Signet Ring Cell Histology Confers Worse Overall Survival in Treated Esophageal Adenocarcinoma

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Background. **Signet ring cell (SRC) histology is regarded as a poor prognostic indicator for esophageal cancer. The objectives of this study were to understand the clinical presentation and stage-specific survival outcomes of patients with SRC and nonsignet adenocarcinoma (AC).**

Methods. **From 2004 to 2016, 140,324 patients were diagnosed with esophageal and gastroesophageal junction cancers in the National Cancer Database. Demographics, tumor variables, and treatment were studied. Overall survival was shown by the Kaplan-Meier method, and random survival forest identified important predictors.**

Results. **SRC patients (N = 3825) comprised roughly 3% of esophageal cancers per year. SRC patients were less likely to present at early stage disease (cStage I: 10.2% vs 17.8% for AC; $P < .001$) and more likely to have pathologic upstaging (28% vs 16%, $P < .001$) and less pathologic downstaging after neoadjuvant therapy (36% vs 48%, $P < .001$). More SRC patients had positive margins after resection (15% vs 6.0%, $P < .001$). In a stage-matched comparison median survival for SRC patients was worse than for AC patients (cStage I: 60 vs 113 months; cStage II: 31 vs 40 months; cStage III: 22 vs 30 months). Clinical tumor and nodal stage, chemotherapy sequence, and age were important predictors of survival.**

Conclusions. **SRC patients had worse survival than their AC counterparts. Worse biology and higher rates of incomplete resection in SRC should steer patients away from undergoing limited resection, such as endoscopic submucosal dissection, even when identified at very early stages. In future esophageal cancer staging iterations, separating SRC from AC appears to be indicated because of their different clinical behavior and response to therapy.**

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Esophageal adenocarcinoma is the most common form of esophageal cancer in the Western world.[1] In an effort to provide patient-specific prognoses, the American Joint Committee on Cancer identified cancer-specific variables that identify higher risk tumors.[1,2] Tumor histology and tumor grade are used to stratify prognosis. However our understanding of esophageal adenocarcinoma subtypes is quite limited in comparison with adenocarcinoma of pulmonary origin where subtype-specific outcomes are better understood and can determine course of therapy.[3]

Signet ring cell (SRC) is a rare mucin-producing subtype of adenocarcinoma that has been demonstrated to have poor prognosis in other gastrointestinal cancers.[4-7] Small single-institutional series comparing esophageal SRC to adenocarcinoma have found varying results.[6,8-10] One study using the Surveillance, Epidemiology, and End Results identified poor prognostic factors for survival but only in esophageal SRC patients.[11]

It is difficult to adequately determine the pathologic and prognostic differences between esophageal SRC and nonsignet adenocarcinoma (AC), because of how rare esophageal SRC is.[12] The objective of this study was to understand the difference in clinical presentation and stage-specific treatment and survival outcomes of patients with esophageal SRC versus those with esophageal AC.

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The Appendix can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2020.04.134] on http://www.annalsthoracicsurgery.org.

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Patients and Methods

Data Source

The National Cancer Database captures about 70% of all new cancers occurring in the United States. This is a joint effort of the American College of Surgeons and the Commission on Cancer to capture and maintain demographic, facility, survival, and cancer-related variables. Only deidentified data from accredited hospitals are collected.[13] The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

Patient Selection

The NCDB was queried for patients diagnosed with esophageal adenocarcinoma from 2004 through 2014. All patients were older than 18 years of age, treated in the United States, and had known survival and treatment information. Patients with SRC adenocarcinoma were identified using the histology code 8490 according to international classification of diseases for oncology. This project was approved by the Institutional Review Board, with patient consent waived.

Variables Collected

Clinical and pathologic data obtained from the NCDB included age, sex, race, modified Charlson-Deyo score, insurance status, education level, income, facility type, facility location, histology, lymphovascular invasion, tumor location, and clinical and pathologic stage. These variables are further described in the NCDB Participant User File data dictionary (for details, see http://ncdbpufbeta.facs.org/?q=node/259).

Data Analysis

Analyses were performed using R Foundation for Statistical Computing (version 3.5.3; Vienna, Austria). Continuous variables are summarized as mean ± SD or equivalent 25th, 50th (median), and 75th percentiles if the distribution was skewed; comparisons were made using the Wilcoxon rank-sum (nonparametric) test. Categorical data are summarized as frequencies and percentages; comparisons were made using the χ^2 test or Fisher's exact test when frequencies were <5.

Survival Analysis

Overall survival was assessed nonparametrically by the Kaplan-Meier method and stratified by SRC and AC. Survival data were unavailable for patients who underwent treatment in 2015 and therefore were not included in survival analysis. Differences in survival were tested between groups using the log-rank test. Random survival forest methodology was used to identify predictors of patient-specific risk-adjusted and cross-validated overall survival for clinical stage I to III SRC patients who underwent standard treatment.[14] Predictors for survival are shown in the Appendix.

All computations used open-source random forest SRC R-software under default settings. Missing data were preimputed without using outcome information by random forest imputation methodology, missForest.[15] Thereafter 1000 classification and survival trees were grown using log-rank splitting. Each tree was constructed using an independent bootstrap sample containing on average 63% of patients (in-sample bootstrapped data) and the rest duplicates. The remaining unused patients (37%), referred to as out-of-bag observations, were used to calculate out-of-bag cross-validated survival for each patient and variable importance measures for each of the independent variables. Positive values indicate variables that are predictive, adjusting for all other variables.

Results

Baseline Characteristics

From 2004 to 2016, 3825 patients were diagnosed with SRC and 87,326 patients with AC. SRC patients comprised between 2.4% and 3% of esophageal cancers per year across the study period (Figure 1). SRC and AC patients were similar in age, gender, race, year of diagnosis, comorbidities, and number of lifetime cancers (Table 1).

Cancer and Treatment Characteristics

SRC patients had more tumors in the lower third of the esophagus, poor differentiation, more locally advanced tumors, but less distant metastases on clinical staging (Table 2). Tumor length was also longer in the SRC group (45 vs 38 mm, $P < .001$). SRC tumors had more lymphovascular invasion as well (10.6% vs 7.6%, $P < .001$).

Pathologic Outcomes

More clinical stage I (27% vs 13%, $P = .003$) and II (28% vs 21%, $P = .049$) SRC patients were pathologically upstaged after resection (Table 3). Among clinical stage II (21% vs 32%, $P = .007$) and III (49% vs 61%, $P = .006$) patients who underwent neoadjuvant chemoradiation and resection, fewer SRC patients had pathologic downstaging and higher rates of positive margins (Table 3). There were no

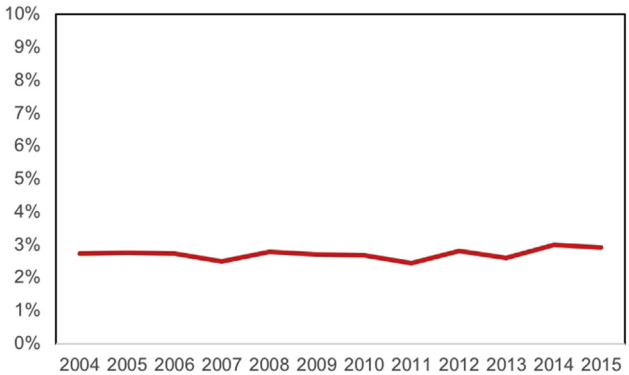

Figure 1. Percentage of signet ring cell cases per year.

Table 1. Baseline Characteristics

Characteristic	Total N	Signet Ring Cell (n = 3825)	Total N	Adenocarcinoma (n = 87,326)	*P*
Age, y	3825	66.1 ± 11.9	87,326	66.4 ± 11.7	.14
Female	3825	549 (14.4)	87,326	12,995 (14.9)	.38
Race	3825		87,326		.048
White		3662 (96)		83,171 (95)	
Asian		44 (1.2)		768 (0.9)	
Black		75 (2.0)		2061 (2.4)	
Other		15 (0.4)		366 (0.4)	
Unknown		29 (0.8)		960 (1.1)	
Year of diagnosis	3825		87,326		.35
2004		288 (7.5)		6088 (7.0)	
2005		292 (7.6)		6259 (7.2)	
2006		301 (7.9)		6746 (7.7)	
2007		280 (7.3)		6962 (8.0)	
2008		323 (8.4)		7225 (8.3)	
2009		325 (8.5)		7439 (8.5)	
2010		310 (8.1)		7102 (8.1)	
2011		287 (7.5)		7320 (8.4)	
2012		339 (8.9)		7644 (8.8)	
2013		324 (8.5)		8035 (9.2)	
2014		379 (9.9)		8151 (9.3)	
2015		377 (9.9)		8355 (9.6)	
Facility type	3774		86,281		<.001
Community program		280 (7.4)		8492 (9.8)	
Commission on Cancer accredited community program		1414 (38)		34,426 (40)	
Academic/research program		1727 (46)		35,075 (41)	
Integrated network program		353 (9.4)		8288 (9.6)	
Geographic location	3774		86,281		<.001
New England		276 (7.3)		6397 (7.4)	
Mid-Atlantic		649 (17)		13,827 (16)	
South Atlantic		614 (16)		16,781 (19)	
East-North Central		721 (19)		17,140 (20)	
East-South Central		183 (4.8)		5200 (6.0)	
West-North Central		388 (10)		7877 (9.1)	
West-South Central		336 (8.9)		6068 (7.0)	
Pacific		196 (5.2)		4110 (4.8)	
Outside the United States		411 (11)		8881 (10)	
Charlson-Deyo score	3825		87,326		.34
0		2773 (73)		63,307 (73)	
1		756 (20)		17,696 (20)	
2		224 (5.9)		4575 (5.2)	
>2		72 (1.9)		1748 (2.0)	
No. of cancers in lifetime	3825		87,326		>0.99
0		3073 (80)		70,672 (81)	
1		144 (3.8)		3345 (3.8)	
2		515 (14)		11,313 (13)	
3		79 (2.1)		1686 (1.9)	
4		12 (0.3)		251 (0.3)	
≥5		1 (0.0)		52 (0.1)	
Unknown		1 (0.0)		7 (0.0)	

Values are mean ± SD or n (%).

Table 2. Cancer and Treatment Characteristics

Characteristic	Total N	Signet Ring Cell (n = 3825)	Total N	Adenocarcinoma (n = 87,326)	*P*
Interval time to first treatment, days	3122	33 [21-47]	69,905	31 [19-47]	.01
Surgery chemo sequence	3245		75,974		<.001
No chemotherapy		2299 (71)		56,505 (75)	
Neoadjuvant chemotherapy		695 (21)		13,357 (18)	
Adjuvant chemotherapy		134 (4.1)		2867 (3.8)	
≥2 before and ≥2 after surgery		77 (2.4)		1216 (1.6)	
Sequence unknown		40 (1.2)		1029 (1.4)	
Surgery radiation sequence	3825		87,316		<.001
No radiation		2811 (74)		67,531 (77)	
Neoadjuvant radiation		803 (21)		15,052 (17)	
Adjuvant radiation		140 (3.7)		3152 (3.6)	
Radiation before and after surgery		6 (0.2)		139 (0.2)	
Sequence unknown		65 (1.7)		1442 (1.7)	
Anatomic location	3825		87,326		<.001
Cervical		6 (0.2)		213 (0.2)	
Thoracic		40 (1.0)		1410 (1.6)	
Abdominal		18 (0.5)		550 (0.6)	
Upper third		34 (0.9)		866 (1.0)	
Middle third		163 (4.3)		4436 (5.1)	
Lower third		3130 (82)		67,000 (77)	
Overlapping lesions		195 (5.1)		3726 (4.3)	
Not otherwise specified		239 (6.2)		9125 (10)	
Grade	3825		87,326		<.001
Well differentiated		15 (0.4)		4397 (5.0)	
Moderately		147 (3.8)		28,238 (32)	
Poorly		2945 (77)		35,715 (41)	
Undifferentiated		115 (3.0)		824 (0.9)	
Unknown		603 (16)		18,152 (21)	
Clinical stage	2764		62,038		<.001
I		283 (10)		11,050 (18)	
II		747 (27)		14,719 (24)	
III		939 (34)		15,967 (26)	
IV		795 (29)		20,302 (33)	
Clinical T	3756		85,902		<.001
c0		3 (0.1)		151 (0.2)	
c1		301 (8.0)		9655 (11)	
c1A		40 (1.1)		2365 (2.8)	
c1B		51 (1.4)		1420 (1.7)	
c2		381 (10)		9776 (11)	
c3		1555 (41)		27,963 (34)	
c4		212 (5.6)		4053 (4.7)	
c4A		57 (1.5)		806 (0.9)	
c4B		37 (1.0)		856 (1.0)	
cX		1111 (30)		27,579 (32)	
pIS		8 (0.2)		1275 (1.5)	
Clinical N	3757		86,032		<.001
c0		1242 (33)		30,720 (36)	
c1		1469 (39)		30,354 (35)	
c2		221 (5.9)		4679 (5.4)	
c3		112 (3.0)		2018 (2.3)	
cX		713 (19)		18,258 (21)	

(*Continued*)

Table 2. Continued

Characteristic	Total N	Signet Ring Cell (n = 3825)	Total N	Adenocarcinoma (n = 87,326)	*P*
Clinical M	3676		83,922		.002
c0		2701 (74)		59,108 (70)	
c1		768 (21)		19,916 (24)	
c1A		62 (1.7)		1354 (1.6)	
c1B		145 (3.9)		3542 (4.2)	
Clinical stage I-III		(n = 1969)		(n = 41,736)	
Interval time to definitive surgery, days	955	120 [90-145]	21,612	113 [56-141]	<.001
Surgery	1929		40,959		<.001
None/no surgery/autopsy		1185 (62)		23,603 (58)	
Esophagectomy with gastrectomy not otherwise specified		124 (6.4)		2671 (6.5)	
Esophagectomy		169 (8.8)		3745 (9.1)	
Esophagectomy with partial gastrectomy		336 (17)		6740 (16)	
Esophagectomy with total gastrectomy		16 (0.8)		369 (0.9)	
Surgery not otherwise specified		94 (4.9)		3761 (9.2)	
Unknown		5 (0.3)		70 (0.2)	
Tumor length, mm	1190	45 [30-67]	25,007	38 [20-53]	<.001
Lymphovascular invasion	1119				<.001
No		302 (27)		8845 (36)	
Yes		119 (11)		1870 (7.6)	
Not available		16 (1.4)		248 (1.0)	
Unknown		682 (61)		13,671 (56)	
Pathologic stage	777		15,707		<.001
I		130 (17)		5728 (38)	
II		275 (37)		5168 (34)	
III		320 (43)		3876 (26)	
IV		23 (3.1)		283 (1.9)	
Pathologic T	1621		34,568		<.001
p0		112 (6.9)		2228 (6.4)	
p1		63 (3.9)		2614 (7.6)	
p1A		41 (2.5)		1899 (5.5)	
p1B		52 (3.2)		1944 (5.6)	
p2		112 (6.9)		2879 (8.3)	
p3		388 (24)		5606 (16)	
p4		15 (0.9)		211 (0.6)	
p4A		8 (0.5)		36 (0.1)	
p4B		3 (0.2)		14 (0.0)	
pIS		6 (0.4)		204 (0.6)	
pX		821 (51)		16,933 (49)	
Pathologic N	1615		34,378		<.001
p0		400 (25)		10,794 (31)	
p1		283 (18)		4681 (14)	
p2		79 (4.9)		1050 (3.1)	
p3		32 (2.0)		380 (1.1)	
pX		821 (51)		17,473 (51)	
Nodes examined	1969		41,736		<.001
0		993 (47)		21,670 (52)	
1-5		134 (6.8)		3088 (7.4)	
6-10		187 (9.5)		3622 (8.7)	
11-15		163 (8.3)		3872 (9.3)	
16+		343 (17)		6736 (16.1)	
Aspiration		53 (2.7)		1112 (2.7)	

(*Continued*)

Table 2. Continued

Characteristic	Total N	Signet Ring Cell (n = 3825)	Total N	Adenocarcinoma (n = 87,326)	*P*
Dissection		14 (0.7)		156 (0.4)	
Sampling		2 (0.1)		48 (0.1)	
Surgical		23 (1.2)		553 (1.3)	
Unknown		117 (5.9)		879 (2.1)	

Values are median [25th-75th percentile] or n (%).

differences in complete response rates between SRC and AC patients (Table 3). Clinical stage II and III SRC patients were more likely to have positive margins after resection (Table 3).

Overall Survival by Stage

In a stage-matched comparison median survival for SRC patients was worse than for AC patients (cStage I, 60 vs 113 months; cStage II, 31 vs 40 months; cStage III, 22 vs 30 months) as shown in Figure 2A. It appears that survival for SRC patients at any given clinical stage is nearly equivalent to 1 stage higher for AC patients (Figure 2A). However these survival differences disappear when only examining patients who underwent R0 resection with at least 15 lymph nodes retrieved (Figure 2B).

Predictors of Overall Survival in SRC

For clinical stage I to III SRC patients who underwent standard treatment, clinical tumor stage, clinical nodal status, surgery, chemotherapy sequence, and age were among the most important predictors (Figure 3, left). Radiation dose was not an important risk-adjusted predictor of overall survival (Figure 3, left). Patients who underwent neoadjuvant and adjuvant chemotherapy had the best risk-adjusted survival (Figure 3, right). Although surgery was an important predictor, the risk-adjusted effect on survival was minimal between the various extents of resection performed (Figure 3, right).

Comment

Principal Findings

SRC esophageal carcinoma is a rare subtype of esophageal adenocarcinoma that has more aggressive tumor characteristics and worse pathologic response to neoadjuvant chemoradiation. It is associated with more positive margins after surgical resection and more pathologic upstaging. These findings, compounded with worse overall survival, suggest a more aggressive tumor biology as compared with AC. However SRC patients may benefit from neoadjuvant and adjuvant chemotherapy versus neoadjuvant alone because these patients had the best risk-adjusted chance of survival.

Clinical Implications

Prior single-institutional studies have attempted to determine the prognosis of SRC histology. Chirieac and coworkers[9] identified 73 patients with SRC of 412 esophageal adenocarcinoma patients. This study found that SRC patients had significantly worse survival when they underwent esophagectomy alone and superior survival after neoadjuvant chemoradiation compared with AC patients. The authors concluded that patients with esophageal SRC or mucinous histology benefited substantially from preoperative chemoradiation and esophagectomy. However these patients were not matched for stage, making it difficult to adequately compare prognoses or recommend optimal treatment. Interestingly the authors found that SRC was associated with more radial margin positivity in both the esophagectomy and neoadjuvant groups, indicating that perhaps SRC does not respond well to chemoradiation. Another single-institutional study found that SRC patients had less pathologic downstaging compared with AC patients after neoadjuvant chemoradiation.[8] Patel and associates[10] furthermore found that tumors with even small components of SRC histology had worse disease-free survival compared with their adenocarcinoma counterparts. Our

Table 3. Pathologic Outcomes After Standard of Care

	Clinical Stage I (Resection Only)			Clinical Stage II (Neoadjuvant Chemoradiation + Resection)			Clinical Stage III (Neoadjuvant Chemoradiation + Resection)		
Outcomes	SRC (n = 59)	AC (n = 3075)	*P*	SRC (n = 127)	AC (n = 2266)	*P*	SRC (n = 157)	AC (n = 2735)	*P*
Upstaged	16 (27)	400 (13)	.003	36 (28)	467 (21)	.049	4 (2.5)	40 (1.5)	.298[a]
Downstage	NA	NA	NA	26 (21)	731 (32)	.007	78 (49)	1671 (61)	.006
Complete response	NA	NA	NA	10(7.9)	164 (7.2)	.926	12 (7.6)	163 (6.0)	.491
Positive margins	7 (13)	184 (6.5)	.126	16 (13)	134 (6.0)	.002	25 (17)	150 (5.6)	<.001

[a]Fisher's exact test.

Values are n (%).

AC, nonsignet adenocarcinoma; NA, not applicable; SRC, signet ring cell.

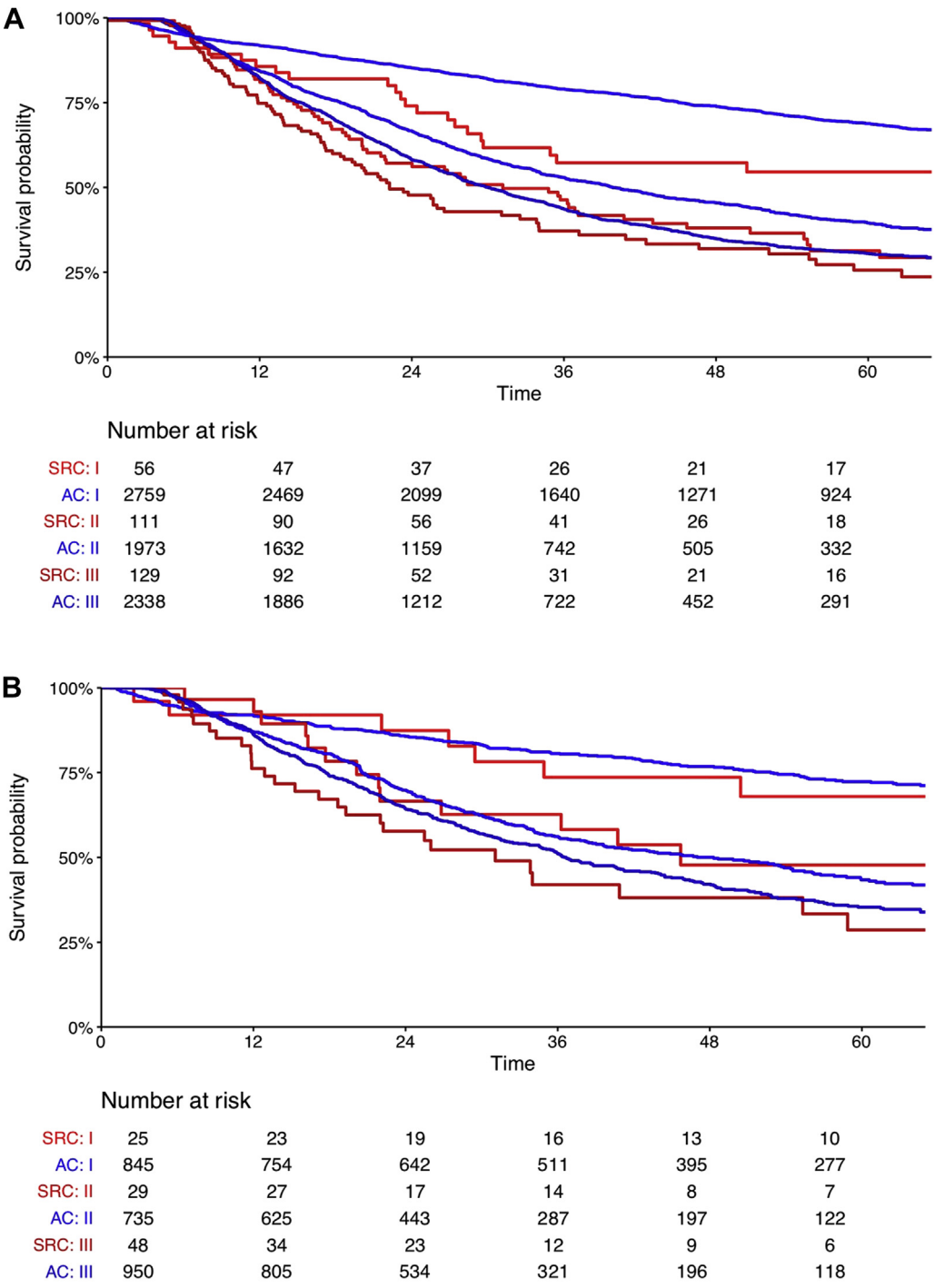

Figure 2. (A) Clinical stage I to III signet ring cell (SRC) versus adenocarcinoma (AC) overall survival after undergoing standard treatment. (B) Clinical stage I to III SRC versus AC overall survival after undergoing standard treatment with R0 resection and ≥15 lymph nodes retrieved.

study corroborates these findings that SRC histology is associated with resistance to chemoradiation.

For patients who were diagnosed at an early stage and required resection only, these data show that more SRC patients were pathologically upstaged after resection, indicating likely occult disease that would not be found after limited resection. Endoscopic submucosal dissection has emerged as a feasible treatment option for superficial esophageal cancers.[16] However endoscopic submucosal dissection is limited by its inability to address regional lymph nodes and adequately treat tumors that end up invading through deeper wall layers than what was believed preoperatively.[16] Given the higher rates of pathologic upstaging after esophagectomy for SRC, limited

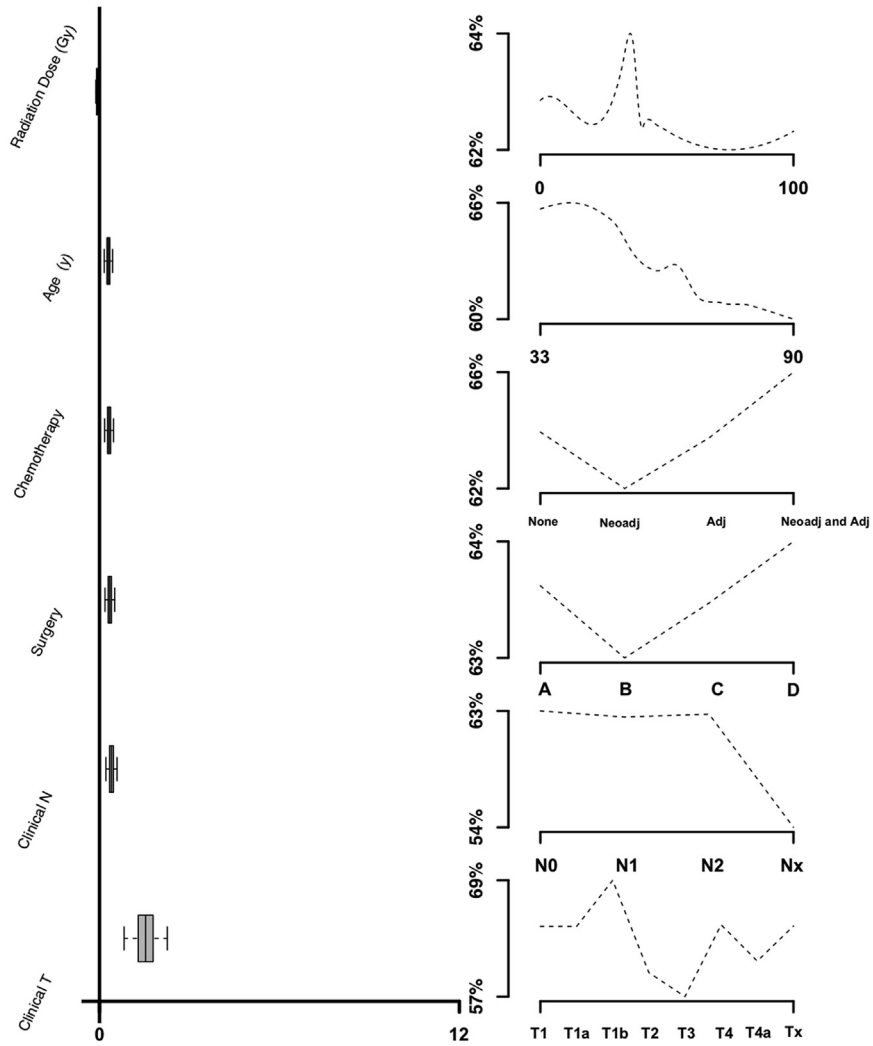

Figure 3. Random survival forest standardized variable importance plot (left panel) with risk-adjusted variable effects (right panel) predicting chances of survival. (A) Esophagectomy with partial gastrectomy. (B) Esophagectomy with total gastrectomy. (C) Esophagectomy. (D) Esophagectomy with gastrectomy (not otherwise specified).

resections such as endoscopic submucosal dissection should not be a treatment option for patients with SRC on preoperative diagnosis. Given the imperfect reliability of endoscopic ultrasound for local staging, perhaps patients with early-stage SRC should be considered for overtreatment.

Interestingly when we examine patients who had an R0 resection with at least 15 lymph nodes retrieved the survival differences between the SRC and AC groups disappears even when matched for stage. This highlights the importance of complete resection and appropriate nodal dissection to improve accuracy of pathologic staging. This also raises the point that to achieve an R0 resection, attention should be paid to intraoperative frozen section. More importantly the surgeon and patient should be prepared for a more extensive resection based on intraoperative findings. A positive gastric margin for a gastroesophageal junction tumor may require a total gastrectomy with either real-time or staged colonic interposition. Such aggressive surgical resections can lead to significant morbidity and changes in quality of life.

The next logical question would be how to improve systemic control for a tumor that does not respond well to neoadjuvant chemoradiation and is hence more likely to recur. These data show that patients who received systemic therapy in the neoadjuvant and adjuvant settings had better overall survival. This could just be a function of selection bias because this is likely a healthier cohort. However one cannot rule out the possibility of a true benefit of systemic therapy for SRC patients. Unfortunately this is a question that can only be answered with prospective trials.

Limitations and Strengths

Our data highlight the differences in natural history of signet and nonsignet histologic subtypes. The NCDB does not capture data on recurrence, which is key in determining the effect of local therapy for SRC. Although it would be ideal to focus only on patients who received all care at 1 reporting institution to ensure the accuracy of treatment data, the rarity of SRC histology prevented us from only focusing on those patients. Exact tumor

location, surgical extent, and chemotherapy and radiation regimens were not well captured, which would have identified the most optimal regimens for what seems to be a radiation-resistant subtype of cancer. However the NCDB still has strength in numbers, which is especially important when studying rare tumors such as SRC esophageal tumors.

Conclusions

Patients with SRC histology have worse survival than patients with AC. Worse biology and higher rates of incomplete resection in SRC should steer patients away from undergoing limited resection, such as endoscopic submucosal dissection, even when identified at very early stages. Neoadjuvant and adjuvant chemotherapy appear to provide survival benefit, whereas radiation dose is not an important predictor of survival in SRC patients. In future esophageal cancer staging iterations, consideration for separating SRC from AC appears to be indicated because of their different clinical behavior and response to therapy.

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