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ORIGINAL RESEARCH

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Extranodal extension in laryngeal squamous cell carcinoma

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Abstract

Objective: Although large retrospective database studies have associated extranodal extension (ENE) with worse survival in several head and neck cancers, the prognostic significance of ENE in laryngeal squamous cell carcinoma (LSCC) remains unclear. Our study examines ENE and overall survival (OS) in LSCC.

Methods: The 2006–2017 National Cancer Database was queried for patients with LSCC undergoing surgical resection and neck dissection, with or without adjuvant therapy. Kaplan–Meier and multivariable Cox regression survival analyses were implemented to identify the independent impacts of pathologic nodal (pN) classification and ENE on OS.

Results: Of 4208 patients satisfying inclusion criteria, 2343 (55.7%) were pN0/ENE-negative, 1059 (25.2%) were pN1-2/ENE-negative, and 806 (19.2%) were pN1-2/ENE-positive. The 5-year OS of pN0/ENE-negative, pN1-2/ENE-negative, and pN1-2/ENE-positive patients was 62.8%, 56.7%, and 32.9%, respectively ($p < .001$). Among pN1-2/ENE-positive patients undergoing no adjuvant therapy, adjuvant radiotherapy alone, and adjuvant chemoradiotherapy, 5-year OS was 24.1%, 30.7%, and 36.7%, respectively ($p < .001$). After adjusting for patient demographics, clinicopathologic features, and adjuvant therapy, ENE-positivity was associated with worse OS than ENE-negativity (adjusted hazard ratio [aHR] 1.76, 95% confidence interval [CI] 1.53–2.02, $p < .001$). pN1/ENE-positivity (aHR 1.82, 95% CI 1.31–2.54) and pN2/ENE-positivity (aHR 1.89, 95% CI 1.49–2.40) were associated with worse OS than pN1/ENE-negativity ($p < .001$). Microscopic (aHR 1.83, 95% CI 1.54–2.18) and macroscopic ENE-positivity (aHR 1.75, 95% 1.35–2.26) were associated with worse OS than ENE-negativity ($p < .001$).

Conclusion: ENE-positivity has prognostic significance in LSCC and is associated with worse OS than ENE-negativity. pN classification did not have prognostic significance independent of ENE. ENE should be carefully considered when determining the prognosis of LSCC and selecting adjuvant therapy.

Level of Evidence: 4.

KEYWORDS

extranodal extension, laryngeal squamous cell carcinoma, National Cancer Database, nodal metastasis, survival

1 | INTRODUCTION

The pathologic tumor-node-metastasis (pTNM) classification is one of the most widely adopted systems to stage surgically resected cancer and communicate the anatomic extent of metastasis.[1] The number, size, and location of metastatic lymph nodes determines pN classification.[1] In addition to pN classification, extranodal extension (ENE) of lymph node metastasis, defined as the expansion of tumor cells beyond the lymph node capsule into perinodal tissue, has prognostic significance in head and neck squamous cell carcinoma (HNSCC).[2–5]

Laryngeal squamous cell carcinoma (LSCC) is one of the most common head and neck malignancies, with an incidence of approximately 13,000 patients per year in the United States.[6–8] Although large retrospective database studies have associated ENE with worse survival in squamous cell carcinoma of several head and neck primary sites, including the oral cavity, oropharynx, and hypopharynx, the prognostic significance of ENE in LSCC remains unclear.[9–12] To date, the prognostic significance of ENE in LSCC has only been investigated in institutional studies—one study of 81 patients showed a lack of statistical significance between ENE-positivity and survival, while another study of 355 patients showed a significant association between ENE-positivity and survival.[13,14] To elucidate the prognostic significance of ENE in LSCC, our study utilizes the National Cancer Database (NCDB) to comprehensively examine the independent impacts of ENE and pN classification on overall survival (OS).

2 | METHODS

2.1 | Data source

The NCDB is jointly sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a hospital-based cancer outcomes registry that collects data from >1500 CoC-accredited hospitals within the United States and captures >70% of all newly diagnosed cancers each year. The NCDB is not responsible for the validity of the statistical analysis and conclusions derived herein. Our study was exempt from review by the Rutgers New Jersey Medical School Institutional Review Board because of the de-identified nature of patient data.

2.2 | Inclusion criteria

Patients included in our study had (1) *International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)* histology ("8070–8074," "8076," "8078"), behavior ("3"), and topography ("C32.0-C32.2") codes consistent with conventional LSCC, (2) either pN0/ENE-negativity, pN1-2/ENE-negativity, or pN1-2/ENE-positivity, (3) no clinically distant metastasis, and (4) definitive treatment with surgical resection and neck dissection, with or without adjuvant therapy.[12] Surgical resection was defined as local tumor destruction, local tumor excision, partial excision, total or radical laryngectomy, pharyngolargyngectomy, or unspecified surgery. Neck dissection was defined as the removal and examination of ≥ 10 regional lymph nodes.[15,16] Patients with unknown grade, pathologic American Joint Committee on Cancer (AJCC) group stage, pTN classification, vital status, or survival time were excluded. Patients undergoing palliative care, salvage surgery, neoadjuvant therapy, or adjuvant chemotherapy alone were also excluded. All staging and classifications were based on the *AJCC Cancer Staging Manual, 7th edition*.

2.3 | Exposure and outcome assessment

Pathologic ENE is recorded under NCDB collaborative stage site-specific factor 9 according to the final diagnosis in the pathology report.[11] Patients were classified as ENE-positive if the regional lymph nodes had either microscopic or macroscopic ENE. ENE-negativity was defined as regional lymph node involvement with no ENE on pathologic examination.

The primary outcome of our study was 5-year OS. Survival time was calculated as the time from diagnosis to either death due to any cause or 5-years of follow-up.

2.4 | Confounders

Potential confounders included age at diagnosis (18–55 years, 56–69 years, ≥ 70 years), sex (male, female), race (White, Black, other), Charlson-Deyo comorbidity score (0, 1, ≥ 2), history of prior malignancy, tumor subsite (glottis, supraglottis, subglottis), tumor diameter, grade, pathologic AJCC group stage, pTN classification, lymphovascular invasion, surgical margin status, and adjuvant therapy (none, adjuvant radiotherapy alone, adjuvant chemoradiotherapy). Microscopic, macroscopic, or unspecified residual tumor were considered positive surgical margins.

2.5 | Statistical analysis

The chi-square test and independent samples *t*-tests were used to compare categorical and continuous variables, respectively, across pN0/ENE-negative, pN1-2/ENE-negative, and pN1-2/ENE-positive cohorts. Kaplan–Meier analysis and the log-rank test were used to estimate 5-year OS. Adjusted hazard ratios (aHRs) for the independent impacts of pN classification and ENE on OS were estimated by multivariable Cox proportional hazards regression. Multivariable Cox analyses included all variables with $p < .05$ on univariable Cox analysis. The proportional hazards assumption was tested with time-dependent covariables and satisfied in all regression models. The interaction between ENE and nodal status was examined because both factors are clinically related. The significance level for all statistical testing and confidence interval (CI) calculations was set at $p < 0.05$. SPSS version 25 (IBM) was used for statistical analysis.

3 | RESULTS

3.1 | Patient demographics, clinicopathologic features, and adjuvant therapy

Of 4208 patients satisfying inclusion criteria, 2343 (55.7%) were pN0/ENE-negative, 1059 (25.2%) were pN1-2/ENE-negative, and 806 (19.2%) were pN1-2/ENE-positive (Table 1). ENE was significantly associated with pathologic AJCC group staging, pT classification, and treatment modality. Compared with pN0/ENE-negative patients, pN1-2/ENE-positive patients more frequently had pathologic AJCC group stage IV (95.0% vs. 47.2%), pT4 classification (50.4% vs. 43.4%), and treatment with adjuvant chemoradiotherapy (61.3% vs. 11.3%) ($p < .001$).

3.2 | Kaplan–Meier survival analysis

The 5-year OS for pN0/ENE-negative, pN1-2/ENE-negative, and pN1-2/ENE-positive patients was 62.8%, 56.7%, and 32.9%, respectively ($p < .001$) (Table 2, Figure 1). Among pN0/ENE-negative patients undergoing no adjuvant therapy, adjuvant radiotherapy alone, and adjuvant chemoradiotherapy, 5-year OS was 63.7%, 61.9%, and 60.7%, respectively ($p = .496$). Among pN1-2/ENE-positive patients undergoing no adjuvant therapy, adjuvant radiotherapy alone, and adjuvant chemoradiotherapy, 5-year OS was 24.1%, 30.7%, and 36.7%, respectively ($p < .001$). The 5-year OS for pN1/ENE-negative, pN1/ENE-positive, pN2/ENE-negative, and pN2/ENE-positive patients was 60.5%, 31.9%, 54.5%, and 31.4%, respectively ($p < .001$) (Figure 2). The 5-year OS for ENE-negative, microscopic ENE-positive, and macroscopic ENE-positive patients was 60.9%, 31.6%, and 30.4%, respectively ($p < .001$) (Figure 3).

3.3 | Multivariable Cox regression survival analysis

After adjusting for age at diagnosis, sex, race, CCI, history of prior malignancy, pathologic AJCC group stage, pT classification, and surgical margin status, ENE-positivity was associated worse OS than ENE-negativity (aHR 1.76, 95% CI 1.53–2.02, $p < .001$) while also adjusting for pN classification (Table 3). Adjusting for pN classification and ENE together, pN1/ENE-positivity (aHR 1.82, 95% CI 1.31–2.54) and pN2/ENE-positivity (aHR 1.89, 95% CI 1.49–2.40) were both associated with worse OS than pN1/ENE-negativity ($p < .001$) (Table 4). Microscopic (aHR 1.83, 95% CI 1.54–2.18) and macroscopic (aHR 1.75, 95% CI 1.35–2.26) ENE were both associated with worse OS than ENE-negativity while also adjusting for pN classification ($p < 0.001$) (Table 5).

4 | DISCUSSION

The prognostic significance of ENE in patients with LSCC undergoing definitive treatment with surgical resection and neck dissection is not well understood. Our study utilizing the NCDB to investigate the prognostic significance of ENE in LSCC found that ENE-positive patients had worse OS than ENE-negative patients, even after stratification of survival analysis by patient demographics, clinicopathologic features, and adjuvant therapy. The survival detriment of ENE-positivity was more pronounced among patients with age ≥ 70 years, female sex, and glottic tumors. Among pN0/ENE-negative patients, adjuvant therapy, adjuvant radiotherapy alone, and adjuvant chemoradiotherapy were all associated with similar OS. Among pN1-2/ENE-positive patients, adjuvant chemoradiotherapy was associated with higher OS than both adjuvant radiotherapy alone or no adjuvant therapy. On multivariable analysis, ENE-positivity remained associated with worse OS, regardless of pN classification and other confounders. The survival detriment of ENE-positivity persisted with both microscopic and macroscopic ENE. pN classification was not associated with OS independent of ENE.

Since ENE was first defined by Bennett et al., many studies have highlighted the association between ENE-positivity and poor survival.[17] Large retrospective database studies of SCC of the oral cavity, oropharynx, and other head and neck primary sites document the survival detriment associated with ENE-positivity.[18,19] The 8th edition of the *AJCC Cancer Staging Manual* has therefore incorporated evidence of ENE in the *N* classification of HNSCC.[20] However, literature describing the role of ENE in outcomes of LSCC is limited. Several smaller institutional studies describe ENE-positivity as portending poorer survival.[13,14,21] To our knowledge, our study is the first to implement a large-scale, multi-institutional design to evaluate the impact of ENE in LSCC survival and distinguish between the microscopic and macroscopic ENE.

Until recently, there was little consensus among pathologists regarding the histologic definition of ENE across head and neck primary sites.[17,18,22] However, the 8th edition of the *AJCC Cancer Staging Manual* and the College of American Pathologist have created standardized criteria allowing for comparable studies between microscopic (≤2 mm from the capsule) and macroscopic ENE (>2 mm from the capsule).[18,19] A prior study describing ENE of the larynx and hypopharynx defined macroscopic ENE as intraoperative transcapsular spread and microscopic ENE as pathologic examination revealing microscopic invasion.[23] With this definition, microscopic ENE was shown to not have an association with poorer survival.[23] The lack of standardization of numerical parameters may explain the discrepancy between the results of this study and the results of our study.

Our study has several limitations. Some data in retrospective databases such as the NCDB may be missing or inaccurate. Our retrospective study design precludes controlling for treatment selection bias. The NCDB does not encode medical comorbidities, tobacco use, disease-specific survival, and locoregional recurrence, which all affect LSCC management and survival. Defining neck dissection as the removal and examination of ≥ 10 lymph nodes may have underestimated the delivery of neck dissection and included patients undergoing less selective nodal resections. The 8th edition of the *AJCC Cancer Staging Manual* is the first to provide an updated, unified definition of ENE, but reporting in the NCDB was only mandated starting in 2018. The number of involved lymph nodes was not adjusted for in

TABLE 1 Patient demographics, clinicopathologic features, and adjuvant therapy.

	pN0/ENE-negative	pN1-2/ENE-negative	pN1-2/ENE-positive	*p*-value
No. of patients (%)	2343 (55.7)	1059 (25.2)	806 (19.2)	
Age at diagnosis, *n* (%)				
Mean (years ± SD)	61.7 ± 10.1	59.7 ± 9.0	61.2 ± 9.4	**<.001**
18–55 years	633 (27.0)	350 (33.1)	228 (28.3)	**<.001**
56–69 years	1207 (51.5)	562 (53.1)	427 (53.0)	
≥ 70 years	503 (21.5)	147 (13.9)	151 (18.7)	
Sex, *n* (%)				
Male	1835 (78.3)	788 (74.4)	587 (72.8)	**.002**
Female	508 (21.7)	271 (25.6)	219 (27.2)	
Race, *n* (%)				
White	1910 (82.0)	840 (80.4)	655 (82.2)	.775
Black	364 (15.6)	180 (17.2)	126 (15.8)	
Other	54 (2.3)	25 (2.4)	16 (2.0)	
Charlson-Deyo comorbidity score, *n* (%)				
0	1415 (60.4)	677 (63.9)	469 (58.2)	.110
1	631 (26.9)	269 (25.4)	233 (28.9)	
≥ 2	297 (12.7)	113 (10.7)	104 (12.9)	
History of prior malignancy, *n* (%)	714 (20.5)	235 (22.2)	183 (22.7)	**<.001**
Subsite, *n* (%)				
Glottis	1026 (43.8)	296 (28.0)	170 (21.1)	**<.001**
Supraglottis	1196 (51.0)	731 (69.0)	618 (76.7)	
Subglottis	121 (5.2)	32 (3.0)	18 (2.2)	
Tumor diameter, cm ± SD	3.4 ± 4.4	4.4 ± 7.5	4.5 ± 5.8	**<.001**
Grade, *n* (%)				
Well-differentiated	229 (9.8)	57 (5.4)	17 (2.1)	**<.001**
Moderately differentiated	1595 (68.1)	690 (65.2)	453 (56.2)	
Poorly differentiated, undifferentiated, anaplastic	519 (22.2)	312 (29.5)	336 (41.7)	
Pathologic AJCC group stage, *n* (%)				
I	261 (11.1)	18 (1.7)	0 (0.0)	**<.001**
II	330 (14.1)	44 (4.2)	2 (0.2)	
III	646 (27.6)	238 (22.5)	38 (4.7)	
IV	1106 (47.2)	759 (71.7)	766 (95.0)	
pT classification, *n* (%)				
1	289 (12.3)	67 (6.3)	44 (5.5)	**<.001**
2	386 (16.5)	119 (11.2)	89 (11.0)	
3	652 (27.8)	354 (33.4)	267 (33.1)	
4	1016 (43.4)	519 (49.0)	406 (50.4)	
pN classification, *n* (%)				
0	2343 (100.0)	0 (0.0)	0 (0.0)	**<.001**
1	0 (0.0)	399 (37.7)	197 (24.4)	
2	0 (0.0)	660 (62.3)	609 (75.6)	
Lymphovascular invasion, *n* (%)				
No	1689 (73.3)	647 (61.9)	267 (33.3)	**<.001**
Yes	416 (18.1)	291 (27.8)	442 (55.2)	
Unknown	199 (8.6)	108 (10.3)	92 (11.5)	

TABLE 1 (Continued)

	pN0/ENE-negative	pN1-2/ENE-negative	pN1-2/ENE-positive	*p*-value
Adjuvant therapy, *n* (%)				
None	1321 (56.4)	316 (29.8)	161 (20.0)	**<.001**
Radiotherapy alone	758 (32.4)	443 (41.8)	151 (18.7)	
Chemoradiotherapy	264 (11.3)	300 (28.3)	494 (61.3)	
Surgical margins, *n* (%)				
Negative	2136 (92.3)	934 (89.5)	631 (80.1)	**<.001**
Positive	177 (7.7)	110 (10.5)	157 (19.9)	

Note: Bold values are significant at $p < 0.05$.
Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; pTN, pathologic tumor-nodal; SD, standard deviation.

TABLE 2 5-year overall survival (%) within strata.

	pN0/ENE-negative	pN1-2/ENE-negative	pN1-2/ENE-positive	*p*-value
Overall	62.8	56.7	32.9	**<.001**
Age at diagnosis, years				
18–55	74.1	60.1	35.0	**<.001**
56–69	63.8	57.7	35.1	**<.001**
≥ 70	47.0	45.5	23.5	**<.001**
Sex				
Male	61.0	55.3	31.8	**<.001**
Female	69.2	61.1	36.0	**<.001**
Race				
White	62.5	57.1	33.3	**<.001**
Black	62.3	55.2	32.7	**<.001**
Other	68.3	40.0	25.9	**.001**
Subsite				
Glottis	63.2	56.9	24.3	**<.001**
Supraglottis	62.8	56.9	35.4	**<.001**
Subglottis	60.2	51.0	29.0	**.025**
Grade				
Well-differentiated	69.3	63.4	46.2	.229
Moderately differentiated	64.3	55.3	29.7	**<.001**
Poorly differentiated, undifferentiated, anaplastic	55.6	58.8	36.7	**<.001**
Pathologic AJCC group stage				
I	78.4	93.5	-	.317
II	72.5	80.8	50.0	.514
III	59.3	66.4	43.3	**.040**
IV	58.4	51.5	32.3	**<.001**
pT classification				
1	77.6	75.4	38.5	**<.001**
2	68.9	67.0	46.7	**<.001**
3	56.8	60.0	41.1	**<.001**
4	60.2	49.5	24.1	**<.001**
pN classification				
0	62.8	-	-	-
1	-	60.5	40.1	**<.001**

(Continues)

TABLE 2 (Continued)

	pN0/ENE-negative	pN1-2/ENE-negative	pN1-2/ENE-positive	*p*-value
2	-	54.5	30.6	**<.001**
Adjuvant therapy				
None	63.7	61.0	24.1	**<.001**
Radiotherapy alone	61.9	55.8	30.7	**<.001**
Chemoradiotherapy	60.7	53.7	36.7	**<.001**

Note: Bold values are significant at $p < 0.05$.
Abbreviations: AJCC, American Joint Committee on Cancer; ENE, extranodal extension; pTN, pathologic tumor-nodal.

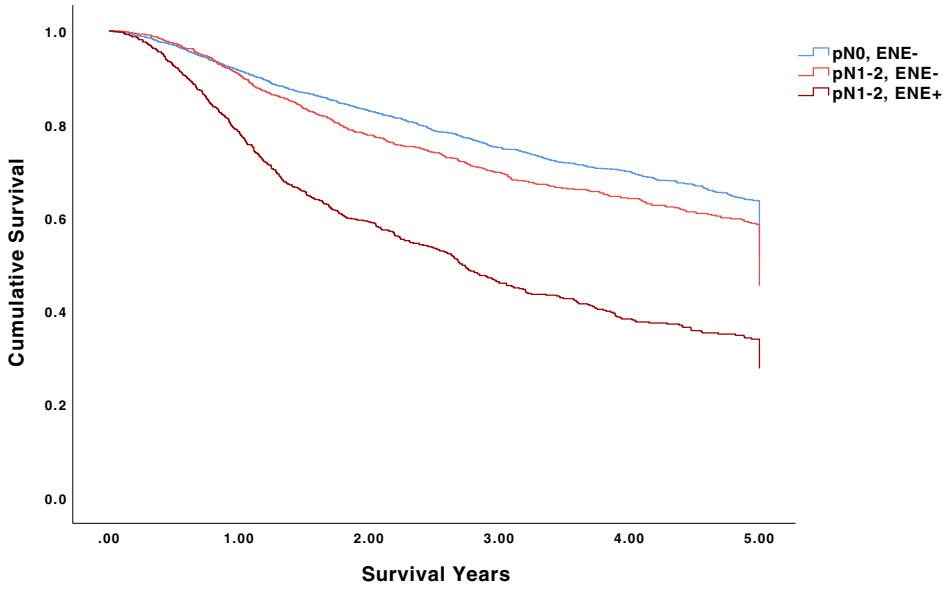

FIGURE 1 5-year overall survival for pN0/ENE-negative, pN1-2/ENE-negative, and pN1-2/ENE-positive patients.

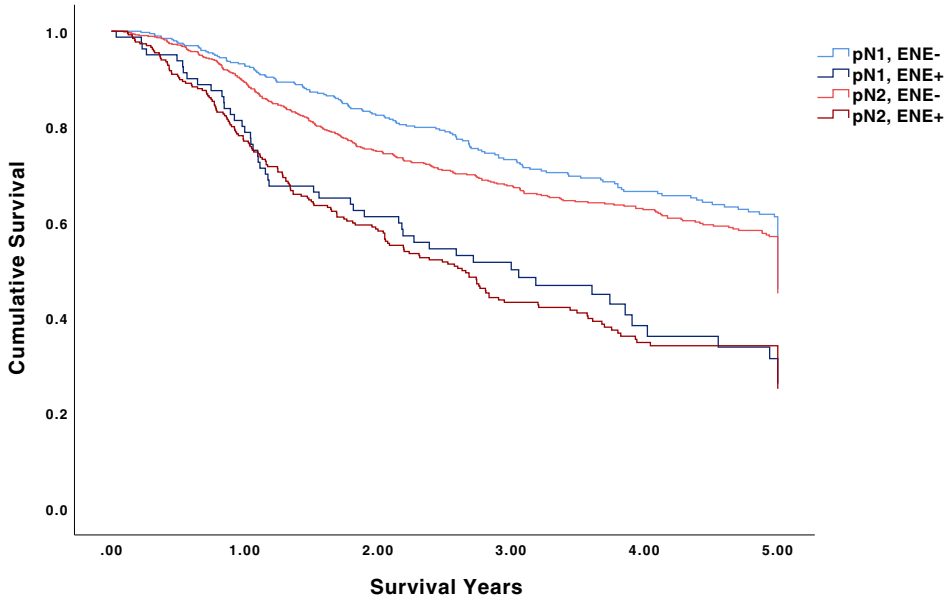

FIGURE 2 5-year overall survival for pN1/ENE-negative, pN1/ENE-positive, pN2/ENE-negative, and pN2/ENE-positive patients.

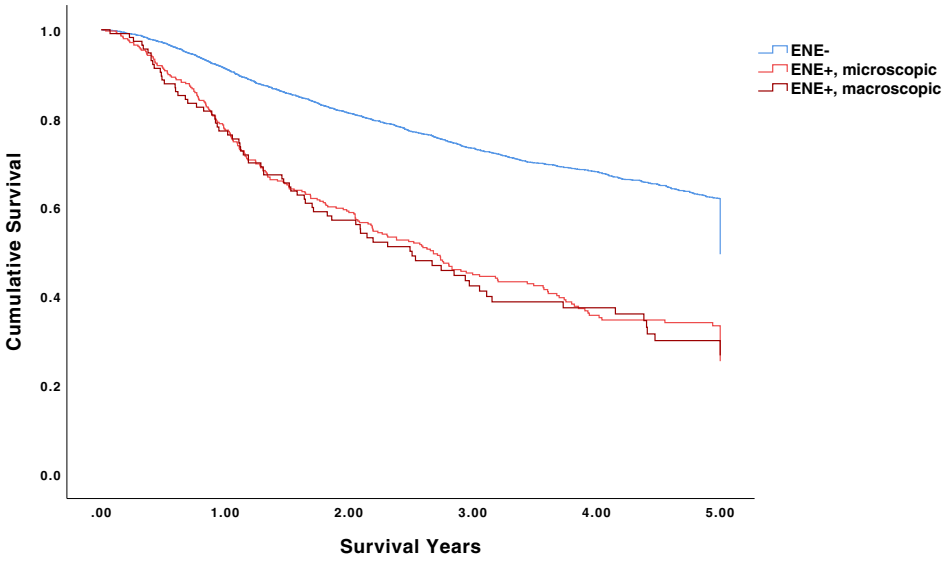

FIGURE 3 5-year overall survival for ENE-negative, microscopic ENE-positive, and macroscopic ENE-positive patients.

TABLE 3 Adjusted hazard ratios for ENE and pN classification among all pN1-2 patients.

	n (%)	aHR[a] (95% CI)	*p*-value
ENE			
Negative	1030 (56.9)	*Ref*	
Positive	779 (43.1)	1.76 (1.53–2.02)	**<.001**
pN classification			
1	576 (31.8)	*Ref*	
2	1233 (68.2)	1.15 (0.99–1.34)	.065

Note: Bold values are significant at $p < 0.05$.
Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CI, confidence interval; ENE, extranodal extension; pTN, pathologic tumor-nodal; Ref, reference.
[a]Adjusted for age at diagnosis, sex, race, Charlson-Deyo comorbidity score, history of prior malignancy, pathologic AJCC group stage, pT classification, and surgical margin status.

TABLE 4 Adjusted hazard ratios for combined ENE and pN classification among all pN1-2 patients.

	n (%)	aHR[a] (95% CI)	*p*-value
pN classification/ENE			
pN1/ENE-negative	386 (28.2)	*Ref*	
pN1/ENE-positive	79 (5.8)	1.82 (1.31–2.54)	**<.001**
pN2/ENE-negative	644 (47.1)	1.03 (0.84–1.26)	.779
pN2/ENE-positive	258 (18.9)	1.89 (1.49–2.40)	**<.001**

Note: Bold values are significant at $p < 0.05$.
Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CI, confidence interval; ENE, extranodal extension; pTN, pathologic tumor-nodal; Ref, reference.
[a]Adjusted for age at diagnosis, sex, race, Charlson-Deyo comorbidity score, history of prior malignancy, pathologic AJCC group stage, pT classification, and surgical margin status.

TABLE 5 Adjusted hazard ratios for negative, microscopic, and macroscopic ENE and pN classification among all pN1-2 patients.

	n (%)	aHR[a] (95% CI)	*p*-value
ENE			
Negative	1030 (69.6)	*Ref*	
Microscopic	337 (22.8)	1.83 (1.54–2.18)	**<.001**
Macroscopic	112 (7.6)	1.75 (1.35–2.26)	**<.001**
pN classification			
1	490 (33.1)	*Ref*	
2	989 (66.9)	1.06 (0.89–1.25)	.519

Note: Bold values are significant at $p < 0.05$.
Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CI, confidence interval; ENE, extranodal extension; pTN, pathologic tumor-nodal; Ref, reference.
[a]Adjusted for age at diagnosis, sex, race, Charlson-Deyo comorbidity score, history of prior malignancy, pathologic AJCC group stage, pT classification, and surgical margin status.

multivariable analysis. Despite these limitations, our study presents a large analysis of the NCDB and suggests that both microscopic and macroscopic ENE have prognostic significance independent of patient demographics, pN classification, adjuvant therapy, and other clinicopathologic confounders.

5 | CONCLUSION

Our study demonstrates that microscopic and macroscopic ENE are both strongly associated with worse OS in LSCC independent of pN classification. pN classification was not associated with OS independent of ENE. Further studies are necessary to inform management of LSCC based on ENE status.

AUTHOR CONTRIBUTIONS

Aman M. Patel: Design, analysis, interpretation, manuscript writing. **Sudeepti Vedula**: Design, analysis, interpretation, manuscript writing. **Ariana L. Shaari**: Design, analysis, interpretation, manuscript writing. **Hannaan S. Choudhry**: Design, analysis, interpretation, manuscript writing. **Andrey Filimonov**: Design, analysis, interpretation, manuscript writing, final approval.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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