4)	19.54 (1.76–217.27)	

LN lymph node, *OR* odds ratio, *CI* confidence interval, *N/A* not applicable, *ASA* American Society of Anesthesiology, *HGD* high-grade dysplasia, *SCC* squamous cell carcinoma

[a]Reference

The frequent pathologic upstaging we have demonstrated challenges current treatment paradigms for early esophageal cancer. Given that the inaccuracy of currently available clinical staging systems can lead to the selection of suboptimal treatment algorithms, we must consider whether alternate tumor characteristics may better predict tumor behavior. This could allow us to select which patients should be treated more aggressively despite clinical staging that suggests early disease.

We have shown that angiolymphatic invasion and signet ring features are predictive of upstaging and nodal metastases, a finding that also has been reported by other

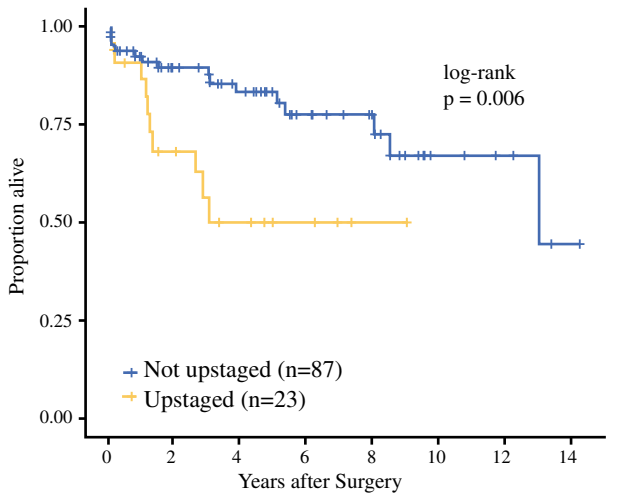
TABLE 4 Uni- and multivariable survival analysis

Predictor	Subgroups	Sample size (dead)	HR (95% CI)	Log-rank or score *P* value
a Univariable analysis of overall survival				
Age	< 65 years[a]	58 (9)	N/A	0.007
	≥ 65 years	52 (17)	3.10 (1.32–7.27)	
Gender	Female[a]	13 (3)	N/A	0.720
	Male	97 (23)	1.25 (0.37–4.20)	
ASA class	1/2[a]	51 (11)	N/A	0.212
	3/4	38 (8)	1.38 (0.55–3.47)	
	Unknown	21 (7)	2.32 (0.89–6.06)	
Smoking	Never[a]	32 (6)	N/A	0.047
	Former	65 (18)	1.37 (0.54–3.48)	
	Current	11 (0)	N/A	
	Unknown	2 (2)	4.84 (0.96–24.34)	
Histologic subtype (post-operative)	HGD[a]	25 (3)	N/A	0.313
	Adenocarcinoma	80 (21)	2.33 (0.69–7.90)	
	SCC	5 (2)	3.22 (0.53–19.46)	
Clinical T	Tis[a]	39 (7)	N/A	0.170
	T1a	32 (7)	1.31 (0.46–3.79)	
	T1b	29 (6)	1.41 (0.47–4.26)	
	T2	10 (6)	3.21 (1.07–9.59)	
Pathologic T	T0	5 (0)	N/A	0.011
	Tis[a]	34 (4)	N/A	
	T1a	34 (7)	1.67 (0.49–5.74)	
	T1b	24 (7)	3.31 (0.96–11.42)	
	T2/T3/T4	13 (8)	5.94 (1.76–20.01)	
Pathologic N	N0[a]	101 (21)	N/A	0.001
	N1/N2	9 (5)	4.84 (1.72–13.62)	
Overall pathologic stage	0[a]	39 (4)	N/A	< 0.001
	1	57 (14)	2.29 (0.75–6.97)	
	2	10 (5)	7.26 (1.86–28.36)	
	3	4 (3)	12.63 (2.75–58.01)	
Upstaged	No[a]	87 (16)	N/A	0.006
	Yes	23 (10)	2.96 (1.31–6.68)	
Clinical grade (differentiation)	HGD[a]	37 (7)	N/A	0.575
	Well	14 (2)	0.75 (0.15–3.73)	
	Moderate	33 (9)	2.01 (0.72–5.64)	
	Poor	15 (4)	1.71 (0.49–5.98)	
	Unknown	11 (4)	1.41 (0.41–4.87)	
Pathologic grade (differentiation)	HGD[a]	25 (3)	N/A	0.176
	Well	20 (6)	2.13 (0.53–8.58)	
	Moderate	44 (9)	1.92 (0.51–7.17)	
	Poor	20 (8)	4.35 (1.12–16.85)	
	Unknown	1 (0)	N/A	
Angiolymphatic invasion	No[a]	98 (22)	N/A	0.143
	Yes	12 (4)	2.22 (0.74–6.66)	
Signet ring features	No[a]	104 (24)	N/A	0.242
	Yes	6 (2)	2.36 (0.54–10.38)	

TABLE 4 continued

Predictor	Subgroups	Sample size (dead)	HR (95% CI)	Log-rank or score *P* value
Days from diagnosis to surgery	< 84[a]	55 (17)	N/A	0.260
	≥ 84	55 (9)	0.63 (0.28–1.42)	
b Multivariable analysis of overall survival				
Age	< 65 years[a]	52 (5)	N/A	0.030
	≥ 65 years	47 (15)	2.63 (1.10–6.30)	
Pathologic stage	0[a]	39 (4)	N/A	0.008
	1	57 (14)	2.15 (0.70–6.61)	
	2	10 (5)	6.61 (1.68–26.05)	
	3	4 (3)	9.05 (1.92–42.63)	

HR hazard ratio, *CI* confidence interval, *N/A* not applicable, *ASA* American Society of Anesthesiology, *HGD* high-grade dysplasia
[a]Reference



Upstaging Status	Size (Died)	1-year OS	2-year OS	5-year OS
Upstaged	23 (10)	91.3%	68.5%	50.2%
Not Upstaged	87 (16)	92.8%	89.7%	83.9%

FIG. 1 Kaplan-Meier curves for overall survival by upstaged status

authors.[20,21] This study also illuminated the fact that T2 tumors considered to be stage 1 (those with low-grade histology) are particularly likely to be upstaged by the presence of nodal disease. This is complementary to additional work showing that high-risk features also may include size greater than 2 cm and high-grade histology (poor differentiation)0.[9,10,15] Such features may be indicative of a more aggressive underlying tumor, and identifying them could help guide future treatment decisions.

Our study had limitations, including its relatively small sample size (n = 110), retrospective nature, and single-institution design. We also were unable to assess or correct for tumor size, a known predictor of high-risk lesions, because this was not tracked in the early years of our registry. Furthermore, our definition of upstaging as a simple dichotomous variable (yes or no) may have slightly less clinical utility than a design that looked more closely at each individual progression in clinical stage. For example, a change from stage 1A to 1B would indicate esophagectomy as the treatment of choice rather than endoscopic therapy and thus was counted in our study as an upstaging event. The disease remains localized, however, and still is technically stage 1. In this setting, the upstaged patient would likely retain a good outcome. Conversely, a patient who progressed from stage 1 to having locally advanced disease (stage 2 or higher) would be expected to have diminished survival. Unfortunately, our sample was too small for each of these specific subsets to be accurately assessed separately. This may explain why, despite the significant association with decreased survival seen in the univariable analysis (and the related Kaplan–Meier curves), upstaging lost its significance when adjustment of other factors in the multivariable model was performed. Future studies could certainly define upstaging more precisely to test whether specific progressions in stage might be associated with an increased risk of death.

Application of these findings to clinical practice will require ongoing research and validation in larger prospective trials. Although the treatment of locally advanced esophageal cancer (stage 2 and higher) has been widely accepted to include neoadjuvant chemoradiotherapy (CRT), followed by surgery,[10,22] the role of esophagectomy or CRT in the management of stage 1 esophageal cancer is a matter of debate.[23] Our results suggest that the presence of high-risk tumor features should call attention to the biology of the disease regardless of the early stage. This invites the question whether a role exists for more aggressive surgical resection rather than endoscopic therapy for high-risk, high-grade dysplasia (HGD) (Tis) or intramucosal carcinoma (T1a), and perhaps even more

importantly, it motivates the inclusion of neoadjuvant chemoradiotherapy for select patients with stage 1 disease whose tumors display the potential for upstaging.

CONCLUSIONS

Upstaging is frequently seen in early esophageal cancers and is substantially more common among patients with angiolymphatic invasion or signet ring features at pathology. These tumor characteristics should raise a high index of suspicion for more aggressive disease. Although further investigation is necessary, these findings highlight the need for the development of better predictive models to identify patients likely to be upstaged. This could help guide the creation of more individualized treatment algorithms for esophageal cancer patients that are based on disease biology rather than simplified clinical staging.

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