Original Article

The Prognosis of N2b and N2c Lymph Node Disease in Oral Squamous Cell Carcinoma Is Determined by the Number of Metastatic Lymph Nodes Rather Than Laterality

Evidence to Support a Revision of the American Joint Committee on Cancer Staging System

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BACKGROUND: A study was conducted to assess for prognostic heterogeneity within the N2b and N2c classifications for oral cancer based on the number of metastatic lymph nodes and to determine whether laterality of neck disease provides additional prognostic information. **METHODS:** An international multicenter study of 3704 patients with oral cancer undergoing surgery with curative intent was performed. The endpoints of interest were disease-specific survival and overall survival. Model fit was assessed by the Akaike Information Criterion and comparison of models with and without the covariate of interest using a likelihood ratio test. **RESULTS:** The median number of metastatic lymph nodes was significantly higher in patients with N2c disease compared to those with N2b disease ($P < .001$). In multivariable analyses stratified by study center, the addition of the number of metastatic lymph nodes improved model fit beyond existing N classification. Next, the authors confirmed significant heterogeneity in prognosis based on the number of metastatic lymph nodes (≤ 2, 3-4, and ≥ 5) in patients with both N2b and N2c disease ($P < .001$). A proposed reclassification combining N2b and N2c disease based on the number of metastatic lymph nodes demonstrated significant improvement in prognostic accuracy compared with the American Joint Committee on Cancer staging system, and no improvement was noted with the addition of a covariate for contralateral or bilateral neck disease ($P = .472$). **CONCLUSIONS:** The prognosis of patients with oral cancer with N2b and N2c disease appears to be similar after adequate adjustment for the burden of lymph node metastases, irrespective of laterality. Based on this finding, the authors propose a modified lymph node staging system that requires external validation before implementation in clinical practice. ***Cancer*** **2014;120:1968–74.** © *2014 American Cancer Society.*

KEYWORDS: head and neck neoplasms, oral squamous cell carcinoma, lymph node metastases, cancer staging, prognosis.

INTRODUCTION

The American Joint Committee on Cancer (AJCC) staging manual categorizes all patients with oral squamous cell carcinoma (SCC) and bilateral or contralateral lymph metastases measuring ≤ 6 cm in greatest dimension as having N2c disease, whereas those with ≥ 2 lymph nodes measuring ≤ 6 cm in greatest dimension are classified as having N2b disease.[1] Although the simplicity and consistency across subsites of the current AJCC staging system for head and neck cancer promotes clinical usefulness, it is widely acknowledged that the prognostic performance is suboptimal in selected subgroups of patients.[2-5] Ideally, a staging system separates patients into distinct prognostic categories that are internally

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homogeneous. However, our clinical experience suggests that the N2b and N2c classifications for oral cancer each encompass a wide spectrum of disease severity with variable prognoses.

There is evidence to suggest that the number of metastatic lymph nodes is of prognostic importance beyond that currently recognized by the AJCC.[6-8] We hypothesized that within the N2b and N2c categories, patients have heterogeneous prognoses based on the number of positive lymph nodes. In addition, we hypothesized that the adverse prognosis associated with N2c neck disease reflects the finding that these patients typically have a higher number of metastatic lymph nodes rather than the laterality of neck disease. The primary objective of the current study was to determine whether there is prognostic heterogeneity in the N2b and N2c lymph node categories based on the number of metastatic lymph nodes. Our secondary objective was to determine whether contralateral or bilateral neck disease provides additional adverse prognostic information beyond the number of positive lymph nodes. To achieve this, we used an international cohort of patients with oral SCC who were treated by primary surgery.

MATERIALS AND METHODS

Study Population

This multicenter international study included pooled data from 11 participating cancer centers regarding patients with oral SCC undergoing surgical resection of the primary tumor and neck dissection. We identified 3781 patients treated between 1990 and 2011 as candidates for inclusion in the current study. After excluding cases with neoadjuvant therapy, perioperative mortality, age < 20 years, and missing data regarding covariates of interest, the final study population consisted of 3704 patients. Ethics approval was obtained from local Institutional Review Board committees of participating centers.

Histopathological Analysis

Procedures at participating centers were in accordance with guidelines for the histopathological assessment of head and neck carcinoma, with assessments performed by pathologists experienced in the examination of head and neck tumors. We assumed some heterogeneity in specimen dissection and tissue handling in view of the extended time period of the study as well as the number of involved institutions, surgeons, and pathologists. This reflects the diversity of clinical practice in head and neck oncology and may enhance the generalizability of the results.

Statistical Analysis

Statistical analysis was performed using Stata statistical software (version 12.0 SE; StataCorp LP, College Station, Tex). All statistics were 2-sided and a P value of $< .05$ was considered statistically significant. The clinical endpoints of interest were overall survival (OS) and disease-specific survival (DSS). OS was calculated from the date of surgery to the date of death or last follow-up. For DSS, patients who died of causes other than oral SCC were censored at the time of death. Patients not experiencing these endpoints were censored at the time of last follow-up. Differences in survival were determined using univariate Cox regression analysis, and cumulative failure curves were generated using the Kaplan-Meier method. Other covariates of interest included age, sex, pathologic T category (T1, T2, T3, and T4), surgical margin status (clear, close [$<$ 5 mm], and involved), extracapsular lymph node spread (absent vs present), time period of primary treatment (1990-1999 vs 2000-2011), and postoperative radiotherapy. Multivariable analyses were performed using Cox proportional hazards regression, stratified by study center. Model diagnostics were performed to check for the proportional hazards assumption.

The additional prognostic value of covariates of interest was determined by: 1) tests of statistical significance in multivariable analyses; 2) the Akaike Information Criterion (AIC), which takes into account how well the model fits the data with penalties for model complexity[9]; and 3) comparison with multivariable models with and without the covariate of interest using a likelihood ratio test to determine whether model fit was significantly improved.

RESULTS

Patient Demographics

The study population included 3704 patients with oral SCC, 2395 of whom were male and 1309 of whom were female. The median age was 54 years (range, 20 years-93 years) and the median follow-up was 39 months. Relevant demographic and clinicopathological details are summarized in Table 1. There were 220 patients with N2c disease with a median of 4 metastatic lymph nodes. By comparison, the median number of positive lymph nodes in the 857 patients with N2b disease was 3, with the difference being statistically significant ($P < .001$). Figure 1 shows the distribution of the total number of metastatic lymph nodes in patients with N2c and N2b disease. We found

TABLE 1. Baseline Clinicopathological Data (n=3704).

Variable	No.	%
Age, y		
≤45	987	26.7
46-55	1055	28.5
56-65	923	24.9
≥66	739	19.9
Sex		
Male	2395	64.7
Female	1309	35.3
Pathological T classification		
T1	548	14.8
T2	1111	30.0
T3	500	13.5
T4	1545	41.7
Pathological N classification		
N0	1973	53.3
N1	581	15.7
N2a	63	1.7
N2b	857	23.1
N2c	220	5.9
N3	10	0.3
TNM stage		
I	416	11.2
II	645	17.4
III	549	14.8
IV	2094	56.5
Adjuvant radiotherapy		
No	1114	30.1
Yes	2587	69.9
Time period of primary treatment		
1990-1999	778	21.0
2000-2011	2926	79.0
Extent of neck dissection		
Selective (I-III or I-IV)	1653	59.2
Comprehensive (I-V)	565	20.2
Bilateral	574	20.6
Study center		
Brescia, Italy	74	2.0
Camargo, São Paulo, Brazil	252	6.8
Cologne, Germany	238	6.4
MSKCC, New York, US	233	6.3
Petach Tikva, Israel	61	1.6
São Paulo, Brazil	236	6.4
SHNCI, NSW, Australia	302	8.2
Southern Illinois	63	1.7
CGMH-Taoyuan, Taiwan	1223	33.0
Tata Memorial Hospital, India	911	24.6
Tel Aviv, Israel	111	3.0

Abbreviations: CGMH, Chang Gung Memorial Hospital; MSKCC, Memorial Sloan-Kettering Cancer Center; NSW, New South Wales; SHNCI, Sydney Head and Neck Cancer Institute.

that 58% of patients with N2b disease had ≥ 3 positive lymph nodes compared with 84% of the N2c subgroup.

Survival Analyses

As shown in Table 2, the total number of metastatic lymph nodes provided additional statistically significant prognostic information in multivariable analyses for both DSS and OS. On average, each additional positive lymph node resulted in a 3% increased risk of death due to oral SCC ($P < .001$). Similar results were obtained when the number of positive lymph nodes was analyzed after logarithmic transformation to take into account the right skewed distribution of data ($P < .001$). We compared multivariable models with and without the number of metastatic lymph nodes and found significant improvement in model fit based on a lower AIC and the likelihood ratio test for both DSS ($P < .001$) and OS ($P < .001$), thereby supporting the hypothesis that it provides additional prognostic value.

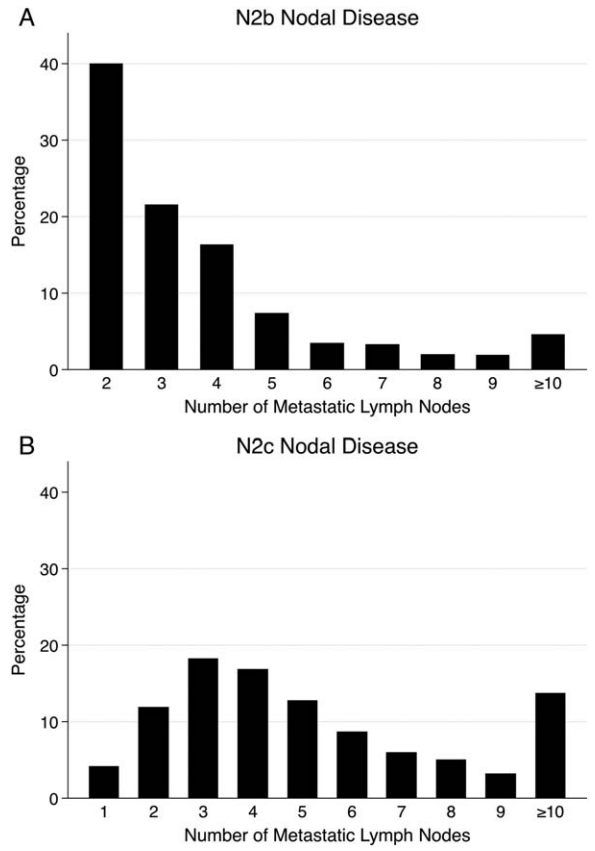

Figure 1. The distribution of the total number of metastatic lymph nodes is shown in patients with (A) N2b and (B) N2c lymph node disease, demonstrating a greater burden of lymph node metastases in patients with N2c oral squamous cell carcinoma.

Next, we demonstrated significant heterogeneity in prognosis based on the total number of metastatic lymph nodes in patients with both N2b and N2c disease (Fig. 2). In patients with N2b disease, the risk of death due to oral SCC for patients with 3 to 4 positive lymph nodes and ≥ 5 positive lymph nodes was 57% and 109% higher, respectively, than in patients with 2 positive lymph nodes ($P < .001$). Similarly, for patients with N2c disease, the risk of death due to oral SCC with 3 to 4 positive lymph

TABLE 2. Multivariable Analysis of DSS and OS to Determine Prognostic Value of Number of Metastatic Lymph Nodes[a]

	DSS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
No. of metastatic lymph nodes[b]	1.03 (1.02-1.05)	<.001	1.03 (1.02-1.04)	<.001
Age (10-y increment)	1.06 (0.99-1.13)	.113	1.20 (1.13-1.26)	<.001
Sex				
Male	Referent		Referent	
Female	0.85 (0.68-1.05)	.134	0.85 (0.71-1.01)	.067
Pathological T classification				
T1	Referent		Referent	
T2	1.84 (1.30-2.59)	.001	1.84 (1.30-2.59)	.001
T3	2.64 (1.83-3.81)	<.001	2.64 (1.83-3.81)	<.001
T4	3.30 (2.32-4.69)	<.001	3.30 (2.32-4.69)	<.001
Pathological N classification				
N0	Referent		Referent	
N1	1.86 (1.42-2.44)	<.001	1.60 (1.30-1.98)	<.001
N2a	1.06 (0.54-2.07)	.861	1.07 (0.62-1.84)	.809
N2b	2.62 (2.00-3.43)	<.001	2.03 (1.64-2.51)	<.001
N2c	2.63 (1.85-3.74)	<.001	1.87 (1.39-2.52)	<.001
N3	2.40 (0.92-6.23)	.073	2.11 (0.95-4.70)	.067
ECS				
Absent	Referent		Referent	
Present	1.64 (1.32-2.05)	<.001	1.59 (1.33-1.91)	<.001
Excision margin				
Clear	Referent		Referent	
Close (<5 mm)	1.26 (0.99-1.61)	.058	1.28 (1.05-1.56)	.013
Involved	2.17 (1.70-2.78)	<.001	2.16 (1.74-2.69)	<.001
Adjuvant therapy				
Nil	Referent		Referent	
Adjuvant PORT ± other	1.06 (0.83-1.36)	.636	0.99 (0.82-1.19)	.897
Decade of primary treatment				
1990-1999	Referent		Referent	
2000-2011	0.67 (0.54-0.84)	.001	0.81 (0.68-0.96)	.017

[a] Cox proportional hazards regression models stratified by study center.
[b] Similar results were obtained when the number of metastatic lymph nodes was analyzed as a continuous variable after logarithmic transformation to account for the right skewed distribution.
Abbreviations: 95% CI, 95% confidence interval; DSS, disease-specific survival; ECS, extracapsular spread; HR, hazards ratio; OS, overall survival; PORT, postoperative radiotherapy.

nodes and ≥ 5 positive lymph nodes was 104% and 159% higher, respectively, than in patients with 1 to 2 positive lymph nodes ($P = .001$). Similar results were obtained for OS, as shown in Figure 2.

As shown in Figure 2, patients with N2b and N2c disease appeared to have a similar prognosis when stratified by the number of metastatic lymph nodes. This was confirmed on formal testing with univariate Cox regression stratified by study center, with no statistically significant difference in DSS noted between patients with N2b and N2c disease with ≤ 2 positive lymph nodes ($P = .829$), 3 to 4 lymph nodes ($P = .838$), or ≥ 5 lymph nodes ($P = .359$). Again, similar results were found for OS. Based on this, we assessed a reclassification of N2b and N2c disease into 3 prognostic groups based on the number of positive lymph nodes. Figures 3A and 3B show these reclassified groups in combination with N0, N1, N2a, and N3 lymph node categories. It is interesting to note that patients with ≥ 5 metastatic lymph nodes have a prognosis comparable to patients with N3 disease. An exploratory multivariable analysis suggested this may be due to an increased risk of distant metastatic failure, which was reported to have occurred in 14% of patients with ≥ 5 lymph nodes, 9% of patients with 3 to 4 lymph nodes, and 6% of patients with 1 to 2 lymph nodes ($P < .001$). In contrast, the rate of distant failure was 2.4% in patients with N0 disease. There were no documented distant metastases in those with N3 disease, presumably due to earlier locoregional failure; however, this was a small group of patients (10 patients).

The revised classification for N2b and N2c disease provided improved model fit and prognostic accuracy compared with the current AJCC staging of this patient group based on a lower AIC and the likelihood ratio test for both DSS ($P < .001$) and OS ($P < .001$). Finally, the addition of a covariate for contralateral or bilateral neck

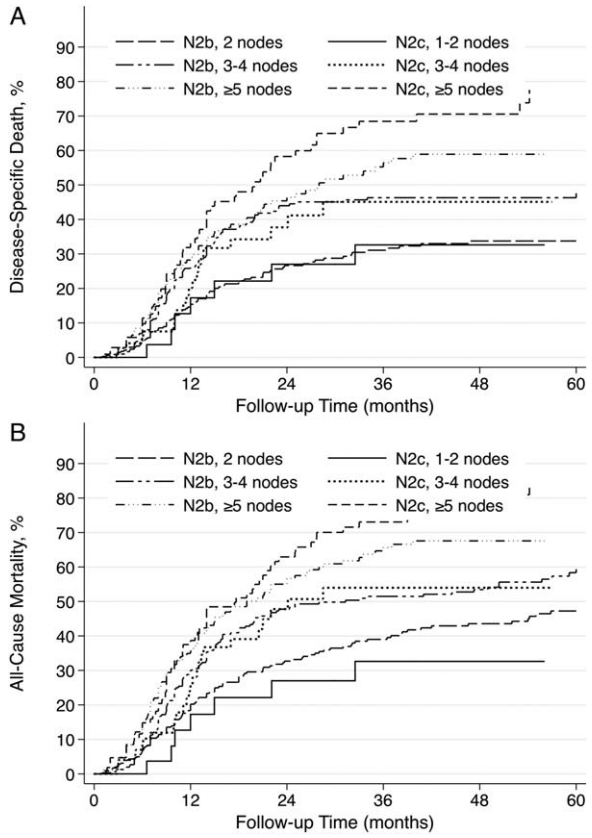

Figure 2. Kaplan-Meier plots of (A) cumulative disease-specific failure and (B) cumulative all-cause mortality are shown based on the number of metastatic lymph nodes for patients with pathologic N2b and N2c disease.

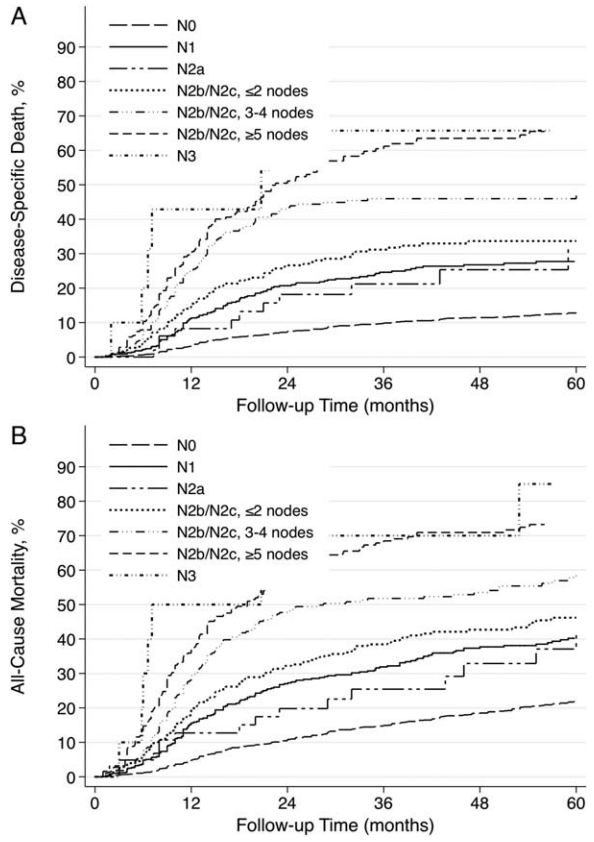

Figure 3. Kaplan-Meier plots of (A) cumulative disease-specific failure and (B) cumulative all-cause mortality are shown in a reclassified lymph node staging system combining patients with N2b and N2c disease after stratification by the number of positive lymph nodes.

disease to the proposed staging system failed to reach statistical significance ($P = .469$) and did not improve model fit (higher AIC and likelihood ratio test, $P = .472$) for DSS. Similar results were found for OS.

DISCUSSION

Since the first edition of the AJCC staging system for oral SCC was published in 1977, bilateral or contralateral lymph node disease has been believe to portend a grave prognosis in patients with oral SCC irrespective of lymph node burden based on the size and number of metastatic lymph nodes.[10] Furthermore, no distinction in prognosis is made between patients with multiple ipsilateral positive lymph nodes irrespective of the number of involved lymph nodes, despite evidence to suggest that this is a heterogeneous group.[6-8] This prompted the current multicenter international study, which demonstrated significant variability in prognosis in patients with both N2b and N2c disease based on the number of metastatic lymph nodes. In addition, we demonstrated that once this is taken into account, the laterality of lymph node disease is not an adverse prognostic factor. Based on this, we suggest a reclassification of N2b and N2c disease based on the number of metastatic lymph nodes that better stratifies these patients into distinct prognostic groups.

We demonstrated that the number of metastatic lymph nodes provides significant additional prognostic value and improved model fit in multivariable analyses. This supports the belief that the existing staging system does not adequately account for the burden of lymph node disease based on number of metastases, and incorporation of this information may enhance prognostic performance. It is interesting to note that the data from the current study suggest that the adverse prognosis associated with increasing number of metastatic lymph nodes is due in part to a propensity for distant metastatic failure, which may have implications for future studies of systemic therapy in patients with oral SCC.

Consistent with our study hypothesis, we demonstrated substantial variation in survival based on the

number of metastatic lymph nodes in patients with both N2b and N2c disease. We elected to classify patients into 3 categories based on tertiles ($\leq$ 2 lymph nodes, 3-4 lymph nodes, and $\geq$ 5 lymph nodes), which provided a relatively even distribution of patients between the 3 groups. However, it is important to note that this was arbitrary and exploratory analyses confirmed that the findings were robust to stratification based on different cutoff values for number of lymph nodes and groups (data not shown).

Finally, we were able to demonstrate that the adverse prognosis associated with N2c disease compared with N2b disease appears to reflect a tendency toward high lymph node disease burden rather than laterality. First, we confirmed that, on average, patients with N2c disease were likely to have a greater number of involved lymph nodes than those with N2b disease. Second, we demonstrated that the prognosis of N2b and N2c disease is similar once patients are stratified based on the number of positive lymph nodes. Third, we assessed a proposed combined reclassification of N2b and N2c disease into 3 prognostic groups based on the number of positive lymph nodes. This demonstrated improved model fit and prognostic accuracy compared with the current AJCC staging of these patients. It is important to note that once the number of metastatic lymph nodes was adequately accounted for, the presence of contralateral or bilateral neck disease appeared to provide no additional prognostic value.

The current AJCC classification of lymph node disease is based largely on concepts established 40 years ago by Chandler et al[11] and Spiro et al[12] at Memorial Sloan-Kettering Cancer Center and Lindberg at The University of Texas MD Anderson Cancer Center,[13] demonstrating predictable patterns of stepwise lymph node drainage with rare instances of isolated contralateral lymph node metastases. Although this remains true, more recent data based on lymphoscintigraphy for sentinel lymph node biopsy have demonstrated that unpredictable lymphatic drainage patterns are more common than previously recognized. Therefore, the presence of a contralateral lymph node metastasis may not represent a more aggressive or advanced disease biology and, if detected and treated early, the patient's prognosis should be similar to that of patients with ipsilateral lymph node disease.

The current study has several limitations. First, it was a retrospective analysis and treatment was not assigned in a randomized fashion. Because an ideal staging system should be useful for guiding treatment decisions as well as prognostication,[3] further research is needed to determine whether the results of this study extend beyond prognostic value and whether selected subgroups of patients should have their treatment deescalated or intensified based on our lymph node reclassification. Second, this study was based on pathological lymph node staging and future studies are needed to determine whether the results are applicable to clinical staging. The major strength of the current study stems from the use of individual pooled data from 11 comprehensive cancer centers worldwide, which should increase the robustness and generalizability of the findings. Despite this, validation using an external patient cohort remains an important step before considering implementation in clinical practice.

The results of the current study indicate that the accepted dogma that N2c lymph node disease portends a less favorable prognosis than N2b disease reflects a tendency toward greater lymph node burden, as defined by the number of metastatic lymph nodes, rather than laterality of disease. This is not unexpected given that the laterality of disease is likely to reflect the location of the primary tumor and lymph node drainage patterns rather than more biologically aggressive or advanced disease per se. Furthermore, we demonstrated improved prognostic performance with a proposed staging reclassification of these patients based on the number of metastatic lymph nodes. Because arguably the most important goal of any staging system is the ability to accurately predict prognosis, a modification to the AJCC lymph node staging system based on these results appears appropriate assuming they can be validated in an external patient cohort. Although these results also raise the possibility of treatment escalation and deintensification in selected patients, this should be limited to the setting of a clinical trial to establish safety and efficacy given the retrospective nature of this analysis.

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