ORIGINAL ARTICLE

Nonregional Lymph Nodes as the Only Metastatic Site in Stage IV Esophageal Cancer

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Received 22 August 2022; revised 29 September 2022; accepted 15 October 2022
Available online - 20 October 2022

ABSTRACT

Introduction: Metastatic involvement of at least one nonregional lymph node currently renders patients with esophageal cancer as having stage IV disease. However, the management and outcomes of patients whose sole determinant of stage IV status is nonregional lymph nodes (abbreviated as "stage IV-nodal" disease) have not been fully characterized.

Methods: In this retrospective cohort study, the National Cancer Database was queried to identify patients 18 years of age or older who were diagnosed with stage IV esophageal cancer between 2016 and 2019. Survival was assessed by Kaplan-Meier analysis and Cox models in the overall sample and a propensity-matched sample. Patients with "stage IV-nodal" disease were compared with patients with systemic metastases involving a single organ or multiple organs.

Results: Overall, 11,589 patients with clinical stage IV esophageal cancer were identified, including 1331 (11.5%) patients with stage IV-nodal disease. Patients with stage IV-nodal disease were more likely to receive chemotherapy (77%) than those with single systemic organ metastases (64%) and multiorgan metastases (63%) ($p < 0.0001$); patients with stage IV-nodal disease were also more likely to receive radiation (49%) than those with single systemic organ metastases (40%) and multiorgan metastases (39%) ($p < 0.0001$). Squamous cell carcinoma (OR = 1.58, 95% confidence interval [CI]: 1.34–1.86, $p < 0.0001$) and academic facility type (OR = 1.24, 95% CI: 1.09–1.4, $p = 0.0009$) were associated with higher likelihood of the stage IV-nodal presentation. Patients with stage IV-nodal disease experienced superior survival (hazard ratio = 0.72, 95% CI: 0.66–0.78, $p < 0.0001$) than those with stage IV-single systemic metastases (reference group) and stage IV-multiorgan disease (hazard ratio = 1.30, 95% CI: 1.24–1.37).

Conclusions: Approximately 12% of patients with stage IV esophageal cancer lack systemic metastases at presentation. These patients with stage IV-nodal disease are more likely to receive treatment and experience superior survival. Further study of the stage IV-nodal population and consideration of a potential stage IV subclassification system is justified.

Keywords: Esophageal cancer; Stage IV; Survival; Distant lymph node metastases; Single-organ metastases

Introduction

Stage IV esophageal cancer is particularly challenging to manage, as evidenced by its 5-year survival hovering

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Disclosure: Dr. Boffa reports receiving financial support from Epic Sciences and being on an advisory panel for Iovance, outside the submitted work. The remaining authors declare no conflict of interest.

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Cite this article as: Zhan PL, Canavan ME, Ermer T, et al. Nonregional lymph nodes as the only metastatic site in stage IV esophageal cancer. *JTO Clin Res Rep*. 2022;3:100426.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100426

at approximately 5%.[1,2] The disease burden at presentation frequently serves as a predictor of what is to come, with patients having oligometastatic cancer (i.e., limited to a few systemic metastases) tending to have a considerably better prognosis than those with more widespread disease (i.e., many lesions throughout the body).[3–5] The relationship between disease burden and prognosis can be incredibly helpful in shared decision-making for patients with advanced esophageal cancer.

A third pattern of stage IV involvement does not involve systemic spread but is instead limited to patients whose cancer involves only nonregional lymph nodes. Thus, the sole determinant of stage IV cancer status of these patients is nonregional lymph node metastasis ("stage IV-nodal"). In other types of cancer, the prognosis and treatment strategies for patients with stage IV-nodal disease have differed from patients with other systemic spread.[6,7] For example, it has recently been suggested that distant lymph node metastases in breast cancer might represent a form of regional disease that benefits from a similar prognosis as nonmetastatic (N3c) disease.[7] Nevertheless, for esophageal cancer, the management and prognostic implications of the stage IV-nodal subset of patients have yet to be fully elucidated.

The National Cancer Database (NCDB), a nationwide clinical data set that captures 72% of all newly diagnosed malignancies in the United States, records the extent and location of metastatic organ involvement at diagnosis, including nonregional lymph nodes.[8,9] Leveraging the breadth of the NCDB, we aimed to better understand the management and outcomes of the stage IV-nodal subset of patients.

Materials and Methods

Data Source

The NCDB is jointly managed by the American College of Surgeons and American Cancer Society. The NCDB 2019 Participant User File,[10] which contains deidentified patient information, was used for this retrospective cohort study, which was performed in accordance with our institutional review board-approved protocol, with consent waived. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology were followed.

Study Population

Patients 18 years of age or older without a previous cancer diagnosis who were diagnosed with having clinical stage IV, histologically confirmed esophageal adenocarcinoma and squamous cell carcinoma (SCC) between 2016 and 2019 were included. Patients were excluded if they had missing information on sites of metastasis at diagnosis (n = 570, 4.9%). A sensitivity analysis comparing the attributes of included and excluded patients did not identify any obvious clinically meaningful differences (data available on request).

Patients were assigned to three comparison groups, with distant disease at presentation (i.e., de novo metastases) limited to the following: nonregional lymph node ("stage IV-nodal"), a single visceral organ ("stage IV-single organ"), or multiorgan ("stage IV-multiorgan") metastases.

Independent Variables

In a manner consistent with previous studies,[11,12] age was included as a categorical variable (18–34, 35–49, 50–64, 65–79, ≥80 y). Other independent variables included sex (female, male), race (white, black, other), ethnicity (Hispanic, non-Hispanic), median household income of the patient's ZIP code of residence (categorized as quartiles: <$40,227, $40,227–$50,353, $50,354–$63,332, ≥$63,333), insurance status (private, uninsured, Medicaid, Medicare, other government), modified Charlson-Deyo Comorbidity Index (CCI) (0, 1, 2, 3+), U.S. Census Division (New England, Middle Atlantic, South Atlantic, East North Central, East South Central, West North Central, West South Central, Mountain, Pacific), facility type (nonacademic, academic), area of residence (metropolitan, urban, rural), year of diagnosis, histology (adenocarcinoma, SCC), and tumor location (cervical esophagus, upper esophagus, midesophagus, lower esophagus, overlapping lesion, unspecified). These variables were selected because they have been associated with prognosis in the literature and are most often included in NCDB analysis.[11,13,14] A comprehensive definition of NCDB variables is available online.[15]

Statistical Analysis

Patient characteristics and differences in treatment for the stage IV-nodal, stage IV-single organ, and stage IV-multiorgan groups were evaluated using the chi-square test. A multivariable logistic regression model incorporating age, sex, race, ethnicity, median income, insurance status, modified CCI, U.S. Census Division, facility type, area of residence, year of diagnosis, histology, and tumor location was used to determine the sociodemographic and tumor attributes associated with the stage IV-nodal presentation.

Unadjusted survival analysis was performed using a Kaplan-Meier curve and the log-rank test to compare the survival of the stage IV-nodal, -single organ, and -multiorgan groups. Adjusted survival was evaluated using two methods. A multivariable Cox proportional hazards regression model was created with the same covariates as the aforementioned logistic regression model, with the exception of tumor location, which was not included

in the survival analysis owing to possible interactions between tumor location and histology with respect to prognosis. The proportional hazards assumption was graphically assessed using a log-log plot, and no violations were evident. To assess adjusted survival in another way, a Kaplan-Meier curve and the log-rank test were used to compare the survival of the stage IV-nodal and stage IV-single organ groups among patients who were propensity score matched with the same covariates as those used for the Cox proportional hazards survival model. Patients were 2:1 matched using a greedy (nearest-neighbor) approach with a caliper of 0.25, and all variables had a standard mean difference of less than 10%. A clustering term for hospitals was added to all adjusted models.

Missing Data Strategy

The median percentage of missing data across all variables was 0.8%, and 22% of patients had at least one piece of missing sociodemographic or socioeconomic covariate data. We did not observe any patterns to the missingness of data and assumed the data to be missing at random. A multiple imputation strategy incorporating age, sex, race, ethnicity, median income, insurance status, modified CCI, area of residence, and year of diagnosis was used to account for missing sociodemographic and socioeconomic data. In the NCDB, facility type and U.S. Census Region are suppressed for patients younger than 40 years of age to protect patient privacy. No patients aged 40 years or older had missing values for facility type or U.S. Census Region; thus, these two variables were not included in the multiple imputation model.

Results

Patients

In total, 11,589 patients with stage IV esophageal cancer were included, including 1331 (12%) with stage IV-nodal disease, 4883 (42%) with stage IV-single organ disease, and 5375 (46%) with stage IV-multiorgan disease (Table 1 and Fig. 1). The median age was 65 (interquartile range: 58–72) years, and 83% were men (n = 9634). Patients with adenocarcinoma represented 79% of the total (n = 9172).

Management

Cancer treatment was evaluated across patterns of organ involvement at presentation (Table 1). In general, patients with stage IV-nodal disease were less likely to go untreated (14%) than those with stage IV disease with single organ (23%) and multiorgan (23%) involvement ($p < 0.0001$). The patients with stage IV-nodal disease were more likely to receive chemotherapy (77%) than those with stage IV-single organ (64%) and stage IV-multiorgan (63%) disease ($p < 0.0001$). Furthermore, patients with stage IV-nodal disease were more likely to receive radiation (49%) than those with stage IV-single organ (40%) and stage IV-multiorgan (39%) disease ($p < 0.0001$). Rates of immunotherapy treatment were similar among the three groups. Across all groups, surgical treatment was rare.

Predictors of the Stage IV-Nodal Presentation

A multivariable logistic regression model was used to identify factors associated with the stage IV-nodal presentation (Table 2). SCC (OR = 1.58, 95% confidence interval [CI]: 1.34–1.86, $p < 0.0001$) and academic facility type (OR = 1.24, 95% CI: 1.09–1.4, $p = 0.0009$) were associated with an increased likelihood of the stage IV-nodal presentation, whereas upper esophageal location (OR = 0.64, 95% CI: 0.45–0.91, $p = 0.01$) and male sex (OR = 0.83, 95% CI: 0.72–0.97, $p = 0.02$) were associated with a decreased likelihood of the stage IV-nodal presentation.

Unadjusted Survival Analysis

Overall, with a median follow-up time of 18.6 months (interquartile range: 6.0–34.6) among surviving patients, patients with stage IV-nodal disease experienced significantly better survival than the other two groups. For the stage IV-nodal group, the median survival (95% CI) was 12.1 (11.0–13.0) months, compared with 7.6 (7.2–7.9) months for the stage IV-single organ group and 5.2 (4.8–5.5) months for the stage IV-multiorgan group (log-rank $p < 0.0001$) (Fig. 2).

Cox Proportional Hazards Model

A multivariable Cox proportional hazards model was performed. The patients with stage IV-nodal disease exhibited the best prognosis (hazard ratio [HR] = 0.72, 95% CI: 0.66–0.78, $p < 0.0001$), followed by those with stage IV-single organ disease (reference group) and those with stage IV-multiorgan disease (HR = 1.30, 95% CI: 1.24–1.37, $p < 0.0001$).

Survival of Propensity-Matched Patients

Adjusted survival was further evaluated by propensity matching patients with stage IV-nodal disease with those with stage IV-single organ disease. The patients with stage IV-nodal disease displayed a better survival (median survival = 12.1 mo, 95% CI: 11.0–13.0) than those with stage IV-single organ disease (median survival = 7.5 mo, 95% CI: 6.9–7.9), with log-rank p less than 0.0001 (Fig. 3).

Sensitivity Analyses

A few sensitivity analyses were performed. In all models, there were no changes in the directionality,

Table 1. Stage IV Esophageal Cancer Baseline Patient Characteristics

Patient, Facility, Tumor, and Treatment Characteristics		Metastatic Involvement[a] Lymph Nodes Only, n (col %) n = 1331	Single Organ,[b] n (col %) n = 4883	Multiorgan,[c] n (col %) n = 5375	Chi-Square *p* Value
Age (y)	18-34	11 (0.8)	30 (0.6)	34 (0.6)	<0.0001
	35-49	90 (6.8)	306 (6.3)	433 (8.1)	
	50-64	571 (42.9)	1949 (39.9)	2340 (43.5)	
	65-79	543 (40.8)	2072 (42.4)	2157 (40.1)	
	≥80	116 (8.7)	526 (10.8)	411 (7.7)	
Sex	Female	271 (20.4)	850 (17.4)	834 (15.5)	<0.0001
	Male	1060 (79.6)	4033 (82.6)	4541 (84.5)	
Race	White	1141 (85.7)	4261 (87.3)	4761 (88.6)	0.01
	Black	119 (8.9)	435 (8.9)	418 (7.8)	
	Other	61 (4.6)	147 (3)	157 (2.9)	
	Missing	10 (0.8)	40 (0.8)	39 (0.7)	
Ethnicity	Non-Hispanic	1259 (94.6)	4577 (93.7)	5036 (93.7)	0.63
	Hispanic	55 (4.1)	217 (4.4)	238 (4.4)	
	Missing	17 (1.3)	89 (1.8)	101 (1.9)	
Median income	<$40,227	211 (15.9)	798 (16.3)	887 (16.5)	0.91
	$40,227-$50,353	274 (20.6)	956 (19.6)	1068 (19.9)	
	$50,354-$63,332	268 (20.1)	972 (19.9)	1103 (20.5)	
	≥$63,333	366 (27.5)	1346 (27.6)	1485 (27.6)	
	Missing	212 (15.9)	811 (16.6)	832 (15.5)	
Insurance status	Private	459 (34.5)	1572 (32.2)	1859 (34.6)	0.0006
	Uninsured	49 (3.7)	196 (4)	255 (4.7)	
	Medicaid	136 (10.2)	478 (9.8)	586 (10.9)	
	Medicare	648 (48.7)	2465 (50.5)	2473 (46)	
	Other Government	23 (1.7)	115 (2.4)	111 (2.1)	
	Missing	16 (1.2)	57 (1.2)	91 (1.7)	
Charlson-Deyo score	0	943 (70.9)	3475 (71.2)	3804 (70.8)	0.27
	1	260 (19.5)	847 (17.4)	959 (17.8)	
	2	73 (5.5)	288 (5.9)	318 (5.9)	
	3+	55 (4.1)	273 (5.6)	294 (5.5)	
U.S. census division	New England	83 (6.2)	297 (6.1)	334 (6.2)	0.23
	Middle Atlantic	202 (15.2)	702 (14.4)	764 (14.2)	
	South Atlantic	280 (21)	1011 (20.7)	1040 (19.4)	
	East North Central	221 (16.6)	972 (19.9)	1044 (19.4)	
	East South Central	94 (7.1)	334 (6.8)	414 (7.7)	
	West North Central	124 (9.3)	393 (8.1)	468 (8.7)	
	West South Central	83 (6.2)	371 (7.6)	396 (7.4)	
	Mountain	59 (4.4)	228 (4.7)	247 (4.6)	
	Pacific	162 (12.2)	511 (10.5)	586 (10.9)	
	Missing	23 (1.7)	64 (1.3)	82 (1.5)	
Facility type	Nonacademic	839 (63)	3336 (68.3)	3622 (67.4)	0.008
	Academic	469 (35.2)	1483 (30.4)	1671 (31.1)	
	Unknown	23 (1.7)	64 (1.3)	82 (1.5)	
Area of residence	Metropolitan	1044 (78.4)	3803 (77.9)	4215 (78.4)	0.99
	Urban	224 (16.8)	861 (17.6)	922 (17.2)	
	Rural	27 (2)	96 (2)	103 (1.9)	
	Missing	36 (2.7)	123 (2.5)	135 (2.5)	
Year of diagnosis	2016	355 (26.7)	1202 (24.6)	1216 (22.6)	0.007
	2017	328 (24.6)	1174 (24)	1367 (25.4)	
	2018	311 (23.4)	1291 (26.4)	1365 (25.4)	
	2019	337 (25.3)	1216 (24.9)	1427 (26.6)	
Histology[d]	Adenocarcinoma	966 (10.5)	3862 (42.1)	4344 (47.4)	<0.0001
	Squamous cell carcinoma	365 (15.1)	1021 (42.2)	1031 (42.7)	

(continued)

Table 1. Continued

Patient, Facility, Tumor, and Treatment Characteristics		Metastatic Involvement[a] Lymph Nodes Only, n (col %) n = 1331	Single Organ,[b] n (col %) n = 4883	Multiorgan,[c] n (col %) n = 5375	Chi-Square *p* Value
Tumor location[d]	Cervical esophagus	13 (15.7)	42 (50.6)	28 (33.7)	<0.0001
	Upper esophagus	44 (11.5)	171 (44.7)	168 (43.9)	
	Midesophagus	185 (15.5)	489 (41.1)	517 (43.4)	
	Lower esophagus	896 (11.7)	3217 (42)	3545 (46.3)	
	Overlapping lesion	81 (10.8)	280 (37.5)	386 (51.7)	
	Unspecified	112 (7.3)	684 (44.8)	731 (47.9)	
Surgery	Local destruction[e]	3 (0.2)	18 (0.4)	13 (0.2)	<0.0001
	Local excision[f]	3 (0.2)	18 (0.4)	8 (0.2)	
	Esophagectomy[g]	47 (3.5)	87 (1.8)	16 (0.3)	
	No surgery	1275 (95.8)	4744 (97.2)	5323 (99)	
	Missing	3 (0.2)	16 (0.3)	15 (0.3)	
Chemotherapy	Any chemotherapy	1022 (76.8)	3138 (64.3)	3406 (63.4)	<0.0001
	No chemotherapy	293 (22)	1675 (34.3)	1908 (35.5)	
	Missing	16 (1.2)	70 (1.4)	61 (1.1)	
Radiation	Any radiation	646 (48.5)	1938 (39.7)	2076 (38.6)	<0.0001
	No radiation	654 (49.1)	2848 (58.3)	3197 (59.5)	
	Missing	31 (2.3)	97 (2)	102 (1.9)	
Immunotherapy	Any immunotherapy	177 (13.3)	686 (14.1)	856 (15.9)	0.005
	No immunotherapy	1148 (86.3)	4181 (85.6)	4511 (83.9)	
	Missing	6 (0.5)	16 (0.3)	8 (0.2)	
Any treatment[h]	Yes	1125 (84.5)	3665 (75.1)	4067 (75.7)	<0.0001
	No (untreated)	187 (14.1)	1137 (23.3)	1231 (22.9)	
	Missing	19 (1.4)	81 (1.7)	77 (1.4)	

[a]The three groups were chosen as a surrogate for oligometastatic versus multiorgan metastatic disease; the prognostic significance of single-organ and multiorgan metastases has been revealed previously.[11]
[b]Excluding distant lymph node metastases.
[c]Including patients with a single systemic organ metastasis and distant lymph node metastases.
[d]Row percentages are provided for these values instead of column percentages.
[e]Local destruction, as defined by the NCDB, included photodynamic therapy, electrocautery, fulguration, cryosurgery, and laser.
[f]Local excision, as defined by the NCDB, included polypectomy, excisional biopsy, and laser excision.
[g]Includes partial and total esophagectomy.
[h]Defined as surgery, chemotherapy, radiation, or immunotherapy in the NCDB. NCDB, National Cancer Database.

significance, or magnitude of the previously described associations between metastatic pattern at presentation and survival (data available on request).

Unadjusted and adjusted survival analyses were stratified by histology, with similar results. Additional treatment variables were added to the Cox proportional hazards survival model (surgery [yes/no], chemotherapy [yes/no], radiation therapy [yes/no], and immunotherapy [yes/no]), with similar HRs for the stage IV-nodal and stage IV-multiorgan metastatic patterns.

A sensitivity analysis was also performed to explore a change in regional lymph node mapping in 2018 that should not have biased the survival findings. The American Joint Committee on Cancer Seventh Edition (corresponding to NCDB years of diagnosis 2016 to 2017) defined regional nodes in esophageal cancer as those that are paraesophageal, from the cervical nodes to the celiac nodes,[16] and included several lung lymph node stations that were not truly regional esophageal nodes.[17] Though they were infrequent sites of metastasis,[18] this was changed in the eight edition (NCDB 2018–2019). The inclusion of lung lymph node stations in the seventh edition of the esophageal regional node map is unlikely to have represented a major source of bias in the current study, because patients with metastases to those stations would not have been included; in other words, there were no misclassifications from this change that would have artifactually elevated the survival of the stage IV-nodal group. A sensitivity analysis was performed by stratifying the survival by year of diagnosis (2016–2017 and 2018; survival information is suppressed for the most recent year in the NCDB), with no differences in the directionality, magnitude, or significance of the findings.

Discussion

In the NCDB, almost 12% of patients with stage IV esophageal cancer lacked systemic metastases at

Table 2. Sociodemographic, Facility and Tumor Characteristics Associated With the Stage IV-Nodal Presentation

Characteristics		OR for Stage IV-Nodal Presentation (95% CI)	*p* Value
Age (y)	18-34	1.16 (0.46-2.93)	0.75
	35-49	0.92 (0.71-1.18)	0.52
	50-64	Ref	—
	65-79	0.93 (0.78-1.1)	0.39
	≥80	0.85 (0.67-1.1)	0.22
Sex	Female	Ref	—
	Male	0.83 (0.72-0.97)	0.02
Race	White	Ref	—
	Black	0.86 (0.68-1.09)	0.21
	Other	1.35 (1.01-1.82)	0.045
Ethnicity	Non-Hispanic	Ref	—
	Hispanic	0.86 (0.64-1.17)	0.34
Median income	<$40,227	Ref	—
	$40,227-$50,353	1.08 (0.89-1.3)	0.45
	$50,354-$63,332	1.03 (0.85-1.26)	0.77
	≥$63,333	1.01 (0.83-1.23)	0.91
Insurance status	Private	Ref	—
	Uninsured	0.82 (0.59-1.12)	0.21
	Medicaid	0.9 (0.73-1.11)	0.32
	Medicare	1.03 (0.86-1.23)	0.74
	Other government	0.81 (0.52-1.27)	0.35
Charlson-Deyo score	0	Ref	—
	1	1.13 (0.97-1.31)	0.12
	2	0.94 (0.73-1.21)	0.62
	3+	0.76 (0.57-1.02)	0.07
U.S. census division	New England	Ref	—
	Middle Atlantic	1 (0.76-1.32)	0.98
	South Atlantic	1.08 (0.82-1.4)	0.59
	East North Central	0.86 (0.65-1.13)	0.28
	East South Central	0.99 (0.71-1.36)	0.94
	West North Central	1.08 (0.8-1.47)	0.6
	West South Central	0.85 (0.61-1.18)	0.33
	Mountain	1 (0.7-1.44)	0.99
	Pacific	1.14 (0.85-1.52)	0.38
Facility type	Nonacademic	Ref	.
	Academic	1.24 (1.09-1.4)	0.0009
Area of residence	Metropolitan	1.01 (0.86-1.19)	0.91
	Urban	Ref	—
	Rural	1.05 (0.68-1.62)	0.82
Year of diagnosis	2016	Ref	—
	2017	0.89 (0.76-1.04)	0.15
	2018	0.81 (0.69-0.96)	0.01
	2019	0.89 (0.76-1.04)	0.14
Histology[a]	Adenocarcinoma	Ref	—
	Squamous cell carcinoma	1.58 (1.34-1.86)	<0.0001
Tumor location[a]	Cervical esophagus	0.87 (0.47-1.61)	0.65
	Upper esophagus	0.64 (0.45-0.91)	0.01
	Midesophagus	Ref	—
	Lower esophagus	0.92 (0.76-1.12)	0.42
	Overlapping lesion	0.79 (0.59-1.05)	0.1
	Unspecified	0.51 (0.39-0.65)	<0.0001

CI, confidence interval; Ref, reference value.
[a]No interactions between histology and esophageal tumor location were noted when an interaction term was introduced.

presentation, instead being classified as stage IV solely because of nonregional lymph node involvement. This proportion of patients with stage IV-nodal disease is consistent with a previous report using data from the Surveillance, Epidemiology, and End Results program database (16.9%).[19]

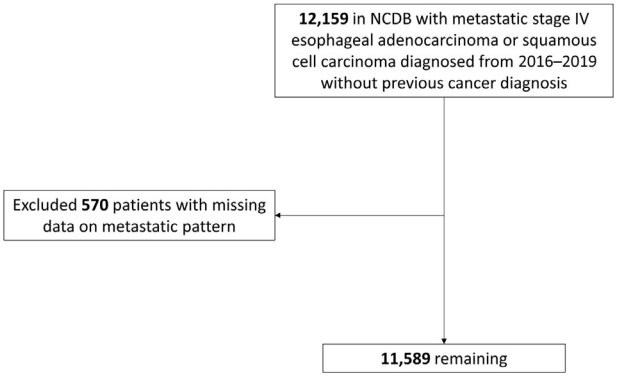

Figure 1. Consort diagram. NCDB, National Cancer Database.

Overall, the patients with stage IV-nodal disease were less likely than other patients with stage IV disease to go untreated; specifically, the patients with stage IV-nodal disease were more likely to receive chemotherapy and radiation. This may reflect attitudes that stage IV-nodal disease represents a more treatable disease and warrants more aggressive treatment.[20]

Patients treated at academic facilities were more likely to present with stage IV-nodal disease. This finding, to our knowledge, has not been reported previously, and we hypothesize that this is due to a better understanding of the current nodal mapping or staging system at academic facilities. Although it has been suggested that patients in university hospital cancer centers undergo more staging procedures,[21] more research is needed to clarify the significance of this finding.

The survival analyses indicate that patients with stage IV esophageal cancer presenting with nonregional lymph node metastases as the only metastatic site have a better prognosis than patients with stage IV cancer with systemic metastases. This is in line with previous reports.[19] One explanation could be that nonregional lymph node metastases represent a less dangerous oncologic event than systemic metastases. This has been described for prostate cancer, in which M1 disease is stratified by nonregional lymph node involvement (M1a), bone involvement (M1b), or other organ involvement (M1c).[6,22,23] Recent study into the prognosis of patients with stage IV breast cancer has also suggested that nonregional lymph node metastases might represent a form of regional disease, with a similar prognosis to nonmetastatic disease.[7] Another potential explanation for the better prognosis observed in the patients with stage IV-nodal disease may relate to lymph node mapping. Any misclassification by clinicians of regional nodes as nonregional would improve the survival of the stage IV-nodal cohort. In addition, it is also possible that the stage IV classification map may currently include a subset of patients that align more

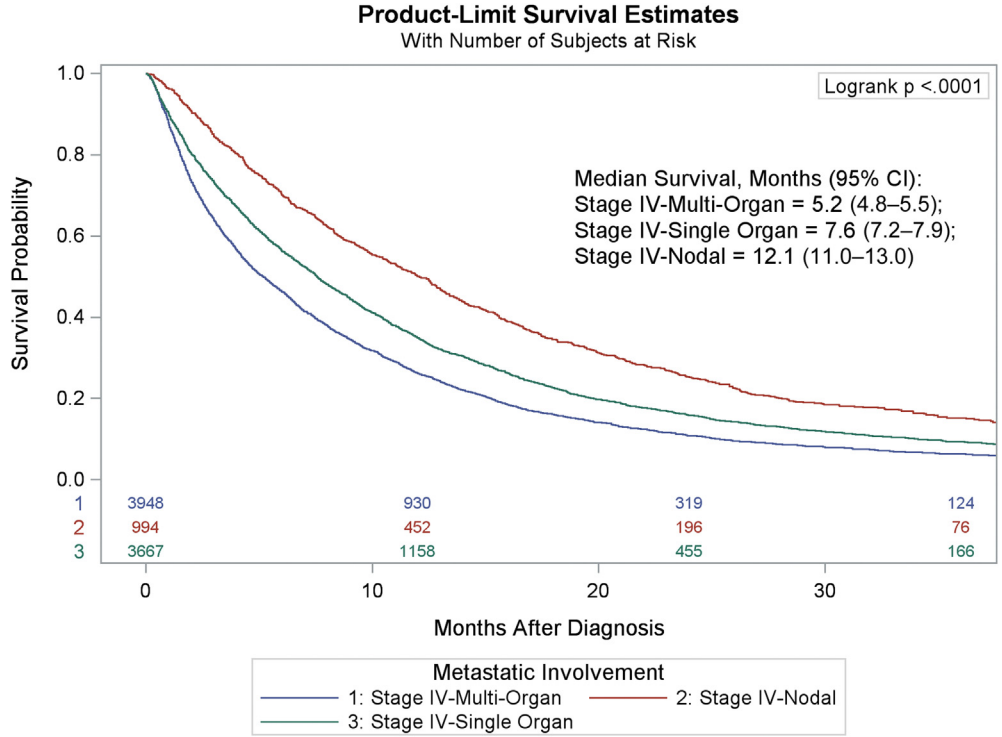

Figure 2. Unadjusted Kaplan-Meier curves for patients with stage IV esophageal cancer. It is noted that GEJ tumors may represent a distinct disease entity. As a sensitivity analysis, a similar survival analysis for gastric cancer was performed, with similar survival patterns as a result (data available on request). CI, confidence interval; GEJ, gastroesophageal junction.

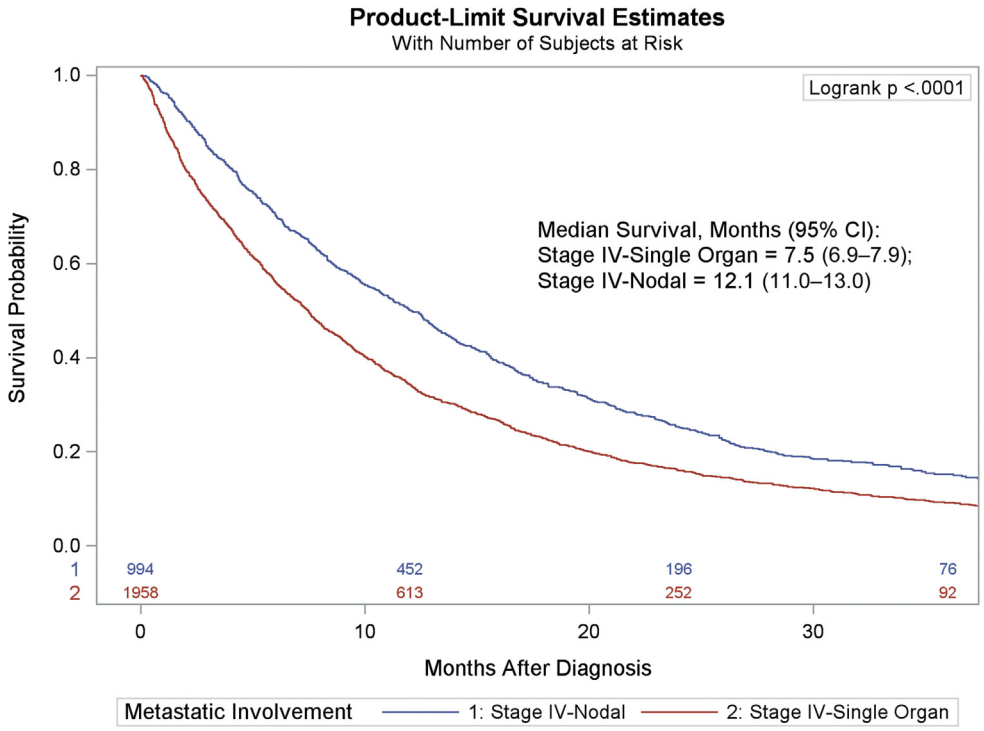

Figure 3. Kaplan-Meier curves comparing stage IV-nodal and stage IV-single organ metastatic involvement among propensity score-matched patients. CI, confidence interval.

with regional lymph nodes. This may be less likely as there have been multiple thoughtful revisions of the esophageal cancer classification system,[16,17] though continued exploration into the prognostic significance of specific sites of lymph node involvement may help to refine our understanding of the lymph node mapping system.

The current study includes a few limitations in addition to those typically attributed to retrospective studies.[24] Though the CCI was included as a covariate in the study, the NCDB does not record the Eastern Cooperative Oncology Group Performance Status, which may represent a potential confounder if patients with stage IV-nodal disease generally had a better performance status. The choice of the patients with stage IV-single organ disease as a comparison group for the patients with stage IV-nodal disease hopefully minimized the effects of performance status as a confounder. In addition, the missingness of T stage, N stage, and grade was high. Because most patients with stage IV esophageal cancer undergo biopsies using small samples (e.g., fine-needle aspiration) to establish a diagnosis and generally do not require further evaluation of T and N stages (as management would not be affected),[25] there would likely be incomplete staging and profiling for any retrospective study of stage IV esophageal cancer. Sensitivity analyses incorporating N stage and grade in the multivariable Cox models revealed similar associations between metastatic pattern and survival (data available on request). The study did not include molecular profiling, which has some correlation with the outcome,[26–30] but it is not currently a component of stage classification. It is possible that the patients with stage IV-nodal disease had molecular characteristics that were more favorable. Data regarding the specific locations of the affected lymph nodes in the NCDB were absent. The NCDB does not record information on staging evaluations (e.g., positron emission tomography/computed tomography, magnetic resonance imaging) or staging biopsies (i.e., whether the distant metastases were tissue confirmed) and provides limited data on how affected sites were managed; for example, although 41 patients received a distant lymph node excision, it is unclear how many patients underwent biopsies and radiation of a nonregional lymph node.

In conclusion, a considerable portion of patients with stage IV esophageal cancer present with metastatic involvement limited to distant lymph nodes. These patients are more likely to be treated aggressively and tend to have a better prognosis than other patients with stage IV cancer. The prognostic information can better prepare clinicians and patients to engage in shared decision-making. Further exploration may identify opportunities to refine the esophageal cancer stage classification system to reflect the superior prognosis of the stage IV-nodal subgroup.

CRediT Authorship Contribution Statement

Peter Lee Zhan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review and editing.

Maureen E. Canavan: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—review and editing.

Theresa Ermer: Investigation, Methodology, Visualization, Writing—review and editing.

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Michael F. Kaminski: Investigation, Validation, Visualization, Writing—review and editing.

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Data Availability

The National Cancer Database is a nationwide clinical surveillance resource oncology data set that captures 72% of all newly diagnosed malignancies in the United States annually and is a joint project of the American Cancer Society and the American College of Surgeons. The American College of Surgeons has a data use agreement with each of its Commission on Cancer-accredited hospitals. Data access can be requested from the American College of Surgeons.

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