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A Prognostic Index for Predicting Lymph Node Metastasis in Minor Salivary Gland Cancer

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A PROGNOSTIC INDEX FOR PREDICTING LYMPH NODE METASTASIS IN MINOR SALIVARY GLAND CANCER

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Abstract

We hypothesized that lymph node involvement in minor salivary gland cancers is associated with clinical and pathological factors commonly available to the clinician after a typical initial workup. Our aim was to identify these factors using a dataset that allowed us to compile the largest series of minor salivary gland cancers in the published literature. Using this dataset we also aimed to characterize the distribution of histological types by primary site, identify the predictors of the use of external beam radiation therapy and neck dissection, and examine the effect of lymph node involvement on survival. Using the SEER database, we identified 2667 minor salivary gland cancers with known lymph node status from 1988 to 2004. Univariate and multivariate analyses were conducted to identify factors associated with the use of neck dissection, the use of external beam radiation therapy, and the presence of cervical lymph node metastases. Kaplan Meier survival curves were constructed to examine the effect of lymph node involvement on survival. 426 (16.0%) patients had neck nodal involvement. Factors associated with neck nodal involvement on univariate analysis included increasing age, male gender, increasing tumor size, high tumor grade, T3-T4 stage, adenocarcinoma or mucoepidermoid carcinomas, and pharyngeal site of primary malignancy. On multivariate analysis, four statistically significant factors were identified, which included male gender, T3-T4 stage, pharyngeal site of primary malignancy, and high-grade adenocarcinoma or high-grade mucoepidermoid carcinomas. The proportions (and 95% confidence intervals) of patients with lymph node involvement for those with 0, 1, 2, 3 and 4

of these prognostic factors were 0.02 (0.01-0.03), 0.09 (0.07-0.11), 0.17 (0.14-0.21), 0.41 (0.33-0.49), and 0.70 (0.54-0.85) respectively. Grade was a significant predictor of metastasis for adenocarcinoma and mucoepidermoid carcinoma but not for adenoid cystic carcinoma. Overall survival was significantly worse at 5, 10, and 15 years for patients with lymph node involvement on presentation. A prognostic index using the four clinicopathological factors listed above can effectively differentiate patients into risk groups of nodal metastasis. The precision of this index is subject to the limitations of SEER data and it should be validated in further clinical studies.

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Introduction

Minor salivary gland cancers represent a rare group of epithelial malignancies. The most common site is the hard palate, but tumors can also arise throughout the oral cavity, as well as the pharynx, larynx, nasal cavity and paranasal sinuses. Tumors of the minor salivary glands are two to three times more likely to be malignant than parotid and submandibular gland tumors.[1-3] Overall, 25% of salivary gland cancers arise in minor salivary glands. These glands account for approximately five percent of saliva production.

Metastasis of most minor salivary gland neoplasms typically occurs by lymphatic spread via the cervical lymph nodes. Cervical lymph node involvement is associated with decreased survival in both major[4-10] and minor salivary gland cancers.[11, 12] Anderson and colleagues analyzed 95 patients diagnosed and treated at the University of Alabama at Birmingham over a 35-year period.[11] In multivariate analysis, three factors were predictive of increased disease-free survival at four years. These were stage I or II cancer, negative surgical margins, and the absence of cervical lymph node metastasis. These results emphasize the need for early detection—in order to treat the patient before they reach advanced stage—and the desirability of treating of cervical lymph nodes when they are present.

Clinically positive lymph nodes are removed by surgical neck dissection often accompanied by neck irradiation. Patients believed to be likely to harbor occult nodal metastasis are treated with an elective neck dissection and/or neck irradiation. Clear, evidence-based guidelines that demonstrate which patients will

present with lymph node metastasis are currently lacking in the literature, although it is known that certain histological types such as adenoid cystic and acinic cell carcinomas are associated with less risk of neck metastasis.[5, 13]

The factors that influence the occurrence of lymph node metastasis in the much more common squamous cell carcinoma of the upper aerodigestive tract have been reported. Woolgar and colleagues investigated the relationship between cervical lymph node metastasis and certain clinical and pathologic factors in 45 patients with tongue or floor of mouth tumors who received neck dissection.[14] They found no relationship between lymph node metastasis and gender, age, primary site, TNM stage, or T stage. There was a significant relationship with the tumor surface dimension and two measures of tumor thickness. This study was limited by a small sample size.

Tumor size and grade of malignancy were shown to predict for the risk of nodal metastasis in univariate analysis by Rodriguez-Cuevas and colleagues.[15] This study included 150 salivary gland tumors, of which only 18 were located in the minor salivary glands. Major gland cancers involved the cervical lymph nodes in 25/132 (18.9%) of cases and minor gland cancers involved the cervical lymph nodes in 4/18 (22%) of cases. Undifferentiated and squamous cell carcinomas (major glands only) had the highest rate of clinical node metastasis: 10/32 (31%). An intermediate group consisted of papillary carcinomas, involving the lymph nodes in 2 of 12 cases (17%), adenoid cystic carcinoma, involving the lymph nodes in 5 of 28 cases (17%), and mucoepidermoid carcinomas, involving the

lymph nodes in 9 of 48 cases (18%). The incidence in acinic cell carcinomas was only 1 in 14 (7%).

Terhaard and colleagues analyzed 565 malignant salivary gland tumors (157 in the minor salivary glands) from the Dutch Head and Neck Oncology Cooperative Group in 2004 for independent prognostic factors for locoregional control.[13] Eighty-nine percent were treated with curative intent. In multivariate analysis, local control was associated with clinical T stage, bone invasion, site, resection margin, and treatment. Regional control was associated with N stage, facial nerve paralysis, and treatment. There was a 9.7 relative risk for local recurrence with surgery alone, compared with surgery plus postoperative radiotherapy and a 2.3 relative risk for regional recurrence. Surgery alone was completed in 20% of the patients and surgery combined with radiation therapy was completed in 68% of the patients. Despite an imbalance of other prognostic factors favoring the surgery only group, the combined group had much lower rates of locoregional recurrence.

In a study looking only at 145 surgically treated parotid carcinomas, Regis de Brito Santos found, in multivariate analysis, histological type (adenocarcinoma, undifferentiated carcinoma, high grade mucoepidermoid carcinoma, squamous cell carcinoma, and salivary duct carcinoma) ($p < 0.001$), T3 or T4 stage ($p = 0.03$), and severe desmoplasia ($p = 0.006$) to be independently associated with lymph node metastasis.[16] In an analysis of the SEER database, Bhattacharyya and Fried examined the predictors of lymph node metastasis also in parotid carcinomas drawing on 1268 cases from 1988 to

1998. They concluded that facial nerve involvement, tumor grade, and squamous cell carcinoma subtype were the most important factors contributing to lymph node metastasis.[17]

The evidence above is the best available for the identification of clinical and pathological associated with lymph node metastasis in minor salivary gland cancers. Unfortunately, most of the studies deal mostly with major salivary gland cancers or squamous cell carcinomas of the upper aerodigestive tract.

This study attempts to answer the question for minor salivary gland cancers using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. The SEER database is a collection of cancer registries that has historically included 14% of the U.S. population. As more registries have been added over the years, that percentage has grown to approximately 25%.

Statement of Purpose, Specific Hypothesis, and Specific Aims of the Thesis

We used the SEER database to compile the largest, population-based dataset of malignant minor salivary gland cancers yet reported. We describe demographic, clinical and pathological characteristics of these tumors including the distribution of histological type by the site of the primary malignancy. We hypothesized that some patient and tumor characteristics commonly known by a clinician faced with the decision to treat the cervical lymph nodes may help define risk classes for lymph node involvement. We examined these associations with

cervical lymph node metastasis both by univariate analysis and while controlling for other variables. A simple prognostic index was derived to predict the presence of lymph node metastasis using the four most important clinicopathological factors. We also analyze the clinicopathological characteristics associated with treatment with external beam radiation therapy and surgical neck dissection. Finally, we examined the survival of patients with lymph node metastasis versus those without.

Methods

All procedures and analysis outlined in the following section were conduced by Shane Lloyd, the thesis candidate. Exemption from IRB review was obtained for this study as the study does not involve human subjects and the data is on a freely available public database.

We queried the National Cancer Institute's SEER registries database to select minor salivary gland malignancies from 1988 to 2004. Minor salivary gland malignancies were defined by primary site and histological criteria as follows. Primary site criteria included cancers of the oral cavity, pharynx, nasal cavity, and larynx. The oral cavity included the lips (C00.0-C00.9), tongue (C020-C023, C028-C029), gingiva (C030-C039, C062), floor of mouth (C040-049), hard palate (C050), and buccal mucosa (C060-C061). The pharynx included the base of tongue (C019), tonsils (C024), soft palate (C051-C052), and all other pharyngeal sites (C090-C139). The larynx included all laryngeal sites (C320-C329). Finally, the nasal cavity was grouped with the nasal cavity itself (C300), the middle ear

(C301) and paranasal sinuses (C310-C319). Pathologic criteria included the salivary gland malignancies described in the World Health Organization International Histological Classification of Tumors.[18] Seventy-four cases were excluded from analysis because they were not the patient's first known head and neck malignancy. Excluding these cases ensures that the source of nodal metastasis is the primary cancer in question. To present a complete population-based survey of the distribution of histological types in the various primary sites, we included patients whether or not their lymph node status was known. In all subsequent analyses, 1259 cases with unknown or unrecorded lymph node status were excluded leaving a final dataset of 2667 patients. Complete patient characteristics are presented for this final set of patients.

All staging information including lymph node involvement represents the information available on the initial workup or upon the completion of the first primary directed surgery or surgeries. Disease progression known to have occurred after the original date of diagnosis is not included. As the SEER program does not record T stage before 2004, we used information recorded in the SEER program on tumor size and extension[19] to assign T stage as defined by the AJCC Cancer Staging Manual, 6th edition, 2002. This method resulted in T stage assignment that was identical to that found in SEER's derived AJCC T stage variable that is available only for 2004.

Clinical and pathological factors potentially associated with neck lymph node metastasis were identified and included patient gender, age, race (Caucasian, African American, or other), site of primary malignancy, tumor grade,

tumor size, T stage, and year of diagnosis. Grade information was grouped into low-grade (well differentiated to moderately differentiated) and high-grade (poorly differentiated or undifferentiated/anaplastic) categories. All variables were examined individually using the Pearson double-sided chi square test for their effect on lymph node involvement. Statistically significant factors were then included in a multivariate logistic regression model. Because more extensive nodal sampling or neck dissection may lead to a higher probability of finding positive lymph nodes, we included an independent variable for the number of nodes examined. Interactions between explanatory variables were also considered. We searched for interaction terms by forcing entry of all variables individually and allowing entry of interaction terms in forward stepwise fashion with a likelihood ratio significance cutoff of 0.05. Finally, the four most significant factors were combined into a categorical variable of 16 groups representing all possible permutations of the presence or absence of these four factors. This categorical variable was then re-entered in the logistic regression with the same covariate controls. Groups with similar odds ratios were combined in order to construct an index predictive of the presence or absence of lymph node involvement in minor salivary gland cancers. This index was then validated using 10-fold cross-validation.

Generally, we omitted cases from our logistic regressions if input variables were missing. This reduces the power and has the potential to introduce bias into our analysis. As a safeguard against this, we used maximum likelihood estimation to impute the missing data in our regression of clinicopathological

factors on lymph node involvement. This is a statistical way of making a best guess at missing variables—such as stage or tumor size—based on the known characteristics of each case with a missing variable. We imputed the data five times and the estimated values were combined to arrive at beta and standard deviation estimates that take advantage of all the data. This was done to affirm the independent statistical significance of each of the variables included in the index. Only known information and no imputed information was used in constructing the index or in other analyses in this study.

The clinicopathological variables listed above were also examined for their association with neck dissection and external beam radiation by logistic regression. A neck dissection was defined as any case with four or more lymph nodes examined by a pathologist. The Hosmer-Lemeshow goodness-of-fit statistic was used to evaluate regression outputs. Patients with distant metastasis were excluded from multivariate analyses of lymph node metastasis and survival analysis. A receiver operator curve was generated for the prognostic index of lymph node involvement in minor salivary gland cancer.

Finally, we generated Kaplan-Meier survival curves for patients with and without lymph node metastasis respectively.

Univariate analysis, multivariate logistic regression, Hosmer-Lemeshow tests, receiver operator curves, and Kaplan-Meier survival curves were computed using SPSS version 16 (SPSS Inc., Chicago, IL). Cross-validation was computed using the R programming language with the Zelig package.[20] Multiple imputation

of missing data was conducted using the R programming language with the Zelig and AmeliaView[21] packages.

Results

Table 1: Location of 4616 Cases of Minor Salivary Gland Cancer by Histological Type.

	Oral Cavity (%)	Pharynx and Tonsils (%)	Nasal Cavity, Sinuses, Middle Ear (%)	Larynx (%)	Total (%)
Adenocarcinoma	654 (29.9)	350 (38.9)	280 (41.4)	100 (62.1)	1384 (35.3)
Mucoepidermoid Carcinoma	991 (45.3)	262 (29.1)	62 (9.2)	18 (11.2)	1333 (34.0)
Adenoid Cystic Carcinoma	436 (19.9)	249 (27.7)	307 (45.4)	30 (18.6)	1022 (26.0)
Acinic Cell Carcinoma	60 (2.7)	14 (1.6)	7 (1.0)	0 -	81 (2.1)
Miscellaneous Carcinoma	48 (2.2)	25 (2.8)	20 (3.0)	13 (8.1)	106 (2.7)
Total *(% of Total in Site)*	2189 *(55.8)*	900 *(22.9)*	676 *(17.2)*	161 *(4.1)*	3926

Percentages in parentheses represent the percentage of cancers in the site that are the histological type in question. Percentages in the bottom row represent the percentage of the total found in that site.

The distribution of histological type by primary tumor site is listed in Table 1. Patient and tumor characteristics and the results of univariate analysis of the effects of each clinical or pathologic factor individually on lymph node metastasis are shown in Table 2. Overall, lymph node metastasis was found in 426 (16.0%) of cases. In patients who underwent surgery and were staged by pathology, 54.2% had lymph node metastasis. In patients who were staged clinically, 8.8% had lymph node metastasis.

Table 2. Patient Characteristics and Clinical and Pathologic Factors and Their Effect on Nodal Involvement in Univariate Analysis.

Baseline Characteristic	Total No. (%)		Incident Nodal Involvement (%)	P-Value*
Gender				< 0.001
Female	1423	(53.4)	11.4	
Male	1244	(46.4)	21.2	
Race				0.052
Caucasian	2101	(79.6)	15.6	
African American	324	(12.3)	20.4	
Other	216	(8.2)	13.4	
Histological Type				< 0.001
Adenoid Cystic Carcinoma	695	(26.1)	10.2	
Acinic Cell Carcinoma	41	(1.5)	2.4	
Mucoepidermoid Carcinoma	929	(34.8)	15.8	
Adenocarcinoma	929	(34.8)	21.3	
Miscellaneous Carcinoma	73	(2.7)	12.3	
Grade				< 0.001
Low-Grade	1299	(73.8)	8.5	
High-Grade	461	(26.2)	39.9	
Primary Site				< 0.001
Mouth	1493	(56.0)	9.7	
Pharynx Including Tonsil	667	(25.0)	32.5	
Nasal Cavity, Sinuses, Middle Ear	397	(14.9)	6.8	
Larynx	110	(4.1)	33.6	
T Stage				< 0.001
T1	945	(44.1)	6.1	
T2	401	(18.7)	20.4	
T3	190	(8.9)	20.5	
T4	514	(24.0)	21.6	
Neck Dissection (> 3 Nodes Examined)				< 0.001
Yes	391	(14.8)	54.2	
No	2257	(85.2)	8.8	
EBRT				< 0.001
Yes	1125	(43.4)	28.5	
No	1466	(56.6)	6.2	

	Total No.	LNs Involved Mean (SE)	No LNs Involved Mean (SE)	
Age	2667	57.7 (0.4)	60.9 (0.7)	< 0.001
Year of Diagnosis	2667	1999	1998	0.005
Tumor Size (mm)	1828	24.6 (0.7)	32.9 (1.1)	< 0.001
Number of Nodes Examined	2667	1.4 (0.1)	15.7 (1.1)	< 0.001

**Pearson Chi square test double-sided p-value. SE: Standard Error.*
The T stage is unknown for 92 patients who had distant metastasis because distant metastasis overrides tumor extension data in SEER coding. LN = Lymph Node.

To arrive at a model that illustrates the relative importance of factors commonly available to physicians considering neck dissection and/or neck irradiation, we included clinical and pathological factors found to be significant on univariate analysis in a multivariate logistic regression on lymph node involvement (Table 3). An interaction was found between grade and histology such that adenocarcinomas and mucoepidermoid carcinomas were more likely to present with lymph node metastasis when they were high-grade. However, grade had no effect on nodal involvement for other histological types or sub-types. We therefore considered low- and high-grade malignancies separately for adenocarcinomas and mucoepidermoid carcinomas but not for the other histological types.

Table 3: Multivariate Logistic Regression of Clinicopathological Factors on Regional Nodal Metastasis.

Variable (Comparison Group for Categorical variables)	Odds Ratio (95% Confidence Interval)	P-Value
Histological Type and Grade		
(v. Adenoid Cystic Carcinoma)		< 0.001 ***
Acinic Cell Carcinoma	0†	
Mucoepidermoid Carcinoma, Low-Grade	1.06 (0.56-2.02)	0.858
Mucoepidermoid Carcinoma, High-Grade	4.04 (2.09-7.80)	< 0.001 ***
Adenocarcinoma, Low-Grade	1.91 (1.04-3.51)	0.037 *
Adenocarcinoma, High-Grade	6.72 (3.48-13.00)	< 0.001 ***
Miscellaneous	1.73 (0.40-7.44)	0.461
Primary Site (v. Mouth)		< 0.001 ***
Pharynx Including Tonsil	3.54 (2.27-5.54)	< 0.001 ***
Nasal Cavity, Sinuses, and Middle Ear	0.71 (0.30-1.69)	0.443
Larynx	1.55 (0.55-4.40)	0.407
T Stage (v. T1)		0.030 *
T2	1.68 (0.95-2.97)	0.074
T3	2.57 (1.19-5.55)	0.017 *
T4	2.25 (1.26-4.04)	0.006 **
Male Sex (v. Female)	2.16 (1.42-3.30)	< 0.001 ***
Tumor Size (mm)	1.00 (0.99-1.01)	0.947
Age	1.01 (1.00-1.02)	0.161
Race (v. Caucasian)		0.268
African American	1.61 (0.91-2.87)	0.105
Other	1.08 (0.49-2.36)	0.852
Controls		
Year of Diagnosis	0.99 (0.95-1.04)	0.698
Number of Nodes Examined (v. None)		< 0.001 ***
1-3	5.43 (2.69-10.97)	< 0.001 ***
> 3	24.01 (14.99-38.46)	< 0.001 ***

*1533 patients are included in this analysis. The p-value is listed for the odds ratio of each variable and for the Wald statistic for inclusion of complete categorical variable groups. Cases with distant metastasis are excluded from this analysis because T stage was not recorded/unknown when there was distant metastasis. The Hosmer-Lemeshow test for this regression had a p-value of 0.023. The NagelKerke R Square is 0.526. ***p < 0.001. **0.001 < p <= 0.010. *0.010 < p <= 0.050. †The number of lymph node positive cases is too small for analysis.*

Controlling for all factors listed, male gender, pharyngeal primary site, T3 or T4 stage, and high-grade adenocarcinoma or high-grade mucoepidermoid carcinoma are statistically significant predictors of regional nodal metastasis. When these four variables were combined into a single categorical variable of 16 groups representing all possible permutations of their presence or absence, they resulted in the odds ratios listed in Table 4. Groups based loosely on these odds ratios were delineated which corresponded with the number, zero through four, of the four variables present. Because of this, a predictive index for lymph node involvement is proposed based on the number present of the following four factors: male gender, pharyngeal primary site, T3 or T4 stage, and high-grade adenocarcinoma or mucoepidermoid carcinoma (Table 5). The area under the receiver operator curve (95% CI) using this index was = 0.757 (0.724-0.790). If one uses a positive test cutoff of one factor present, the sensitivity and specificity were 95.4% and 28.4%. Using two factors as the positive test cutoff results in a sensitivity and specificity of 66.9% and 72.2%, using three factors results in a sensitivity and specificity of 35.6% and 94.0%, and using all four factors results in a sensitivity and specificity of 10.0% and 99.4%. When the predictive capability of the logistic regression model which uses the number of factors present examined using 10-fold cross validation, the average squared prediction error was 0.0923 indicating accurate prediction of the presence or absence of lymph node involvement when dividing the data into training and validating sets differently 10 times.

Table 4: Odds Ratios of Combinations of the Presence or Absence of Four Factors.

	Lymph Node Positive		Logistic Regression	
Variable	Cases Lymph Node Positive	Proportion (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)	P-Value
All Factors Absent	9/457	0.02 (0.01-0.03)		
One Factor Present				
Male	17/326	0.05 (0.03-0.08)	2.18 (0.92-5.19)	0.078
T3-4	22/219	0.10 (0.06-0.14)	3.77 (1.62-8.77)	0.002
Pharynx	18/163	0.11 (0.06-0.16)	3.99 (1.65-9.62)	0.001
High-Grade ADC or MEC	8/45	0.18 (0.07-0.30)	5.562 (1.79-17.33)	0.003
Two Factors Present				
Male and T3-4	19/191	0.10 (0.06-0.14)	3.69 (1.55-8.81)	0.003
Male and Pharynx	15/99	0.15 (0.08-0.22)	6.08 (2.38-15.55)	< 0.001
T3-4 and High-Grade ADC or MEC	6/31	0.19 (0.05-0.33)	6.64 (1.88-23.52)	< 0.001
T3-4 and Pharynx	7/35	0.20 (0.07-0.33)	6.94 (2.12-22.76)	0.001
Male and High-Grade ADC or MEC	15/41	0.37 (0.22-0.51)	11.70 (4.14-33.07)	< 0.001
Pharynx and High-Grade ADC or MEC	10/20	0.50 (0.28-0.72)	16.29 (4.58-57.92)	< 0.001
Three Factors Present				
All but Pharynx	20/60	0.33 (0.21-0.45)	17.25 (6.65-44.75)	< 0.001
All but High-Grade ADC or MEC	13/40	0.33 (0.18-0.47)	21.03 (7.39-59.87)	< 0.001
All but Male	8/15	0.53 (0.28-0.79)	29.64 (7.09-123.98)	< 0.001
All but T3-4	19/30	0.63 (0.46-0.81)	49.65 (16.04-153.75)	< 0.001
All Four Factors Present				
All	23/33	0.70 (0.54-0.85)	79.16 (26.07-240.35)	< 0.001

Odds ratios compare groups to the group with no factors present. ADC: Adenocarcinoma. MEC: Mucoepidermoid carcinoma. N = 1805

As mentioned above, we also used maximum likelihood estimation to accomplish multiple imputation of missing data to increase the power of our regression and eliminate potential sources of bias. The results of this process are found in Table 6. The same four factors included in the index are again shown to be significant although to slightly different degrees.

Table 5: Predictive Index of Lymph Node Involvement in Minor Salivary Gland Cancer.

	Predictive Index		Logistic Regression	
Variable	Cases Lymph Node Positive	Proportion (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)	P-Value
Number of Factors (v. 0)				
0	9/457	0.02 (0.01-0.03)		< 0.001
1	65/753	0.9 (0.07-0.11)	3.29 (1.56-6.93)	0.002
2	72/417	0.17 (0.14-0.21)	6.15 (2.91-13.04)	< 0.001
3	60/145	0.41 (0.33-0.49)	24.47 (10.96-54.61)	< 0.001
4	23/33	0.70 (0.54-0.85)	81.64 (26.71-249.54)	< 0.001

The logistic regression includes the covariate controls listed in Table 3. Hosmer-Lemeshow statistic p-value is 0.133 indicating no difference between predicted and observed values. NagelKerke R square is 0.464.

Multivariate logistic regressions were conducted to determine the factors associated with a patient's receiving a neck dissection or EBRT. Patients with T2-T4 stage tumors were more likely to receive neck dissection than patients with T1 stage tumors. Patients more likely to receive a neck dissection were those with T2-T4 tumors, those with high-grade tumors, and those living in Connecticut. Patients with tumors occurring in the sinuses/nasal cavity/middle ear were less likely to receive neck dissection.

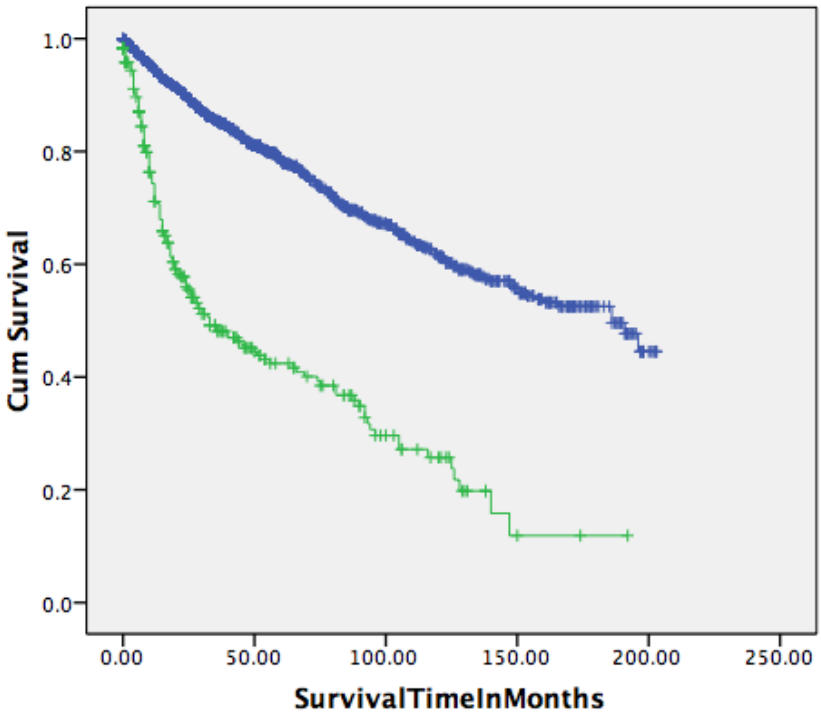
Forty-six percent of patients received EBRT. Patients who received surgical neck dissection were also more likely to receive EBRT. Patients with adenoid cystic carcinoma were more likely to receive EBRT, as were older patients, those with T2-T4 stage, and those with high-grade tumors. Patients less likely to receive EBRT were those with tumors occurring in the oral cavity, those living in Los Angeles, and those diagnosed in the later years of the study.

Table 6: Multivariate Logistic Regression of Clinicopathological Factors on Regional Nodal Metastasis Using Imputed Data

Variable (Comparison Group for Categorical variables)	Odds Ratio (95% Confidence Interval)	P-Value
Histological Type and Grade		
(v. Adenoid Cystic Carcinoma)		
Acinic Cell Carcinoma	0.60 (0.13-2.65)	0.51
Mucoepidermoid Carcinoma, Low-Grade	1.14 (0.82-1.59)	0.43
Mucoepidermoid Carcinoma, High-Grade	3.79 (2.72-5.28)	< 0.001 ***
Adenocarcinoma, Low-Grade	1.21 (0.90-1.63)	0.21
Adenocarcinoma, High-Grade	4.10 (2.90-5.80)	< 0.001 ***
Miscellaneous	1.15 (0.56-2.38)	0.70
Primary Site (v. Mouth)		
Pharynx Including Tonsil	3.05 (2.09-4.44)	< 0.001 ***
Nasal Cavity, Sinuses, and Middle Ear	0.54 (0.39-0.76)	< 0.001 ***
Larynx	1.84 (1.18-2.88)	0.01
T4 Stage (v. T1-3)	1.87 (1.42-2.47)	< 0.001 ***
Male Sex (v. Female)	1.57 (1.28-1.95)	< 0.001 ***
Tumor Size (mm)	1.00 (1.00-1.00)	0.65
Age	1.01 (1.00-1.01)	0.04 *
Race (v. Caucasian)		
African American	1.09 (0.81-1.46)	0.58
Other	0.98 (0.60-1.60)	0.92
Controls		
Year of Diagnosis	0.99 (0.97-1.00)	0.15

Finally, survival curves were generated to depict the relative survival of patients with nodal metastasis versus those with no nodal metastasis (Figure 1). For patients who were lymph node negative on presentation, the 5-, 10-, and 15-year Kaplan-Meier overall survival (Standard Error in parentheses) was 78.4 (1.2), 61.3 (1.9), and 52.5 (2.4). For patients with lymph node involvement on presentation, the 5-, 10-, and 15-year Kaplan-Meier overall survival was 42.4 (3.4), 25.7 (3.9), and 11.9 (5.0).

Figure 1: Survival By Lymph Node Status.



The upper curve represents patients who were lymph node negative on presentation and the lower curve represents patients with lymph node involvement on presentation.

Discussion

Location of Minor Salivary Gland Malignancies and Distribution of Histological Types

We present the largest population-based dataset on the distribution of histological type by primary site to date. The oral cavity was the most common site and the hard palate the most common sub-site. We report a larger proportion of mucoepidermoid carcinoma than adenoid cystic carcinoma overall as opposed to others' findings that adenoid cystic carcinoma is the most common type.[1, 3, 22]

Adenoid cystic carcinoma was the most prevalent sinonasal minor salivary gland malignancy, mucoepidermoid was most prevalent in the oral cavity, and adenocarcinomas were common in the pharynx and larynx.

The frequency at which certain histological types of minor salivary gland cancers were diagnosed has changed over time. For example, polymorphous low-grade adenocarcinomas were diagnosed only in the later years of the study period from 2000-2004 and a total of 141 of these tumors were diagnosed during that time. The separation of adenocarcinomas into low-and high-grade groups should neutralize the absence of this diagnosis in the earlier years for the purposes of our analysis. Mixed pleomorphic carcinoma is a diagnosis that has come into usage only in the later years of the study.[1] Only 11 cases were found of this type.

Grade as a Predictive Factor of Lymph Node Metastasis

Grade was predictive of nodal metastasis for adenocarcinoma and mucoepidermoid carcinoma but not for other histological types and sub-types. There was no statistically significant difference in the rate of lymph node metastasis between low and high-grade adenoid cystic carcinoma (ACC). Spiro and colleagues have similarly found that dividing ACC by grade was unhelpful for determining prognostic information for these tumors.[3, 23] However, grade has been found by some authors to be helpful in predicting survival in ACC.[24, 25] It is important to note that lymph node metastasis is generally considered less important than local and distant control in ACC, and distant metastases occurs

commonly even without neck nodal involvement in adenoid cystic carcinoma.[24-27] All but one acinic cell carcinomas in this study were low-grade. Similarly, all myoepithelial carcinomas were low-grade as were many adenocarcinoma sub-types. Other histological types for which grade was not a statistically significant predictor of metastasis included mixed malignant tumor and pleomorphic carcinoma. The sample size may be insufficient to detect an interaction between grade and some histological sub-types including oxyphilic adenocarcinoma, ductal carcinoma, and carcinosarcoma.

Race as a Potential Predictive Factor of Lymph Node Metastasis

Our results suggest that African American patients may be more likely to present with nodal metastasis on univariate analysis. However, this was a trend that did not achieve statistical significance. Also, this trend dissipated when controlling for other factors on multivariate analysis. The factors controlled for include markers of disease severity like T stage and grade. This suggests that African American patients may be presenting with more advanced disease. African American patients have been shown to have a higher incidence and mortality regarding cancers of the oral cavity, pharynx and larynx than their white counterparts.[28, 29] In one study of oral and squamous cell carcinomas, African American patients had decreased survival while controlling for stage and treatment.[30] Differences in mortality and survival across racial groups are also more pronounced in men than in women.[28]

A Prognostic Index for Predicting Lymph Node Metastasis in Minor Salivary Gland Cancer

While our reported rate of lymph node involvement of 16.0% is approximately commensurate with other published studies, a large, in depth case series may characterize the actual rate more accurately than SEER data. However, because minor salivary gland cancers are relatively rare, a case series this large may not be forthcoming in the immediate future.

Occult nodal metastasis for major salivary malignancies is between 12 and 20 percent.[31-33] In a study of adenoid cystic carcinomas of the major and minor salivary glands, Spiro and colleagues reported a rate of lymph node involvement of 7.4% on initial presentation with an additional 7.0% developing positive lymph nodes subsequently.[34] Occult nodal metastasis in high-grade adenocarcinoma was 40% in a small study by Sheahan and colleagues.[35] They found occult disease in two out of five necks dissected electively. High tumor grade was also correlated with occult metastasis in a study by Rodriguez-Cuevas and colleagues.[15] In 36 elective neck dissections for major salivary gland cancers, 50% of high-grade tumors had occult metastasis while no low-grade tumors had occult metastasis. Because of limitations inherent to SEER data, it is not possible to determine which node positive patients had clinically occult nodal metastasis discovered in the operating room. However, our results have implications for these patients. Because the data represent a wide range of disease progression on presentation, patients who presented late with clinical nodal metastasis but who would have been clinically metastasis free had they

presented earlier are included. Three of the four factors found to be predictive of nodal metastasis in our analysis are characteristics that do not change over the progression of the malignancy such as histological type, primary site and gender. Therefore, it is reasonable to think that clinically N0 patients presenting with these factors are likely to go on and develop lymph node metastasis or already have occult metastasis at presentation. Our results should be validated in a set of patients with clinically N0 disease who also undergo neck dissection for pathological staging.

Recommendations For Using The Index

While we do not assert that the percentages presented in the prognostic index are directly predictive of occult nodal metastasis, we do recommend consideration of the four factors listed when considering elective lymph node treatment. We would advocate that patients with three or four of the four factors should receive elective neck treatment. Patients with two of the factors should also be strongly considered for elective neck treatment with neck dissection, adjuvant radiation therapy, or both. It is also worth cautioning that even patients with only one of the factors in the index may be appropriate candidates for elective therapy, especially if the one factor is high-grade adenocarcinoma or mucoepidermoid carcinoma. Because SEER data fails to capture neck relapses in patients who were N0 for the first 4 months after diagnosis, figures hovering around the cutoff range for elective treatment in the patients with one or two factors may actually be appropriate candidates. On the other hand, if

pretreatment staging with high resolution CT and ultrasound has failed to reveal regional lymphadenopathy, and the clinician feels the risk of occult metastasis is low, the model may also be used to identify patients who should have close follow up for regional progression. As with any prognostic tool, this index will not find complete applicability for each patient.

Elective neck dissection or radiation therapy treatment of the neck even in high-risk patients may not convey local regional control or survival benefit. However, Tran and colleagues reported that post-operative radiation therapy improved local control in an analysis of 62 patients with minor salivary gland cancer arising in the oral cavity.[36] In a separate report, they found better locoregional control with postoperative radiation therapy in 25 patients with minor salivary gland cancers of the paranasal sinuses or nasal cavity.[37] In a series of 256 minor salivary gland tumors in China, Chou and colleages showed that patients with positive cervical metastasis found during neck dissection had higher survival than those with no neck dissection.[38] The methods employed were not robust enough to establish the superiority of elective dissection in N0 patients however.

It is interesting to note that increasing size of the primary tumor was correlated with a patient receiving a neck dissection while it was not predictive of nodal metastasis while controlling for other factors. In some sites such as the sinuses and nasal cavity, tumors can attain large sizes before they present clinically. In the case of the sinuses or nasal cavity, lymphatic involvement is less likely. While T stage was found to be a significant factor predicting nodal

metastasis, it is surprising that it did not eclipse other factors in the index as might be expected.

Dealing With Missing Data

The SEER program has a standard rate of case ascertainment of 98%.[39] However, staging and tumor grade information is often incomplete. Of 3926 patients identified with minor salivary gland tumors, lymph node metastasis was only recorded for 2667. Furthermore, stage and grade information was not recorded for many patients such that the dataset of patients with no missing data pertinent to lymph node metastasis was only 1533. If these cases are not missing at random, then our regression has the potential to be biased. Statistical analysis indeed revealed some differences between the set of cases with fully recorded grade and stage information versus the set of cases excluded because of missing data. Cases with missing information tended to be in the earlier years of the dataset, come from certain geographic registries, be of Caucasian race, have high tumor grade, and have tumors in sites other than the mouth. Not significantly different between the two sets were T stage, tumor size, gender, age, and the use of external beam radiation therapy.

In general, we excluded cases with missing data from multivariate logistic regression analysis. As a safeguard against the reduction in power and the potential introduction of bias into our analysis, we used maximum likelihood estimation to impute the missing data into our regression of clinicopathological factors on lymph node involvement. This helped affirm the independent statistical

significance of each of the variables included in the index. All four of these variables were independently associated with lymph node metastasis to a p-value of less than 0.001, although their respective odds ratios differed from our main analysis. Older age was also found to be marginally significantly associated with lymph node metastasis in this analysis. Again, this imputation was used only as an exercise in testing the importance of missing variables in our construction of the prognostic index. As indicated in the methods section, multiple imputation was not used in constructing the index.

General Limitations of SEER Data

Besides occasional missing data regarding grade and stage, SEER has some other important limitations that should be mentioned. One that is often cited is the lack of margin status. This is a more important consideration in studies that analyze the effects of various treatments on survival. For example, a study that examines the effect of adjuvant radiation therapy on survival for head and neck cancer must deal with the fact that patients with positive margins after surgery are more likely to receive adjuvant radiation therapy but also have a poorer prognosis. Other factors can be controlled for and one can exclude cases based on the extent of surgery but marginal status will remain a confounding variable.

Another deficiency in SEER data is the lack of detail regarding the type, dose, energy, and techniques of radiation used. This is a problem for the present study only in our analysis of the clinicopathological characteristics associated with the used of external beam radiation therapy. Many of the patients were likely

treated only palliatively with lower doses and less extensive fields. Thus, they were not in essence “selected” for treatment in the sense that we imply.

Choosing Target Volumes for Elective Treatment of the Neck: Skip Metastasis

Beyond knowing that certain minor salivary gland cancers metastasize to the neck, and that these patients might require elective treatment, the clinician needs a basis for selecting a target volume in the neck. This section and the next will present some current trends on treating two patterns of lymph node metastasis: skip metastasis and contralateral metastasis to the neck.

A consensus on neck target selection guidelines for squamous cell carcinomas of the head and neck was reached at the 43rd annual meeting of the American Society of Therapeutic Radiology and Oncology in San Francisco, November 2001. This consensus was reported by Eisbruch and colleagues in 2002 and applies only to patients with nodal stages N0 or N1.[40] The guidelines state that clinical involvement of levels II or III always calls for treatment of levels Ib and IV ipsilaterally. Level V is always treated with ipsilateral involvement of levels II-IV. Lateral T1-T2 floor of mouth tumors require treatment of ipsilateral levels I-III and contralateral I-II. Ipsilateral level IV and contalateral level III are added for tumors of higher T stage. Tongue tumors of tumor stage T1-T2 require treatment of ipsilateral levels I-IV. More advanced T stages or tumors of the anterior tongue require the same levels contralaterally. Finally, buccal mucosa and retromolar trigone tumors require treatment of levels I-III ipsilaterally.

Furthermore, it was suggested that extracapsular extension of any lymph node calls for treatment of that neck level at a higher dose. For lateralized tumors of any head and neck site, contralateral neck treatment should be added when the N stage is greater than N1.

For neck stages N2 and greater, treatment of ipsilateral levels I-V has been advocated in a consensus opinion published in 2006 by Gregoire and others.[41] They recommend that the retrostyloid space be included in this volume if level II is involved, and that the supra-clavicular fossa be included if levels IV or Vb are involved. These authors also repeat the recommendations of a consensus opinion published in 2003 for the N0 or N1 patient.[42] Specifically, they state that in the N0 or N1 patient, when a positive lymph node abuts a muscle, or shows radiological evidence of muscular infiltration, that the muscle should be included in the CTV, at least within the level at which the invasion occurs and with 1 cm margins. Also, they recommend that when an involved lymph node borders on two adjacent levels, that both levels should be treated. Finally, for the post-operative patient, the abovementioned 2006 consensus recommendation was to include the entire operative bed, especially in the case of extracapsular extension. Then, for the post-operative patient, they repeat the recommendations of including the retrostyloid space in case of level II involvement and the supraclavicular fossa in case of level IV or Vb involvement, the inclusion of invaded muscles, and the inclusion of adjacent levels when a pathologically positive node borders on an undissected level.

Deciding Target Volumes for Elective Treatment of the Neck: Contralateral Lymph Node Involvement

Contralateral lymph node involvement (CLNI) is not common but presents a challenge for the clinician who must decide whether to treat the contralateral neck. Most published studies on CNLI report on squamous cell carcinomas uniquely or include a small minority of minor salivary gland histologies. The overall rate of CLNI on presentation is variable in published studies and ranges from 3.0 to 9.2%.[43-47] Longitudinal studies place the lifetime rate of CLNI for oral cavity SCC from 9.4 to 17.3%.[46, 48, 49]

To consider some of the issues pertinent to determining which tumors metastasize to the contralateral neck, it is useful to study the example of the oral tongue cancer. Lymphatic metastasis from the tongue can follow different patterns depending on the location of the primary tumor. It has been suggested by Feind and others that more anterior tumors are at a higher risk for CLNI.[45] They reported CLNI in 4 of 21 (19.0%) of tumors of the anterior 1/3 of the tongue and in 3 of 80 (3.8%) of tumors of the middle 1/3 of the tongue. However, in the former group, extension to the floor of mouth was noted in all patients with CLNI.

Tumors that involve the midline are known to be associated with higher rates of CLNI. Increasing risk with further graded extension to and across the midline was first reported in 1951 by Martin and others[50] and more recently by Kowalski and others.[46, 50] Several papers have been published that attempt to define other clinicopathological predictors of CLNI.[45-48, 51, 52] However, a rational basis for why factors such as T stage, histopatholigical grade and depth of

invasion should cause lateralized tumors to metastasize to the contralateral neck has generally been lacking. The crux of the rationale for CLNI is most likely anatomical. Lymphatic capillaries and collecting trunks that cross the midline exist and are utilized more frequently the more centrally located the primary lesion.[45] Vascular emobilization and perineural infiltration are two other factors that provide an anatomically rational explanation for increased CLNI and they were shown to correlate with CLNI by Kowalski and others.[46] Gonzalez-Garcia and others found that peritumoral inflammation correlated with CLNR.[52] A depressed immune response in this case may allow for more widespread dissemination of metastases, including across the midline to the contralateral neck.

Both early and relapse/failure CLNI are known to confer a poor prognosis in oral cavity SCC. Gonzalez-Garcia and others reviewed 203 patients with SCC of the lateral aspect of the tongue longitudinally and found cervical lymph node relapse in 29 patients.[52] Of those with relapse in the ipsilateral neck, 14 of 20 (70%) eventually died of the disease. Of those with relapse in the contralateral neck 8 of 9 (89%) eventually died of the disease.

In the same study, relapse in the contralateral neck occurred only when there was no contralateral neck dissection such as in 6 of 80 patients with (T2, T3, T4) N0 tumors or tumors with cervical nodes less than 3 cm without extracapsular extension. There were no cases of CLNR in 49 N0 or N1 patients with lateral tumors that invaded midline of the tongue and who underwent modified type III radical neck dissection. However, when considering all patients,

the association between contralateral neck dissection and decreased CLNR was not statistically significant. These data suggest that bilateral neck dissection was at least effective in this small group of patients with tumors invading the midline.

In a study of stage I and II oral cavity SCC, Lim and others found only one case of occult CLNI in 25 elective contralateral neck dissections in a total patient sample of 54.[53] Patients were followed for a mean of 56.3 months and no cases of CLNR were found. All patients had unilateral lesions that did not extend across the midline.

The type of elective contralateral neck dissection warranted may or may not include Level IV. Woolgar and others showed that large mobile SCCs that extend across the midline often exhibit an erratic pattern of CLNI and they recommend neck dissection down to level IV bilaterally in these patients.[47] Kowalski and others found that in 41 patients submitted to contralateral modified radical neck dissection for oral cavity SCC, only once were nodes found in Level IV.[46] Twenty-four patients who did not receive elective contralateral neck dissection had positive lymphatic involvement in Levels I-III, as did 19 of 79 who submitted to a contralateral supraomohyoid neck dissection. Northrup and others noted that CLNR occurred almost exclusively in the subdigastric area.[49] Prins-Braam and others suggested that when contralateral nodes are found, they are usually found at an anatomically higher level than positive ipsilateral nodes.[54]

Adenoid Cystic Carcinoma: A Special Case

While most minor salivary gland tumors metastasize through the lymphatics via then neck, one class, adenoid cystic carcinoma, is known to commonly metastasize through perineural invasion as well.

ACC has been found more commonly in the minor salivary glands than in the major salivary glands by some authors.[27, 55] In a yet to be published report, we found slightly more single-primary cases of ACC treated by definitive surgical resection in the major salivary glands (1117) than in the minor salivary glands (995) in population-based data. Of the major salivary glands, the parotid gland and submandibular glands harbored the biggest share of cancers (567 and 471 respectively) and the oral cavity with its various sub-sites was most frequently involved among minor salivary gland sites (618).

Buchholz and colleagues have had success treating adenoid cystic carcinomas with fast neutron radiotherapy.[56] They reported 5-year actuarial local control and locoregional control rates of 76% and 63%, respectively. Eighty-one percent (17/21) of patients treated with neutron therapy alone and 100% (13/13) of the patients treated with neutron therapy and surgery achieved local control.

Conclusions

We present a population based survey of minor salivary gland malignancy and an analysis of the predictors of lymph node metastasis. African Americans with minor salivary gland cancer may present with more advanced disease. Grade is a significant predictor of metastasis for adenocarcinoma and

mucoepidermoid carcinoma but not for adenoid cystic carcinoma and other subtypes. Tumor size is often considered in the decision to perform neck dissection, yet it was not a significant predictor of nodal metastasis on multivariate analysis. We present a prognostic index of lymph node involvement for minor salivary gland cancer that uses the presence or absence of four factors—male gender, pharyngeal primary site, T3 or T4 stage, and high-grade adenocarcinoma or mucoepidermoid carcinoma. This index effectively differentiates patients into risk groups for nodal metastasis.

References

1. Buchner A, Merrell PW, Carpenter WM. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. J Oral Pathol Med 2007;36:207-14.
2. Eveson JW, Cawson RA. Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Pathol 1985;146:51-8.
3. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head Neck Surg 1986;8:177-84.
4. Bhattacharyya N, Fried MP. Determinants of survival in parotid gland carcinoma: a population-based study. Am J Otolaryngol 2005;26:39-44.
5. Harbo G, Bundgaard T, Pedersen D, Sogaard H, Overgaard J. Prognostic indicators for malignant tumours of the parotid gland. Clin Otolaryngol Allied Sci 2002;27:512-6.
6. Hocwald E, Korkmaz H, Yoo GH, et al. Prognostic factors in major salivary gland cancer. Laryngoscope 2001;111:1434-9.
7. Kane WJ, McCaffrey TV, Olsen KD, Lewis JE. Primary parotid malignancies. A clinical and pathologic review. Arch Otolaryngol Head Neck Surg 1991;117:307-15.
8. Lima RA, Tavares MR, Dias FL, et al. Clinical prognostic factors in malignant parotid gland tumors. Otolaryngol Head Neck Surg 2005;133:702-8.
9. Theriault C, Fitzpatrick PJ. Malignant parotid tumors. Prognostic factors and optimum treatment. Am J Clin Oncol 1986;9:510-6.
10. Zbaren P, Schupbach J, Nuyens M, Stauffer E, Greiner R, Hausler R. Carcinoma of the parotid gland. Am J Surg 2003;186:57-62.
11. Anderson JN, Jr., Beenken SW, Crowe R, et al. Prognostic factors in minor salivary gland cancer. Head Neck 1995;17:480-6.
12. Lopes MA, Santos GC, Kowalski LP. Multivariate survival analysis of 128 cases of oral cavity minor salivary gland carcinomas. Head Neck 1998;20:699-706.
13. Terhaard CH, Lubsen H, Van der Tweel I, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. Head Neck 2004;26:681-92; discussion 92-3.
14. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head Neck 1995;17:463-72.
15. Rodriguez-Cuevas S, Labastida S, Baena L, Gallegos F. Risk of nodal metastases from malignant salivary gland tumors related to tumor size and grade of malignancy. Eur Arch Otorhinolaryngol 1995;252:139-42.
16. Regis De Brito Santos I, Kowalski LP, Cavalcante De Araujo V, Flavia Logullo A, Magrin J. Multivariate analysis of risk factors for neck metastases in surgically treated parotid carcinomas. Arch Otolaryngol Head Neck Surg 2001;127:56-60.

17. Bhattacharyya N, Fried MP. Nodal metastasis in major salivary gland cancer: predictive factors and effects on survival. Arch Otolaryngol Head Neck Surg 2002;128:904-8.
18. Seifer G. Histological typing of salivary gland tumors. World Health Organization International Histological Classification of Tumors, 2nd ed. Berlin: Springer-Verlag; 1991.
19. Johnson C, Adamo M (eds.). SEER Program Coding and Staging Manual 2007. In. Bethesda, MD; 2007.
20. Zelig: Everyone's Statistical Software. 2007. (Accessed at http://GKing.harvard.edu/zelig.)
21. King G, James Honaker, Anne Joseph and Kenneth Scheve. Analyzing Incomplete Political Science Data: An Alternative Algorithm for Multiple Imputation. American Political Science Review 2001;95:49-69.
22. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. Otolaryngol Head Neck Surg 1999;120:834-40.
23. Spiro RH, Huvos AG. Stage means more than grade in adenoid cystic carcinoma. Am J Surg 1992;164:623-8.
24. Huber PE, Debus J, Latz D, et al. Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons or mixed beam? Radiother Oncol 2001;59:161-7.
25. Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg 1997;174:495-8.
26. Douglas JG, Laramore GE, Austin-Seymour M, Koh W, Stelzer K, Griffin TW. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J Radiat Oncol Biol Phys 2000;46:551-7.
27. Stell PM, Cruikshank AH, Stoney PJ, Canter R, McCormick MS. Adenoid cystic carcinoma: the results of radical surgery. Clin Otolaryngol Allied Sci 1985;10:205-8.
28. Miller B, Kolonel LN, Bernstein L, Young, Jr. JL, Swanson GM, West D, Key CR, Liff JM, Glover CS, Alexander GA, et al (eds). Racial/Ethnic Patterns of Cancer in the United States 1988-1992: National Cancer Institute; 1996.
29. Shavers VL, Harlan LC, Winn D, Davis WW. Racial/ethnic patterns of care for cancers of the oral cavity, pharynx, larynx, sinuses, and salivary glands. Cancer Metastasis Rev 2003;22:25-38.
30. Nichols AC, Bhattacharyya N. Racial differences in stage and survival in head and neck squamous cell carcinoma. Laryngoscope 2007;117:770-5.
31. Armstrong JG, Harrison LB, Thaler HT, et al. The indications for elective treatment of the neck in cancer of the major salivary glands. Cancer 1992;69:615-9.
32. Korkmaz H, Yoo GH, Du W, et al. Predictors of nodal metastasis in salivary gland cancer. J Surg Oncol 2002;80:186-9.
33. Zbaren P, Schupbach J, Nuyens M, Stauffer E. Elective neck dissection versus observation in primary parotid carcinoma. Otolaryngol Head Neck Surg 2005;132:387-91.
34. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. Am J Surg 1974;128:512-20.

35. Sheahan P, Byrne M, Hafidh M, Toner M, Simon C. Neck dissection findings in primary head and neck high-grade adenocarcinoma. J Laryngol Otol 2004;118:532-6.
36. Tran L, Sidrys J, Sadeghi A, Ellerbroek N, Hanson D, Parker RG. Salivary gland tumors of the oral cavity. Int J Radiat Oncol Biol Phys 1990;18:413-7.
37. Tran L, Sidrys J, Horton D, Sadeghi A, Parker RG. Malignant salivary gland tumors of the paranasal sinuses and nasal cavity. The UCLA experience. Am J Clin Oncol 1989;12:387-92.
38. Chou C, Zhu G, Luo M, Xue G. Carcinoma of the minor salivary glands: results of surgery and combined therapy. J Oral Maxillofac Surg 1996;54:448-53.
39. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40:IV-3-18.
40. Eisbruch A, Foote RL, O'Sullivan B, Beitler JJ, Vikram B. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of the targets. Semin Radiat Oncol 2002;12:238-49.
41. Gregoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol 2006;79:15-20.
42. Gregoire V, Daisne JF, Geets X, Levendag P. Selection and delineation of target volumes in head and neck tumors: beyond ICRU definition. Rays 2003;28:217-24.
43. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:160-7.
44. Droulias C, Whitehurst JO. The lymphatics of the tongue in relation to cancer. Am Surg 1976;42:670-4.
45. Feind CR, Cole RM. Contralateral spread of head and neck cncer. Am J Surg 1969;118:660-5.
46. Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR. Factors influencing contralateral lymph node metastasis from oral carcinoma. Head Neck 1999;21:104-10.
47. Woolgar JA. Histological distribution of cervical lymph node metastases from intraoral/oropharyngeal squamous cell carcinomas. Br J Oral Maxillofac Surg 1999;37:175-80.
48. Kurita H, Koike T, Narikawa JN, et al. Clinical predictors for contralateral neck lymph node metastasis from unilateral squamous cell carcinoma in the oral cavity. Oral Oncol 2004;40:898-903.
49. Northrop M, Fletcher GH, Jesse RH, Lindberg RD. Evolution of neck disease in patients with primary squamous cell carcinoma of the oral tongue, floor of mouth, and palatine arch, and clinically positive neck nodes neither fixed nor bilateral. Cancer 1972;29:23-30.
50. Martin H, Del Valle B, Ehrlich H, Cahan WG. Neck dissection. Cancer 1951;4:441-99.
51. Pfreundner L, Pahnke J, Wameling S. [Analysis of cervical lymph node metastasis of oropharyngeal carcinoma in relation to extent of the primary tumor]. Laryngorhinootologie 1996;75:223-30.

52. Gonzalez-Garcia R, Naval-Gias L, Sastre-Perez J, et al. Contralateral lymph neck node metastasis of primary squamous cell carcinoma of the tongue: a retrospective analytic study of 203 patients. Int J Oral Maxillofac Surg 2007;36:507-13.
53. Lim YC, Lee JS, Koo BS, Kim SH, Kim YH, Choi EC. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. Laryngoscope 2006;116:461-5.
54. Prins-Braam PM, Raaijmakers CP, Terhaard CH. Location of cervical lymph node metastases in oropharyngeal and hypopharyngeal carcinoma: implications for cranial border of elective nodal target volumes. Int J Radiat Oncol Biol Phys 2004;58:132-8.
55. Prokopakis EP, Snyderman CH, Hanna EY, Carrau RL, Johnson JT, D'Amico F. Risk factors for local recurrence of adenoid cystic carcinoma: the role of postoperative radiation therapy. Am J Otolaryngol 1999;20:281-6.
56. Buchholz TA, Shimotakahara SG, Weymuller EA, Jr., Laramore GE, Griffin TW. Neutron radiotherapy for adenoid cystic carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1993;119:747-52.

Table and Figure Legends

Table 1: *Percentages in parentheses represent the percentage of cancers in the site that are the histological type in question. Percentages in the bottom row represent the percentage of the total found in that site.*

Table 2: **Pearson Chi square test double-sided p-value. SE: Standard Error. The T stage is unknown for 92 patients who had distant metastasis because distant metastasis overrides tumor extension data in SEER coding. LN = Lymph Node.*

Table 3: *1533 patients are included in this analysis. The p-value is listed for the odds ratio of each variable and for the Wald statistic for inclusion of complete categorical variable groups. Cases with distant metastasis are excluded from this analysis because T stage was not recorded/unknown when there was distant metastasis. The Hosmer-Lemeshow test for this regression had a p-value of 0.023. The NagelKerke R Square is 0.526. ***p < 0.001. **0.001 < p <= 0.010. *0.010 < p <= 0.050.* †*The number of lymph node positive cases is too small for analysis.*

Table 4: *Odds ratios compare groups to the group with no factors present. ADC: Adenocarcinoma. MEC: Mucoepidermoid carcinoma. N = 1805*

Table 5: *N is the number of cases that fall in the group. The logistic regression includes the covariate controls listed in Table 3. Hosmer-Lemeshow statistic p-value is 0.133 indicating no difference between predicted and observed values. NagelKerke R square is 0.464.*

Figure 1: *The blue curve represents patients who were lymph node negative on presentation and the green curve represents patients with lymph node involvement on presentation.*