12-15-2020

Inclusion of extranodal extension in the lymph node classification of cutaneous squamous cell carcinoma of the head and neck

Moran Amit

Chuan Liu

Frederico O Gleber-Netto

Sameer Kini

Samantha Tam
Henry Ford Health, stam2@hfhs.org

See next page for additional authors

Recommended Citation

Amit M, Liu C, Gleber-Netto FO, Kini S, Tam S, Benov A, Aashiq M, El-Naggar AK, Moreno AC, Rosenthal DI, Glisson BS, Ferrarotto R, Wong MK, Migden MR, Baruch EN, Li G, Khanna A, Goepfert RP, Nagarajan P, Weber RS, Myers JN, and Gross ND. Inclusion of extranodal extension in the lymph node classification of cutaneous squamous cell carcinoma of the head and neck. Cancer 2020.

Authors

Moran Amit, Chuan Liu, Frederico O Gleber-Netto, Sameer Kini, Samantha Tam, Avi Benov, Mohamed Aashiq, Adel K El-Naggar, Amy C. Moreno, David I. Rosenthal, Bonnie S. Glisson, Renata Ferrarotto, Michael K. Wong, Michael R. Migden, Erez N. Baruch, Guojun Li, Anshu Khanna, Ryan P. Goepfert, Priyadharsini Nagarajan, Randal S. Weber, Jeffrey N. Myers, and Neil D. Gross

Original Article

Inclusion of Extranodal Extension in the Lymph Node Classification of Cutaneous Squamous Cell Carcinoma of the Head and Neck

Moran Amit, MD, PhD [1]; Chuan Liu, MD[1]; Frederico O. Gleber-Netto, DDS, PhD [1]; Sameer Kini, MD[1]; Samantha Tam, MD, MPH [2]; Avi Benov, MD, MHA[3,4]; Mohamed Aashiq, MBBS[1]; Adel K. El-Naggar, MD[5]; Amy C. Moreno, MD [6]; David I. Rosenthal, MD[6]; Bonnie S. Glisson, MD[7]; Renata Ferrarotto, MD [7]; Michael K. Wong, MD[8]; Michael R. Migden, MD[9]; Erez N. Baruch, MD, PhD[10]; Guojun Li, MD, PhD[1]; Anshu Khanna, MPH [1]; Ryan P. Goepfert, MD [1]; Priyadharsini Nagarajan, MD, PhD[5]; Randal S. Weber, MD[1]; Jeffrey N. Myers, MD, PhD[1]; and Neil D. Gross, MD [1]

BACKGROUND: The prognostic performance of the recently updated American Joint Committee on Cancer lymph node classification of cutaneous head and neck squamous cell carcinoma (HNSCC) has not been validated. The objective of this study was to assess the prognostic role of extranodal extension (ENE) in cutaneous HNSCC. **METHODS:** This was a retrospective analysis of 1258 patients with cutaneous HNSCC who underwent surgery with or without adjuvant therapy between 1995 and 2019 at The University of Texas MD Anderson Cancer Center. The primary outcome was disease-specific survival (DSS). Local, regional, and distant metastases-free survival were secondary outcomes. Recursive partitioning analysis (RPA) and a Cox proportional hazards regression model were used to assess the fitness of staging models. **RESULTS:** No significant differences in 5-year DSS were observed between patients with pathologic lymph node-negative (pN0) disease (67.4%) and those with pN-positive/ENE-negative disease (68.2%; hazard ratio, 1.02; 95% CI, 0.61-1.79) or between patients with pN-positive/ENE-negative disease and those with pN-positive/ENE-positive disease (52.7%; hazard ratio, 0.57; 95% CI, 0.31-1.01). The RPA-derived model achieved better stratification between high-risk patients (category III, ENE-positive with >2 positive lymph nodes) and low-risk patients (category I, pN0; category II, ENE-positive/pN1 and ENE-negative with >2 positive lymph nodes). The performance of the RPA-derived model was better than that of the pathologic TNM classification (Akaike information criterion score, 1167 compared with 1176; Bayesian information criterion score, 1175 compared with 1195). **CONCLUSIONS:** The number of metastatic lymph nodes and the presence of ENE are independent prognostic factors for DSS in cutaneous HNSCC, and incorporation of these factors in staging systems improves the performance of the American Joint Committee on Cancer lymph node classification. ***Cancer* 2020;0:1-8**. © *2020 American Cancer Society*.

KEYWORDS: American Joint Committee on Cancer (AJCC), extranodal extension, prognosis, skin, squamous cell carcinoma, staging, survival.

INTRODUCTION

Extranodal extension (ENE), defined as extension of cancer cells through the lymph node capsule, has emerged as an independent indicator of disease aggressiveness in multiple malignancies.[1] The presence of ENE has been associated with a higher rate of regional recurrence, distant metastasis, and poor survival.[2] This led to the incorporation of ENE in the eighth edition (2018) of the American Joint Committee on Cancer (AJCC) lymph node classification system (the *AJCC Cancer Staging Manual*, eighth edition [AJCC 8]).[3] Similar to the pathologic lymph node (pN) classification of oral and human papillomavirus–negative oropharyngeal squamous cell carcinoma (SCC), in patients with cutaneous SCC of the head and neck (HNSCC), the presence of ENE results in upstaging of the lymph node classification.[4-7] However, given the lack of data regarding the impact of ENE on survival in cutaneous

Corresponding Authors: Neil D. Gross, MD, Department of Head and Neck Surgery, Unit 1445, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030 (ngross@mdanderson.org); Moran Amit, MD, PhD, Department of Head and Neck Surgery, Unit 123, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX (mamit@mdanderson.org).

[1]Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Department of Otolaryngology–Head and Neck Surgery, Henry Ford Health System and Henry Ford Cancer Institute, Detroit, Michigan; [3]Medical Corps, Israel Defense Forces, Tel Hasomer, Ramat Gan, Israel; [4]The Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel; [5]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [6]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [7]Department of Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [8]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [9]Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [10]Program for Innovative Microbiome and Translational Research (PRIME-TR), The University of Texas MD Anderson Cancer Center, Houston, Texas

We thank Erica Goodoff of Editing Services, Research Medical Library at The University of Texas MD Anderson Cancer Center, for editing the article.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33373, **Received:** July 13, 2020; **Revised:** August 25, 2020; **Accepted:** November 4, 2020, **Published online** Month 00, 2020 in Wiley Online Library (wileyonlinelibrary.com)

HNSCC, incorporating ENE into lymph node classification in the staging system increases the risk of lymph node stage migration, which would lead to substantial misclassification of the true disease stage. For example, if ENE does not affect survival rates, moving patients with ENE to a higher risk group would result in a false improved prognosis in patients with early stage disease (AJCC 8 stages I and II) as well as in patients with advanced-stage disease (AJCC 8 stages III and IV). This risk should be weighed against the benefits of improved risk stratification and consistency.[8]

According to the most recent (ie, eighth edition) AJCC TNM classification staging system for cutaneous HNSCC, all patients with ENE should be upstaged to an N3b classification; whereas, in mucosal SCC, the pN classification is further stratified according to the number of involved lymph nodes (ie, SCC with a single ENE-positive lymph node is classified as N2a; but, if the cancer has spread to many lymph nodes and at least 1 has ENE, the SCC is classified as N3b).[3] Here, we evaluated the prognostic performance of the AJCC lymph node classification system, as well as a modified model incorporating ENE with the number of metastatic lymph nodes, in a large cohort of patients with surgically treated cutaneous HNSCC.

MATERIALS AND METHODS

We performed a retrospective study of patients with cutaneous HNSCC who received treatment in our center. In total, 1360 patients were surgically treated for cutaneous HNSCC between 1995 and 2019; of these, 368 patients had a minimum follow-up of 1 month and were included in the analysis (Table 1). Detailed pathologic information on the neck dissection specimen, including the overall number of dissected and metastatic lymph nodes and the presence of ENE, was collected for these patients (Fig. 1A). Bilateral neck dissection was performed in 25 patients (6.8%); in these patients, we analyzed the total number of dissected lymph nodes. The median number of lymph nodes studied per patient was 25 (range, 7-126 lymph nodes). Adjuvant radiotherapy was received by 175 patients (47.6%), and concurrent radiotherapy with systemic therapy was received by 87 patients (23.6%) with T3-T4 or N2-N3 tumors, ENE, involved margins, or perineural invasion. The overall radiation dose was 55-60 grays, and radiation fields included the primary site (89 of 368 patients; 24.2%), the neck (26 of 368 patients; 7.1%), or both the primary site and the neck (147 of 368 patients; 40.0%). The most commonly used systemic therapy was platinum-based chemotherapy (ie, cisplatin or carboplatin; n = 57) followed by cetuximab (n = 13); taxane was administered to 10 patients, and erlotinib was administered to 7 patients.

TABLE 1. Characteristics of the Patients Included in the Study, n = 368

Characteristic	No. (%)
Age: Mean ± SD, y	69.3 ± 11.0
Sex	
Men	38 (10.3)
Women	330 (89.7)
Tumor classification	
T1	74 (20.1)
T2	68 (18.5)
T3	155 (42.1)
T4	47 (12.8)
Tx	24 (6.5)
Lymph node classification	
N0	217 (59.0)
N1	39 (10.6)
N2	29 (7.9)
N3	83 (22.6)
Treatment	
Surgery alone	106 (28.8)
Surgery + radiotherapy	175 (47.6)
Surgery + radiotherapy +systemic therapy	87 (23.6)
Chronic immunosuppression	
No	292 (79.3)
Yes	76 (20.7)

For patient classification, we used disease-specific survival (DSS) (defined as the length of time from the start of treatment to the date of death from the disease) as the primary dependent variable in a recursive partitioning analysis (RPA)-based model; independent variables were pN classification, the number of excised neck lymph nodes, and the presence of ENE (see Supporting Table 1).[6] This analysis allowed us to group the patients according to their outcome and explore variations in the independent variables in each group. Recurrence-free survival was defined as the length of time after primary treatment ended to the date of any observed signs or symptoms of cancer recurrence.

DSS was calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate differences in DSS rates. Adjusted hazard ratios (HRs) were calculated using a Cox proportional hazards model.[9] Variables used for multivariable risk adjustment based on clinical relevance to HNSCC included age, sex, immune compromise (absent or present), total number of lymph nodes (as a continuous variable), pN classification, ENE (absent or present), perineural invasion (absent or present), margin status (positive, <5 mm, or negative), pathologic tumor (T) classification, and treatment (surgery, surgery with adjuvant radiotherapy, or surgery with adjuvant chemoradiotherapy).[10] We

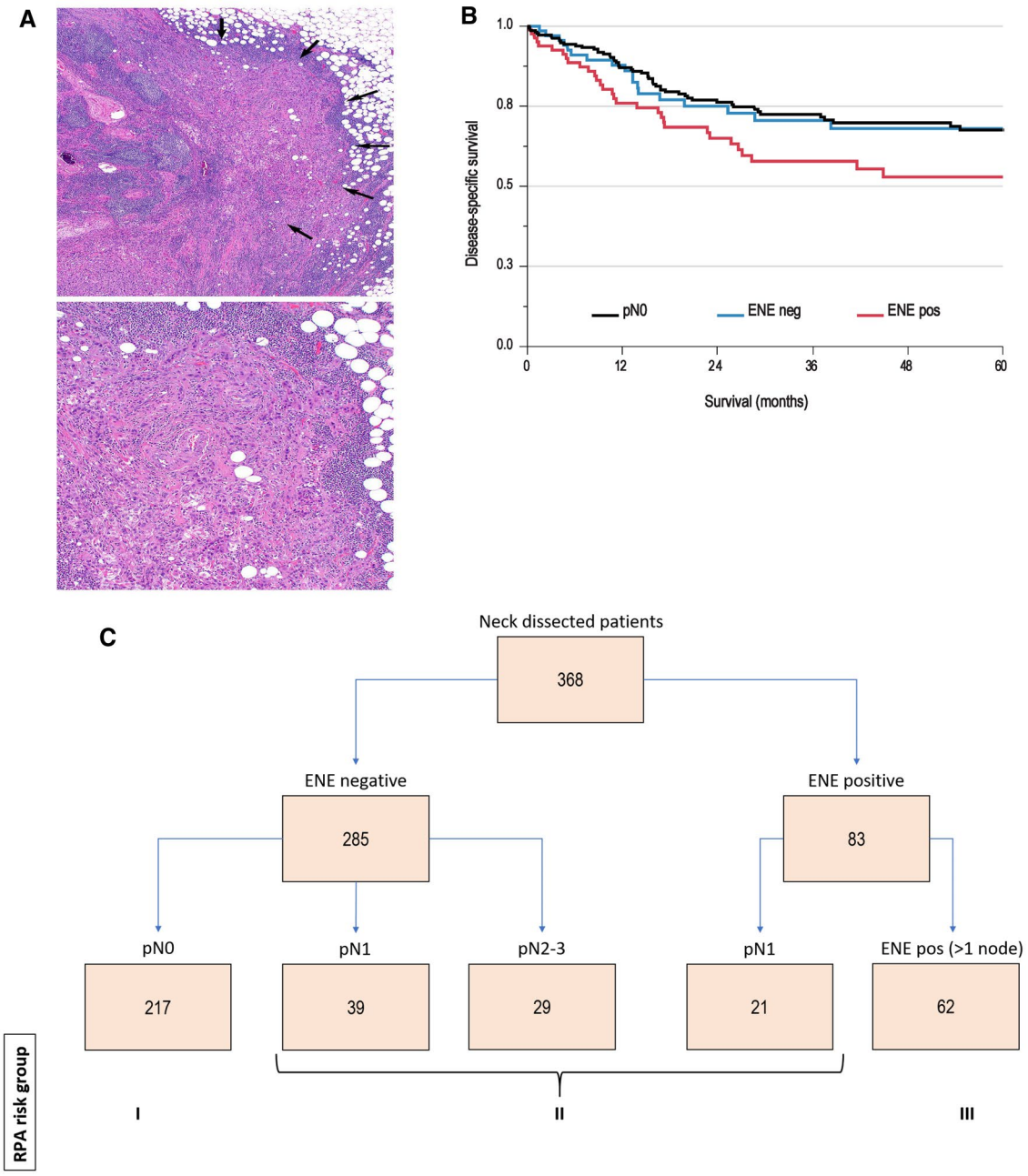

Figure 1. (A) Extranodal extension (ENE) is observed in a lymph node with (*Top*) metastatic squamous cell carcinoma (SCC) showing ENE into the surrounding perinodal fibroadipose tissue (arrows; H&E stain, original magnification ×40) and (*Bottom*) SCC cells intimately admixed with and surrounding the adipocytes (H&E stain, original magnification ×200). (B) Kaplan-Meier curves illustrate disease-specific survival by American Joint Committee on Cancer pathologic lymph node (pN) classification. Neg indicates negative; pN0, pathologic lymph node-negative; pos, positive. (C) Recursive partitioning analysis (RPA) classification of risk groups (I, II, and III) is illustrated.

used the AJCC 8 lymph node classification staging system for cutaneous HNSCC.[3] Significance for all analyses was defined as $P < .05$, and 2-sided statistics were used. All data were analyzed using JMP version 14.0.0 (SAS Institute Inc).

The best-fitting model that included ENE was identified using the Akaike information criterion (AIC) and Bayesian information criterion, which considered the model fit and complexity using our data set. To estimate the predictive ability of each model (ie, the RPA-based

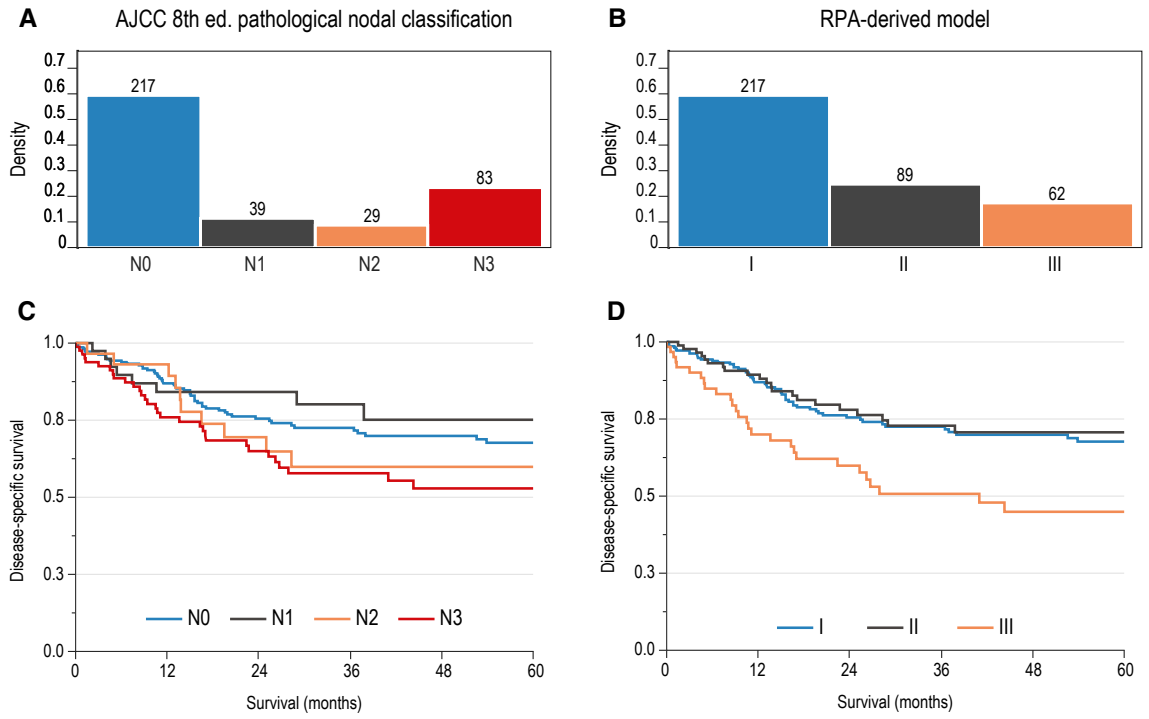

Figure 2. (A,B) The distribution of cases in the study cohort is illustrated according to (A) the American Joint Committee on Cancer (AJCC) eighth edition lymph node (N) classification and (B) recursive partitioning analysis (RPA) risk group (I, II, and III). (C,D) Kaplan-Meier curves illustrate disease-specific survival according to (C) AJCC pathologic N classification and (D) RPA risk group.

model and the AJCC lymph node classification system), we used the Harrell concordance index (c-index). The c-index was used to estimate the probability of concordance between the observed and expected DSS and is expressed as a value between 0 and 1.0.[11] The predictive discrimination of the models was quantified using the concordance probability estimate and the AIC. To calculate c-indices, concordance probability estimates, and AIC values, we used the Stata/IC software (version 14.2; StataCorp).

RESULTS

The 5-year DSS rate for all 368 patients was 64.3% (95% CI, 58.8%-69.5%). The 5-year DSS rates were 67.4% (95% CI, 60.2%-74.1%) for pN0 patients, 68.2% (95% CI, 55.6%-78.8%) for pN-positive patients without ENE (pN-positive/ENE-negative), and 52.7% (95% CI, 41.2%-64.1%) for pN-positive patients with ENE (pN-positive/ENE-positive) (Fig. 1B). DSS was significantly better in pN0 patients than in pN-positive/ENE-positive patients (HR, 0.59; 95% CI, 0.38-0.91) but did not differ between pN0 patients and pN-positive/ENE-negative patients (HR, 1.02; 95% CI, 0.61-1.79).

Patients who received adjuvant radiotherapy and had pN0 lesions had a significantly higher 5-year DSS rate (70%) those with pN-positive/ENE-positive lesions who received adjuvant radiotherapy (51%; HR, 0.48; 95% CI, 0.26-0.92) (see Supporting Table 2). Otherwise, adjustment for treatment regimen resulted in no significant differences between patient groups.

To stratify the risk for cancer-specific death, we used ENE as the first splitting variable of the RPA classification tree and the number of metastatic lymph nodes as the second. This classification resulted in 5 terminal risk groups (Fig. 1C). Groups 2 and 3 (ie, pN-positive/ENE-negative) and group 4 (pN1/ENE-positive) had similar DSS, hence those risk groups were categorized as a single risk group. The distribution of cases between the different risk groups is presented in Figure 2A.

The adjusted DSS for patients with AJCC pN2 lesions was very similar to that for patients with pN0 lesions (5-year DSS rate, 60% for pN2 and 68% for pN0; HR, 0.79; 95% CI, 0.41-1.51), and the difference in DSS between pN0 patients and those with advanced regional disease (pN3) was 14.9% (HR, 0.59; 95% CI, 0.38-0.90) (Fig. 2B). The difference in DSS between high-risk

patients in the RPA-derived model (category III: ie, ENE-positive with >2 positive lymph nodes) and low-risk patients (category I: ie, pN0; or category II: pN1/ENE-positive or pN1/ENE-negative with >2 positive lymph nodes) was 23.2% (5-year DSS rate, 45% for high-risk patients and 68% for low-risk patients; HR, 0.45; 95% CI, 0.30-0.74). The performance of the RPA-derived model was better than that of the AJCC pN classification system, with a higher c-index (0.572 vs 0.525), lower AIC score (1167 vs 1176), and a lower Bayesian information criterion score (1175 vs 1195).

Overall, 88 patients had a recurrence; of those, 39 patients had local recurrence, 34 patients had regional recurrence, and 29 patients had distant recurrence. Grouping of patients who had a single metastatic lymph node and ENE with pN2 patients (RPA category 2) resulted in better 5-year regional recurrence-free survival rates than those observed in patients with multiple positive lymph nodes (pN2; 86% vs 73%; $P = .04$) (Table 2). Otherwise, there were no statistically significant differences in recurrence-free survival rates among risk groups in the RPA-derived system or according to the AJCC pN classification.

To further evaluate the impact of clinicopathologic variables, we performed a multivariable analysis that included sex, age, immunosuppression status, perineural invasion, margin status, T classification, total number of lymph nodes excised, and treatment (Table 3). In the multivariable model including the AJCC pN classification system, the only significant predictive factor for DSS was age ($P = .01$). AJCC pN classification was not a significant predictor of DSS ($P = .07$). When we used the RPA-derived lymph node classification system in the multivariable model instead of the AJCC pN classification system (Table 3), age ($P = .02$) and lymph node classification ($P = .007$) were independently associated with DSS. A model comparison using the AIC and the Bayesian information criterion demonstrated that the adjusted RPA-derived lymph node classification system model performed better than the AJCC pN classification system model, with lower AIC (725 vs 731) and Bayesian (771 vs 787) values.

Finally, to assess the interactions between T and N classification and their potential impact on overall stage, we compared the performance of the overall AJCC 8 staging system with 2 RPA-based overall staging systems using all patients who had available data (n = 1258) (see Supporting Table 3). This analysis revealed a higher c-index and concordance probability estimate with a lower AIC score for both RPA models compared with the AJCC system for overall survival and DSS (see Supporting Table 4). These results indicate a noninferior performance of the RPA-based models in predicting outcomes compared with AJCC staging (Table 4).

TABLE 2. Five-Year Disease-Specific Survival Rate and Corresponding Hazard Ratios and Confidence Intervals for the American Joint Committee on Cancer Eighth Edition Pathologic Lymph Node Classification and Recursive Partitioning Analysis-Derived Risk Groups

Classification	No. of Patients	5-Year DSS Rate	HR (95% CI)
AJCC pN			
pN0	217	0.68	1.00 (Reference)
pN1	39	0.75	1.31 (0.62-2.75)
pN2	29	0.60	0.79 (0.41-1.51)
pN3	83	0.53	0.59 (0.38-0.90)
RPA risk group			
I	217	0.68	1.00 (Reference)
II	89	0.71	1.08 (0.66-1.76)
III	62	0.45	0.47 (0.30-0.74)

Abbreviations: AJCC, American Joint Committee on Cancer; DSS, disease-specific survival; HR, hazard ratio; pN, pathologic lymph node classification; RPA, recursive partitioning analysis.

TABLE 3. Five-Year Recurrence-Free Survival Rates for Local, Regional, and Distant Recurrence Among Patients With Various Lymph Node Status According the American Joint Committee on Cancer Eighth Edition Classification System and Recursive Partitioning Analysis-Derived Risk Groups

	5-Year Recurrence-Free Survival Rate (95% CI)		
Classification	Local	Regional	Distant
AJCC pN			
pN0	0.88 (0.82-0.92)	0.9 (0.84-0.94)	0.89 (0.81-0.93)
pN1	0.87 (0.7-0.95)	0.89 (0.7-0.96)	0.94 (0.69-0.99)
pN2	0.83 (0.63-0.93)	0.73 (0.51-0.88)	0.88 (0.7-0.96)
pN3	0.83 (0.72-0.9)	0.9 (0.8-0.95)	0.86 (0.75-0.92)
RPA risk group			
I	0.88 (0.82-0.92)	0.9 (0.84-0.94)	0.89 (0.81-0.93)
II	0.87 (0.77-0.93)	0.86 (0.75-0.93)	0.91 (0.8-0.96)
III	0.79 (0.66-0.89)	0.86 (0.72-0.93)	0.85 (0.71-0.92)

Abbreviations: AJCC, American Joint Committee on Cancer; pN, pathologic lymph node classification; RPA, recursive partitioning analysis.

DISCUSSION

The rationale for incorporating ENE into the AJCC pN classification system for HNSCC relied on data derived mostly from mucosal HNSCC.[4-7] The classification system should inform treatment planning, enable seamless communication between providers, allow consistent treatment response assessment, and improve patient counseling.[12] In the current study, we demonstrated that

TABLE 4. Multivariable Analysis of Clinicopathologic Factors Associated With Disease-Specific Survival When Including the American Joint Committee on Cancer Pathologic Lymph Node Classification System (Eighth Edition) and the Recursive Partitioning Analysis-Derived Model

	Multivariable Analysis			
	AJCC		RPA	
Variable	HR (95% CI)[a]	*P*	HR (95% CI)	*P*
Age	1.02 (1.00-1.05)	.0150	1.02 (1.00-1.04)	.0262
Sex		.3226		.4167
Men	Referent		Referent	
Women	1.61 (0.62-4.13)		1.48 (0.57-3.83)	
Immunosuppression		.4755		.4347
No	Referent		Referent	
Yes	1.24 (0.68-2.28)		1.27 (0.69-2.32)	
AJCC tumor classification		.3201		.4049
T1	Referent		Referent	
T2	1.33 (0.55-3.24)		1.27 (0.52-3.08)	
T3	0.69 (0.29-1.62)		0.73 (0.31-1.69)	
T4	0.59 (0.21-1.38)		0.55 (0.22-1.41)	
Perineural invasion		.9175		.9775
Absent	Referent		Referent	
Present	1.03 (0.55-1.94)		1.00 (0.53-1.89)	
Surgical margin status		.5775		.4921
Negative	Referent		Referent	
Positive	1.22 (0.60-2.46)		1.27 (0.63-2.58)	
No. of excised lymph nodes	0.99 (0.97-1.01)	.5486	0.99 (0.97-1.01)	.4313
Adjuvant therapy		.9643		
None	Referent		Referent	.8861
Adjuvant radiotherapy	1.04 (0.53-2.01)		1.10 (0.57-2.12)	
Adjuvant chemoradiotherapy	0.96 (0.46-1.99)		0.96 (0.46-2.00)	
AJCC lymph node classification		.070	NA	
pN0	Referent			
pN1	1.08 (0.41-2.80)			
pN2	0.50 (0.22-1.13)			
pN3	0.52 (0.30-0.89)			
RPA model risk group	NA			.0079
I			Referent	
II[a]			0.85 (0.46-1.58)	
III			0.41 (0.23-0.72)	

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; NA, not applicable; pN, pathologic lymph node classification; RPA, recursive partitioning analysis.
[a]For RPA risk group II compared with group III, the HR is 0.47 (95% CI, 0.23-0.95; $P = .035$).

inclusion of the number of metastatic lymph nodes with the presence of ENE improved the prognostic performance of the AJCC pN classification system, thus potentially allowing better attainment of these objectives with no to minimal impact on staging system complexity.[13]

Our data suggest that the presence of ENE is associated with a worse outcome, but not in a linear way. Although incorporating ENE into early lymph node categories (pN1) did not result in a better risk stratification compared with pN-positive patients without ENE, patients with multiple positive lymph nodes and ENE represented a separate risk group. These results indicate that ENE and the number of positive lymph nodes are complementary in their predictive value. Still, using the AJCC 8 pN classification system for cutaneous HNSCC did not lead to adequate separation of the risk groups.

The presence of ENE reflects the tumor's ability to metastasize through lymphatics and locally invade the lymph node capsule.[14] Although both phenomena occur in the lymphatic system, these are different biologic processes; the former requires the cancer cell to disseminate through the lymphovascular system, and the latter requires further invasion by tumor cells of perinodal adipose tissue. However, the same mechanism in both locations permits the tumor to increase aggressiveness and metastatic potential. This aggressive tumor biology has been previously associated with dismal patient outcomes.[14-16] Our multivariable analysis indicated that, in cutaneous HNSCC, this might not be the case. A recent study examining the prognostic value of ENE and soft-tissue metastases confirmed that neither ENE nor soft-tissue metastasis was an independent predictor of DSS.[2] The authors explained that the absence of a significant difference in outcome may have been because of a lack of power and, similar to our cohort, they observed higher rates of adjuvant radiotherapy in the ENE-positive patient group, which may have diminished the impact of ENE on DSS. The authors concluded that soft-tissue metastasis is a progression of the same process responsible for ENE. Taken together, these findings suggest that, in cutaneous HNSCC, lymph node ENE represents a histologic continuum of the invasive malignant process and is not an independent biologic feature of a subset of tumors.

The clinical importance of ENE stems from sentinel studies done in the 1990s examining postoperative adjuvant therapy approaches for patients who had been surgically treated for SCC in the upper aerodigestive tract.[17,18] These studies demonstrated that pathologic features such as ENE and positive surgical margins can be used as patient-selection indicators for postoperative concomitant chemoradiotherapy. For mucosal SCC, these criteria are still being used today, and in the latest (eighth) edition of the AJCC staging manual, ENE has been included for the purposes of pN classification.[3] However, ENE was not included in a similar way for other mucosal malignancies, reflecting the understanding that its biologic impact is different in each tumor. In some tumors, such as human papillomavirus-related oropharyngeal SCC, ENE was not even included in the lymph node classification

system, and the AJCC system instead relied mainly on the number of involved lymph nodes.

In the current study, we observed that these features, ie, the number of metastatic lymph nodes and the presence of ENE, are complementary.[19] Hence, a staging system that incorporates both features, such as the RPA-derived model proposed here, will perform better than the existing lymph node classification system. The role of ENE as a prognostic feature is particularly important in cutaneous SCC because the rates of lymph node metastasis are lower than in mucosal SCC, and both therapeutic and elective neck dissections are performed less commonly in cutaneous SCC.

Consistent with published data, our findings indicate a significant correlation between prognosis and the number of lymph nodes combined with ENE.[19] Although we observed no differences in survival between patients without regional metastasis and those who had lymph node metastasis but no ENE, in patients with ENE, we were able to detect a difference in outcome according to the size and number of positive lymph nodes (pN1 vs pN2-pN3). Further analysis showed that the adjusted DSS of pN-positive/ENE-negative patients was similar to that of pN1/ENE-positive patients, hence we grouped these patients into the same risk category. The c-index model comparison indicated that the RPA-derived system had better performance than the AJCC pN classification system.

An important role of the staging system is to provide accurate treatment guidance; this, in turn, will increase the treatment efficacy and minimize toxicity. Our data suggest that, among patients with ENE (currently categorized as N3 by the AJCC pN classification system), those with a single metastatic lymph node have better outcomes than those with multiple lymph node disease. Hence, postoperative chemoradiotherapy in patients with ENE might be reserved for patients who have more advanced regional disease, and the role of concurrent chemotherapy in addition to adjuvant radiotherapy in patients who have a single metastatic lymph node and ENE should be prospectively evaluated.

Although our results represent a single-center cohort of patients, a potential limitation of the current study is the risk of inconsistent surgical technique and processing of the pathologic specimens. For instance, the extent of ENE is inconsistently noted clinically (eg, by imaging or physical examination indicating direct skin invasion) but is not routinely documented in the pathology synoptic report by our dermatopathologists. However, ENE is routinely documented in tertiary centers and cancer centers as part of the staging. Moreover, the yield of neck dissection in our cohort is similar to previously reported mean lymph node yields, with very similar variations in the total number of excised lymph nodes.[20-22]

In conclusion, incorporation of ENE and the number of metastatic lymph nodes into the AJCC pN classification of cutaneous HNSCC enhances the prognostic performance of the staging system. This modification increased the simplicity of the system (3 risk levels rather than 4) and resulted in better risk stratification. The proposed system should be considered in future reviews of the AJCC TNM classification system after external validation.

FUNDING SUPPORT

The authors would like to thank the Moon Shots Program for their support (MA). The authors would also like to thank the NIH/NCI for their support under award numbers P30CA016672 and 1R37CA242006 (MA).

CONFLICT OF INTEREST DISCLOSURES

Renata Ferrarotto reports personal fees from Regeneron-Sanofi, Ayala, Klus, Medscape, Carevive, and Prelude, outside the submitted work. Michael K. Wong reports personal fees from Merck, Castle, Bristol-Myers Squibb, EMD-Serono, Pfizer, and Regeneron, outside the submitted work. Neil D. Gross reports grants from Regeneron, and personal fees from Genzyme, Shattuck Labs, and PDS Biotechnology, outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Moran Amit: Concept; acquisition and performance of the analysis; drafting of the text, tables, and figures; responsibility for the overall content; review of the final document; and approval for publication. **Priyadharsini Nagarajan**, **Anshu Khanna**, **Sameer Kini**, and **Chuan Liu:** Data acquisition, review of the final document, and approval for publication. **Avi Benov**, **Mohamed Aashiq**, **Frederico O. Gleber-Netto**, and **Samantha Tam:** Substantial contributions to the analysis, review of the final document, and approval for publication. **Adel K. El-Naggar**, **Mohamed Aashiq**, **Amy C. Moreno**, **David I. Rosenthal**, **Bonnie S. Glisson**, **Renata Ferrarotto**, **Michael K. Wong**, **Michael R. Migden**, **Guojun Li**, **Ryan P. Goepfer**t, **Randal S. Weber**, and **Jeffrey N. Myers:** Concept, review of the final document, and approval for publication. **Neil D. Gross:** Concept; drafting of the text, tables, and figures; responsibility for the overall content; review of the final document; and approval for publication. **Erez N. Baruch:** Substantial contributions to the analysis, review of the final document, and approval for publication.

REFERENCES

1. Dunne AA, Muller HH, Eisele DW, Kessel K, Moll R, Werner JA. Meta-analysis of the prognostic significance of perinodal spread in head and neck squamous cell carcinomas (HNSCC) patients. *Eur J Cancer*. 2006;42:1863-1868.
2. Hasmat S, Mooney C, Gao K, et al. Regional metastasis in head and neck cutaneous squamous cell carcinoma: an update on the significance of extra-nodal extension and soft tissue metastasis. *Ann Surg Oncol*. 2020;27:2840-2845.
3. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers—major changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual. *CA Cancer J Clin*. 2017;67:122-137.
4. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. *Head Neck*. 2010;32:714-722.
5. Myers JN, Greenberg JS, Mo V, Roberts D. Extracapsular spread. A significant predictor of treatment failure in patients with squamous cell carcinoma of the tongue. *Cancer*. 2001;92:3030-3036.

6. de Juan J, Garcia J, Lopez M, et al. Inclusion of extracapsular spread in the pTNM classification system: a proposal for patients with head and neck carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2013;139:483-488.
7. Wreesmann VB, Katabi N, Palmer FL, et al. Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. *Head Neck*. 2016;38(suppl 1):E1192-E1199.
8. Prabhu RS, Magliocca KR, Hanasoge S, et al. Accuracy of computed tomography for predicting pathologic nodal extracapsular extension in patients with head-and-neck cancer undergoing initial surgical resection. *Int J Radiat Oncol Biol Phys*. 2014;88:122-129.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
10. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol*. 2016;152:419-428.
11. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982;247:2543-2546.
12. Patel SG, Lydiatt WM. Staging of head and neck cancers: is it time to change the balance between the ideal and the practical? *J Surg Oncol*. 2008;97:653-657.
13. Sahin AA, Gilligan TD, Caudell JJ. Challenges with the 8th edition of the AJCC Cancer Staging Manual for breast, testicular, and head and neck cancers. *J Natl Compr Canc Netw*. 2019;17:560-564.
14. Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement. *Arch Otolaryngol Head Neck Surg*. 1994;120:1370-1374.
15. Woolgar JA, Rogers SN, Lowe D, Brown JS, Vaughan ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. *Oral Oncol*. 2003;39:130-137.
16. Barzan L, Talamini R. Analysis of prognostic factors for recurrence after neck dissection. *Arch Otolaryngol Head Neck Surg*. 1996;122:1299-1302.
17. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945-1952.
18. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937-1944.
19. Greenberg JS, Fowler R, Gomez J, et al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. *Cancer*. 2003;97:1464-1470.
20. Bhattacharyya N. The effects of more conservative neck dissections and radiotherapy on nodal yields from the neck. *Arch Otolaryngol Head Neck Surg*. 1998;124:412-416.
21. Agrama MT, Reiter D, Cunnane MF, Topham A, Keane WM. Nodal yield in neck dissection and the likelihood of metastases. *Otolaryngol Head Neck Surg*. 2003;128:185-190.
22. Jose J, Coatesworth AP, MacLennan K. Cervical metastases in upper aerodigestive tract squamous cell carcinoma: histopathologic analysis and reporting. *Head Neck*. 2003;25:194-197.