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 N1 or N2 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.

Keywords: oral cavity; squamous cell carcinoma; neck dissection; nodal ratio; nodal density

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 meta-
static 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 impor-
tance 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 (N1 or N2) squamous
cell 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 popula-
tion 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 approx-
imately 26% of the overall United States popula-
tion, and contains information on 7,032,878
cases of cancer diagnosed since 1973.2 In addi-
tion to cancer incidence and prevalence, infor-
mation 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 data-
based 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 remain-
der of the oral cavity, lip subsites were excluded
in this study. Tumors originating in the orophary-
ynx were also excluded.

Histology was limited to squamous cell carci-
noma (M8052–8078 in the ICD-O-2 morphologic
codes). Verrucous carcinoma and carcinomas in
situ were excluded. Records examined were lim-
ited to those of patients with N0-N2 regional dis-
estease. Oral cavity tumors as second- or third-
primary tumors were excluded. The number of
regional lymph nodes identified at regional dis-
section and the number of positive lymph nodes
are both available within the SEER database.
The type of neck dissection performed (eg, selec-
tive, modified radical, or radical), however, is
not.

“Neck dissection” is used throughout the
manuscript to encompass both the surgical pro-
cedure of regional lymphadenectomy in the neck
as well as the pathologic review of that lymph-
adenectomy. 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 sta-
tistics for demographic and clinical factors were
generated. Survival times were directly avail-
able 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 statisti-
cally significant covariates in a multivariate Cox
proportional hazards model.

To create risk groups, we used the “maxi-
mally selected rank statistic” method described
in Lausen and Schumacher17 to select an
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 \(< .05 \) were considered statistically significant.

RESULTS

Patient Demographics. Between 1988 and 2005, 2955 new cases of \( T_{1,4}N_{1,2} \) 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\% CI: 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>
<thead>
<tr>
<th>Table 2. Patient demographics.</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
</tr>
<tr>
<td>Number of positive nodes</td>
</tr>
<tr>
<td>N-ratio, %</td>
</tr>
</tbody>
</table>

Summary statistics for the patient population.
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).

**DISCUSSION**

Nodal metastasis is consistently one of the strongest determinants of survival in patients with oral cavity cancer. In addition, occult metastasis to cervical lymph nodes is one of the major prognostic factors for survival in those patients with clinically negative necks. Neck dissections should allow for correct staging for prognosis and as well as determination of the need for adjuvant therapies. 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 T1 and T2 patients with squamous cell carcinomas of the head and neck increased

![Figure 1. Kaplan-Meier survival curve for squamous cell carcinoma of the oral cavity by nodal ratio. The differences are statistically significant.](image)

### Table 3. Cox proportional hazards results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison*</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-ratio</td>
<td>–</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>T</td>
<td>Overall</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>T₂ vs T₁</td>
<td>$&lt;.0001$</td>
<td>1.45 (1.26–1.67)</td>
<td>$&lt;.0001$ 1.40 (1.22–1.61)</td>
</tr>
<tr>
<td>T₃ vs T₁</td>
<td>$&lt;.0001$</td>
<td>1.96 (1.65–2.33)</td>
<td>$&lt;.0001$ 1.94 (1.63–2.31)</td>
</tr>
<tr>
<td>T₄ vs T₁</td>
<td>$&lt;.0001$</td>
<td>2.37 (2.06–2.72)</td>
<td>$&lt;.0001$ 2.01 (1.73–2.34)</td>
</tr>
<tr>
<td>N</td>
<td>N₂ vs N₁</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Sex</td>
<td>Female vs Male</td>
<td>.02 1.13 (1.02–1.26)</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Race</td>
<td>Overall</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Black vs White</td>
<td>$&lt;.0001$</td>
<td>1.42 (1.24–1.62)</td>
<td>$&lt;.0001$ 1.38 (1.2–1.59)</td>
</tr>
<tr>
<td>Other vs White</td>
<td>.14</td>
<td>1.16 (0.95–1.41)</td>
<td>.42 1.08 (0.89–1.32)</td>
</tr>
<tr>
<td>Site</td>
<td>Overall</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Floor of Mouth vs Tongue</td>
<td>$&lt;.0001$</td>
<td>1.61 (1.44–1.81)</td>
<td>$&lt;.0001$ 1.41 (1.25–1.59)</td>
</tr>
<tr>
<td>Gum and other mouth vs Tongue</td>
<td>$&lt;.0001$</td>
<td>1.49 (1.32–1.67)</td>
<td>.02 1.18 (1.03–1.35)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>–</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
<tr>
<td>Number of positive nodes</td>
<td>–</td>
<td>$&lt;.0001$</td>
<td>$&lt;.0001$</td>
</tr>
</tbody>
</table>

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.

### Table 4. N-ratio risk stratification.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison*</th>
<th>$p$ value</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-ratio</td>
<td>Overall</td>
<td>$&lt;.0001$</td>
<td>1.19 (1.04–1.37)</td>
</tr>
<tr>
<td></td>
<td>Moderate vs. Low</td>
<td>.01</td>
<td>1.55 (1.37–1.75)</td>
</tr>
<tr>
<td></td>
<td>High vs. Low</td>
<td>$&lt;.0001$</td>
<td>1.55 (1.37–1.75)</td>
</tr>
</tbody>
</table>

Multivariate analysis of N-ratio groupings.
*High-risk = N-ratio $\geq$ 12.5%; Moderate-risk = N-ratio 6–12.5%; Low-risk = N-ratio < 6%
with the nodal yield in neck dissection specimens. 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.

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. 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.

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. 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.

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, 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 N1 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, 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 N0 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 costruc-
ture 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 artifi-
cially decrease nodal ratio. However, the discov-
ery 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.

N3 patients were specifically excluded from
this study because it becomes increasingly diffi-
cult to determine whether a nodal metastasis of
greater than 6 cm in size is a single metastasis
or multiple, matted metastases. N0 patients, as
well, were excluded because the concept of nodal
ratio becomes moot in these patients. In addi-
tion, there are specific risk factors that have
been identified with respect to tumor character-
istics and regional metastases that predispose to
a worse prognosis. Specifically, perineural and
lymphovascular invasion in the primary tumor,
and extracapsular extension in regional metas-
tases all portend a worse prognosis and may be
indicators for the addition of adjuvant radio-
therapy. This information, unfortunately, cannot
be captured from SEER. The most recent
iteration of the SEER database (patients diag-
nosed after 2004) will include data on extra-
capsular 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 patho-
logic risk factors is borne out in population-
based studies, and whether it impacts on the
results presented here, deserves future exami-
nation. There may be a confounding between
nodal ratio and absolute number of nodes in
this article, given that both are significantly cor-
related 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, the model fit
between both predictors is approximately equiv-
alent. 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 conclu-
sions. 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 defini-
tion, retrospective and nonrandomized. In addi-
tion, 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 N0 and found to be N1
on staging neck dissection. The incidental find-
ing of nodal disease in this patient significantly
decreases their overall and cause-specific sur-
vival, 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 ret-
rospective 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 explora-
tion of this concept using institutional data and
randomized prospective trials regarding treatment protocols are warranted.

REFERENCES


