ORIGINAL ARTICLE

IMPACT OF NODAL RATIO ON SURVIVAL IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

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Abstract: *Background.* The association between nodal ratio and survival has not been assessed in squamous cell carcinomas of the head and neck.

Methods. This is a population-based analysis, using the Surveillance, Epidemiology, and End-Results database, to determine whether nodal ratio impacts survival in patients with oral cavity squamous cell carcinoma.

Results. Between 1988 and 2005, 2955 new diagnoses of N_1 or N_2 squamous cell carcinoma of the oral cavity were identified. The mean nodal ratio was 16.9%. Nodal ratio was found to be strongly statistically associated with overall survival in both univariate and multivariate analyses. Patients could be stratified into low- (0% to 6%), moderate- (6% to 12.5%), and high-risk (>12.5%) groups based on nodal ratio.

Conclusions. In patients with squamous cell carcinoma of the oral cavity, an increased nodal ratio is a strong predictor of decreased survival. Risk of death can be stratified based on nodal ratio. © 2009 Wiley Periodicals, Inc. *Head Neck* **31:** 1129–1136, 2009

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Oral cavity squamous cell carcinoma is a significant national and international public health issue and is responsible for over 7000 deaths annually in the United States.[1,2] The National Cancer Institute predicted that, within the United States, 34,360 new cases of cancers of the oral cavity and pharynx would be diagnosed in 2007.[2] Treatment protocols and prognosis vary widely, especially for more advanced tumors, and are based almost exclusively on the stage of cancer at diagnosis.[3–5] Occult metastasis to the neck may occur in up to 34% of patients with squamous cell carcinomas of the oral cavity in the absence of clinical or radiographic evidence of regional spread.[6] As a result, neck dissections are often performed electively for many tumors of the oral cavity.

The discovery of regional spread in patients with oral cavity carcinoma begs the question of the extent of regional dissection that occurred. It follows reason that discovery of a positive node in a more limited regional dissection may imply the presence of residual disease in the neck; a more extensive dissection may provide for more certainty that this single focus of metastatic disease is truly isolated. Thus, the ratio between metastatic nodes and examined lymph nodes (referred to as nodal ratio throughout this article) may be of prognostic importance in head and neck cancer. The extent of regional nodal dissection has been documented to be of importance in gastric cancer, endometrioid uterine cancer, and colorectal carcinoma, with an increase in survival shown with the resection of higher numbers of regional nodes.[7–16] No such documentation has yet been published in the head and neck.

The primary objective of the study was to determine, using population-based data, whether nodal ratio impacted survival in patients with node-positive (N_1 or N_2) squamous call carcinoma of the oral cavity.

MATERIALS AND METHODS

The Surveillance, Epidemiology, and End-Results (SEER) database is a population-based cancer registry that captures 17 distinct population groups in 198 counties in the United States, namely the states of Connecticut, Kentucky, California (excepting the urban areas listed below), New Jersey, Louisiana, Hawaii, Iowa, New Mexico, and Utah; the metropolitan areas of Detroit, Atlanta, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, and San Jose-Monterey; the Alaskan Native registry; and 10 predominantly African-American counties in rural Georgia. This database represents approximately 26% of the overall United States population, and contains information on 7,032,878 cases of cancer diagnosed since 1973.[2] In addition to cancer incidence and prevalence, information regarding staging and treatment is included within the fields of this database. With each subsequent modification of the database, more information is added, allowing the database to be used for large-scale, population-based studies.

Cases of oral cavity carcinoma diagnosed between 1988 and 2005 were extracted from the SEER-17 database. The data were standardized according to schema published second and third editions of the *International Classification of Disease for Oncology* (ICD-O-2 and ICD-O-3). Cancers were limited to the oral cavity, which was defined as the oral tongue (C02.0–02.3, C02.8–02.9), upper and lower gingiva (C03.0–03.9), floor of mouth (C04.0–04.9), hard palate (C05.0, C05.8–05.9), buccal mucosa (C06.0), oral vestibule (C06.1), retromolar trigone (C06.2), and areas labeled "unspecified mouth" or "unspecified oral cavity" (C06.8–06.9). Because the pathophysiology of cancers of the lip is felt to be different to that of cancers of the remainder of the oral cavity, lip subsites were excluded in this study. Tumors originating in the oropharynx were also excluded.

Histology was limited to squamous cell carcinoma (M8052–8078 in the ICD-O-2 morphologic codes). Verrucous carcinoma and carcinomas in situ were excluded. Records examined were limited to those of patients with N_0-N_2 regional disease. Oral cavity tumors as second- or third-primary tumors were excluded. The number of regional lymph nodes identified at regional dissection and the number of positive lymph nodes are both available within the SEER database. The type of neck dissection performed (eg, selective, modified radical, or radical), however, is not.

"Neck dissection" is used throughout the manuscript to encompass both the surgical procedure of regional lymphadenectomy in the neck as well as the pathologic review of that lymphadenectomy. The extent of neck dissection examined, as a result, comprises the extent of surgical resection as well as the thoroughness of pathologic review. SEER does not contain enough data to allow the separation of these 2 steps in the diagnosis and treatment of patients with carcinoma of the oral cavity.

Data extracted from the SEER database was analyzed using SAS version 9.1 (SAS Institute, Cary, NC) and R version 2.1.1. Descriptive statistics for demographic and clinical factors were generated. Survival times were directly available from the SEER database. Survival curves were generated using the Kaplan-Meier method. Univariate Cox Proportional-Hazards regression was used to test the association of Nodal Ratio with Overall Survival, as a continuous predictor. Potential covariates including Age at diagnosis, T-stage, N-stage, race, sex, and surgery site were also tested for association with survival outcomes. Nodal ratio was adjusted by statistically significant covariates in a multivariate Cox proportional hazards model.

To create risk groups, we used the "maximally selected rank statistic" method described in Lausen and Schumacher[17] to select an

Table 1. Patient demographics.

Variable	No.	%
Sex		
Female	849	28.7
Male	2106	71.3
Race		
Black	343	11.6
Other	182	6.2
White	2424	82.2
Site		
Floor of mouth	640	21.7
Gum and other mouth	653	22.1
Tongue	1662	56.2
T		
T1	734	24.8
T2	1075	36.4
T3	340	11.5
T4	806	27.3
N		
N1	1066	36.1
N2	1889	63.9
Radiation		
Postoperative	2219	75.1
None	600	20.3
Preoperative	93	3.1
Pre- and postoperative	14	0.5
Intraoperative	6	0.2
Unknown sequence	23	0.8

Demographic distribution of the patient population.

optimum cut-point. Briefly, the algorithm located the cut-point that maximized the log-rank test statistic. The resulting log-rank p value was then adjusted for multiple testing. All statistical tests were 2-sided and p values $\leq .05$ were considered statistically significant.

RESULTS

Patient Demographics. Between 1988 and 2005, 2955 new cases of $T_{1\text{-}4}N_{1\text{-}2}$ oral cavity squamous cell carcinoma were identified in the SEER database. Of these, 2106 (71.3%) were male and 2424 (82.2%) were white. The majority (63.9%) had N_2 disease; the remainder were N_1. Six hundred patients (20.3%) were not treated with adjuvant radiotherapy; 2219 (75.1%) underwent postoperative adjuvant therapy. The remaining patients had brachytherapy, neoadjuvant radiotherapy, or a combination of surgery and radiotherapy in an unknown sequence. Patient demographics are summarized in Tables 1 and 2.

The mean number of nodes assessed was 26.4 in patients with N_1 disease and 32.5 in patients with N_2 disease, with a range in both groups from 1 to 89 nodes removed. On average, patients had 3.33 nodes positive, with a mean nodal ratio of 16.9% and a median nodal ratio of 9.1% (range, 1.1% to 100%). Average follow-up in this set of patients was 33.1 months (range, 0–205 months).

Overall Survival. In the entire cohort of patients, median survival was 30 months from diagnosis (95% CI: 28–33 months), with 37.4% of patients alive at 5 years (95% CI: 35.5% to 39.5%). As expected, increasing T and N classification correlated with worse survival, as did the female sex (35.6% vs 38.1% 5-year survival, HR 1.13 [95% CI: 1.02–1.26], $p = .02$), black race when compared with white race (23.7% vs 32.3% 5-year survival, HR 1.42 [95% CI: 1.24–1.62], $p < .0001$), and site of primary tumor (44.5% for tongue, 25.7% for floor of mouth [HR 1.61, 95% CI: 1.44–1.81], and 31.3% for gingival and other oral cavity tumors [HR 1.49, 95% CI: 1.32–1.67]; $p < .0001$ when compared against tongue). In addition, increased age at diagnosis correlated with decreased survival (HR 1.019; 95% CI 1.015–1.023, $p < .0001$), as did absolute number of positive nodes (HR 1.049; 95% C 1.040–1.058, $p < .0001$). These results are summarized in Table 3.

Nodal Ratio. In univariate analysis, nodal ratio was significantly correlated with survival (HR 1.043 [95% CI: 1.022–1.065], $p < .0001$). Because nodal ratio ranges from 0% to 100%, the reported hazard ratio compares patients with a 10% difference in nodal ratio. In multivariate analysis, all the mentioned covariates remained statistically significant with the exception of gender ($p = .23$); removal of sex from the analysis did not change the significance of the effect of nodal ratio on survival (adjusted HR 1.051 [95% CI: 1.029–1.073], $p < .0001$).

Given this significant association between nodal ratio and overall survival, we attempted to determine a cut-point nodal ratio which

Table 2. Patient demographics.

Variable	Mean	Std Dev	Range
Age at diagnosis, y	59.41	12.46	20–99
Number of positive nodes	3.33	4.19	1–90
N-ratio, %	16.9	21.5	1.1–100

Summary statistics for the patient population.

Table 3. Cox proportional hazards results.

Parameter	Comparison*	Univariate		Multivariate	
		p value	HR (95% CI)	*p*-value	HR (95% CI)
N-ratio	–	<.0001	1.043 (1.022–1.065)	<.0001	1.051 (1.029–1.073)
T	Overall	<.0001		<.0001	
	T_2 vs T_1	<.0001	1.45 (1.26–1.67)	<.0001	1.40 (1.22–1.61)
	T_3 vs T_1	<.0001	1.96 (1.65–2.33)	<.0001	1.94 (1.63–2.31)
	T_4 vs T_1	<.0001	2.37 (2.06–2.72)	<.0001	2.01 (1.73–2.34)
N	N_2 vs N_1	<.0001	1.28 (1.15–1.42)	<.0001	1.25 (1.12–1.39)
Sex	Female vs Male	.02	1.13 (1.02–1.26)	N/A	N/A
Race	Overall	<.0001		<.0001	
	Black vs White	<.0001	1.42 (1.24–1.62)	<.0001	1.38 (1.2–1.59)
	Other vs White	.14	1.16 (0.95–1.41)	.42	1.08 (0.89–1.32)
Site	Overall	<.0001			
	Floor of Mouth vs Tongue	<.0001	1.61 (1.44–1.81)	<.0001	1.41 (1.25–1.59)
	Gum and other mouth vs Tongue	<.0001	1.49 (1.32–1.67)	.02	1.18 (1.03–1.35)
Age at diagnosis	–	<.0001	1.019 (1.015–1.023)	<.0001	1.018 (1.013–1.022)
Number of positive nodes	–	<.0001	1.049 (1.040–1.058)	N/A	N/A

Predictors of survival in univariate and multivariate analysis.
**T, N, sex, race, and site are categorical variables; number of positive nodes, N-ratio, and age at diagnosis were treated as continuous variables.*

would allow division of patients into high- and low-risk groups. Using maximally selected rank statistical methods, with adjustment of the *p*-value for multiple testing, we found that 2 cut-offs maximized the log-rank statistic. Patients with a nodal ratio less than 6% fared the best (47.0% 5-year survival), followed by patients with a nodal ratio between 6% and 12.5% (37.5%, HR 1.19 [95% CI: 1.04–1.37]); patients with a nodal ratio of 12.5% or higher fared the worst (29.5%, HR 1.55 [95% CI: 1.37–1.75], overall adjusted p value $< .0001$). In multivariate analysis, adjusting for all covariates except gender, the significance of these cut-points remains highly significant ($p < .0001$). (see Figure 1 and Table 4).

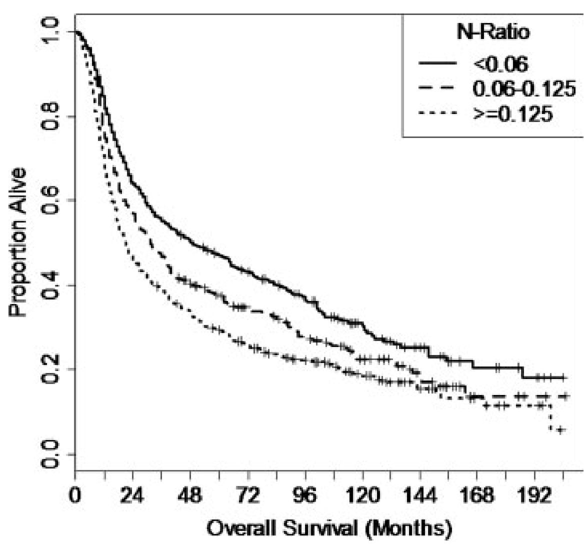

FIGURE 1. Kaplan-Meier survival curve for squamous cell carcinoma of the oral cavity by nodal ratio. The differences are statistically significant.

DISCUSSION

Nodal metastasis is consistently one of the strongest determinants of survival in patients with oral cavity cancer.[18,19] In addition, occult metastasis to cervical lymph nodes is one of the major prognostic factors for survival in those patients with clinically negative necks.[18] Neck dissections should allow for correct staging for prognosis and as well as determination of the need for adjuvant therapies.[18,20,21] However, an adequate number of nodes need to be removed in order to correctly stage patients. Agrama et al have demonstrated, also using SEER registry data, that the likelihood of finding cervical metastases in T_1 and T_2 patients with squamous cell carcinomas of the head and neck increased

Table 4. N-ratio risk stratification.

Parameter	Comparison*	*p* value	Adjusted hazard ratio (95% CI)
N-ratio risk group	Overall	<.0001	
	Moderate vs. Low	.01	1.19 (1.04–1.37)
	High vs. Low	<.0001	1.55 (1.37–1.75)

Multivariate analysis of N-ratio groupings.
**High-risk = N-ratio ≥12.5%; Moderate-risk = N-ratio 6–12.5%; Low-risk = N-ratio <6%*

with the nodal yield in neck dissection specimens.[22] Compared with a nodal yield of less than 13 nodes, cervical metastases were more likely to be found for any nodal yield greater than 20. A similar relationship has also been found with other solid cancers.[23]

The prognostic implication of neck dissections, therefore, may be limited by the extent of the regional dissection undertaken. It is unclear whether the prognostic value of a single lymph node in a limited neck dissection is the same as that of a single lymph node found as part of a more comprehensive neck dissection. Studies in colorectal, breast, gastric, and endometrioid uterine cancer have reported a positive association between the number of nodes dissected and survival.[7–16,23–28] On the basis of these and similar results, various guidelines for the minimum number of nodes removed have been proposed in the colon cancer literature.[12–14,29–34]

The improved prognosis that results from increasing nodal yield may be related to phenomenon of stage migration, a change in the distribution of cancer stagings resulting from either a change in the staging system or the development of new technology allowing more sensitive detection of tumor spread.[12] With a higher number of nodes assessed, there is a lower risk that nodal metastases are missed. As a result, nodal ratio, or the ratio between metastatic and examined lymph nodes, may be an important prognostic variable in a number of other solid cancers including gastric cancer, breast cancer, and uterine cancer.[9–12,15,22,26,28,35–38]

Although there is, therefore, increasing recognition of the importance of a minimal acceptable number of lymph nodes retrieved and examined in other solid cancer sites, there currently is no literature in the head and neck to make recommendations for such a standard. The current study sought to answer this question in patients with lesions in the oral cavity.

The SEER database is a publicly available database of all cancer diagnoses in 17 different population groups within the United States. The demographics of the patients within the database approximate, but do not exactly match, the overall demographics of the U.S. population as a whole,[39] but the database does allow for robust population-based analyses to be performed.

In patients with squamous cell carcinoma of the oral cavity, nodal ratio is a very important prognostic indicator of survival. As nodal ratio increases, survival decreases; this is most marked as nodal ratio crosses 2 cutoffs: Low-risk patients have a nodal ratio of 6% or less. Moderate risk lies between 6% and 12.5%; patients with a nodal ratio higher than 12.5% fare the worst. It should be noted that, on average, patients underwent neck dissections with higher nodal ratios than this cut-point and therefore fell within the high-risk group.

It also bears mention that it is not possible, in this study, to differentiate between the extent of neck dissection and the extent of pathologic review of that regional dissection. A comprehensive neck dissection is not just a function of the extent of surgery performed but also includes the extent to which the specimen is subjected to pathologic examination. A more complete neck dissection with a cursory review of the dissection specimen by the pathologist would render the same results in this article as a less-than-complete regional dissection with a thorough review. What is, however, borne out is that the number of regional lymph nodes assessed to render the patient N_1 significantly impacts on survival. This may be because tumor is physically left behind in the neck, or because a less-than-complete neck dissection effectively understages a patient, preventing additional treatment from being delivered.

Although there are some authors who advocate more limited neck dissections for patients with squamous cell carcinoma of the oral cavity,[40,41] these population-based results appear to suggest otherwise. This study may also help determine the need for further adjuvant treatment in patients with incidentally noted single-positive lymph nodes. However, since it is impossible to distinguish in the SEER database patients who are initially diagnosed as N_0 and found to be N_+ on staging neck dissection (all staging information in SEER is pathologic), this question deserves further study.

Since the type of neck dissection performed (ie, radical vs modified radical vs selective neck dissection) is not available in the SEER database, this article cannot make recommendations or suggestions based on this classification scheme. However, even if this information were available it would likely be less reliable than absolute nodal counts due to variability in surgical technique, classification, and comprehensiveness of pathologic assessment of neck dissection specimens. There does exist the possibility, however, that the survival advantage afforded by neck dissections with a large number of nodes assessed may be influenced by either costructure ablation (eg, sternocleidomastoid muscle or internal jugular vein), or center expertise (including the experience of the surgeon and/or pathologist), and thus the number of lymph nodes assessed may in fact be a surrogate for other factors associated with improved survival. However, studies from other solid tumor sites have shown that absolute nodal count and nodal ratio are independent prognostic predictors of survival on multivariable analysis.

Laterality of regional dissection was not evaluated in this study. By convention, many midline oral cavity tumors warrant bilateral neck dissection, which automatically increases the number of nodes identified and may artificially decrease nodal ratio. However, the discovery of a contralateral node in such a patient would already increase their N classification; a bilateral neck dissection with the discovery of only ipsilateral nodes decreases it, and, given a therefore lower nodal ratio, does so with more confidence that there is no hidden burden of regional disease.

N_3 patients were specifically excluded from this study because it becomes increasingly difficult to determine whether a nodal metastasis of greater than 6 cm in size is a single metastasis or multiple, matted metastases. N_0 patients, as well, were excluded because the concept of nodal ratio becomes moot in these patients. In addition, there are specific risk factors that have been identified with respect to tumor characteristics and regional metastases that predispose to a worse prognosis. Specifically, perineural and lymphovascular invasion in the primary tumor, and extracapsular extension in regional metastases all portend a worse prognosis and may be indications for the addition of adjuvant radiotherapy.[42] This information, unfortunately, cannot be captured from SEER. The most recent iteration of the SEER database (patients diagnosed after 2004) will include data on extracapsular extension in head and neck patients. At this point, however, there is no meaningful follow-up in the database on these patients. Whether the prognostic power of these pathologic risk factors is borne out in population-based studies, and whether it impacts on the results presented here, deserves future examination. There may be a confounding between nodal ratio and absolute number of nodes in this article, given that both are significantly correlated with survival in univariate analysis. Because nodal ratio includes total number of positive nodes in its calculation, it is difficult to control for this confounding. However, using the Aikake information criterion,[43] the model fit between both predictors is approximately equivalent. This is, however, an indirect test at best.

This article, like any population-based study, is limited by the information captured in large population based databases. The data examined represent a relatively heterogeneous pool of patients from divergent sites within the United States. Treatment protocols obviously vary across institutions, and the reasons behind the withholding of radiation from some patients are not evident. Although this allows for a modicum of bias, the bias is diluted by the size of the examined cohort and the variety of sites at which treatment is rendered. The fact that this article incorporates a significant amount of data from across various treatment sites, ethnic groups, socioeconomic classes, and ages lends credibility to the generalizability of its conclusions. However, we have undertaken a separate study to validate these findings using patients treated at the University of Toronto. This awaits publication.

Population-based studies are also, by definition, retrospective and nonrandomized. In addition, only information entered into SEER by the cancer registrars throughout the 17 sites is included in the database. It is also impossible to distinguish in the SEER database patients who are initially diagnosed as N_0 and found to be N_1 on staging neck dissection. The incidental finding of nodal disease in this patient significantly decreases their overall and cause-specific survival, and management of that dilemma remains unclear. Recurrence rates alone also cannot be captured from the information available in SEER, which is also an important endpoint. Some of these limitations can be addressed with large multi-institutional series with detailed retrospective or prospective databases.

CONCLUSIONS

In patients with squamous cell carcinoma of the oral cavity, the ratio of positive nodes to the number of nodes examined, or nodal ratio, is a strong predictor of overall survival, independent of tumor size or extent, extent of regional metastasis, age, race, or sex. Further exploration of this concept using institutional data and randomized prospective trials regarding treatment protocols are warranted.

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