Published in final edited form as:

Am J Clin Oncol. 2012 October ; 35(5): 468–473. doi:10.1097/COC.0b013e3182195619.

The Prognostic Importance of Midline Involvement in Oral Tongue Cancer

Shane Lloyd, M.D.^{*}, James B. Yu, M.D.^{*}, Lynn D. Wilson, M.D., M.P.H.^{*}, Benjamin L. Judson, M.D.[‡], and Roy H. Decker, M.D., Ph.D.^{*}

^{*}Department of Therapeutic Radiology Yale School of Medicine, New Haven, CT

[‡]Department of Surgery, Division of Otolaryngology Yale School of Medicine, New Haven, CT

Abstract

Objectives—To examine the importance of midline involvement and other clinicopathological factors in predicting the rate of contralateral lymph node metastasis and survival in oral tongue squamous cell carcinoma.

Methods—We used SEER data to identify a cohort of 5430 patients with laterally rising tumors. Clinicopathological factors examined as potentially predictive of contralateral lymph node metastasis included extension to midline, T classification, anatomical site, grade, histological sub-type, race, age, and gender. Survival analysis included the above factors plus lymph node status.

Results—T1 tumors and lateral T2 and T3 tumors had rates of contralateral lymph node metastasis ranging from 0.7-0.9% on presentation. T4 lesions and midline crossing T2 and T3 lesions had corresponding rates of 8.3 to 13.0%. Primary extension across the midline was associated with a mean survival about half that of strictly lateral tumors and its significance was maintained in multivariate analysis.

Conclusions—Patients with T1 disease or T2-3 disease that doesn't cross midline are in a different prognostic class from patients with T2-3 disease that crosses midline or T4 tumors. These results give the strongest evidence to date that involvement of the midline is a powerful predictor for decreased survival in oral tongue squamous cell carcinoma.

Introduction

Involvement of cervical lymphatics is thought to be the most important indicator of a poor outcome in squamous carcinoma (SCC) of the oral tongue. Nodal metastasis can decrease survival substantially (1, 2). Patients with contralateral lymph node metastasis have a particularly poor prognosis (1, 3). It is known that extension of the primary tumor to the midline increases the risk of contralateral lymph node metastasis (4, 5) and other clinicopathological predictors have been examined with varying results (5-9). The tendency

Corresponding Author and Requests for Reprints: Roy H. Decker, M.D., Ph.D. Yale University School of Medicine, Department of Therapeutic Radiology, LL-516 Smilow, P.O. Box 208040, New Haven, Connecticut 06510-3221. Tel: 203.737.2758; Fax: 203.785.4622; roy.decker@yale.edu.

The authors have no conflicts of interest, financial or otherwise, to report.

Data in this manuscript were presented in an oral presentation at the American Radium Society 91st Annual Meeting, Vancouver, British Columbia, Canada, April 27, 2009.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

for tumors that involve the midline to metastasize to the contralateral lymph nodes raises the question of a different survival in these patients. This would be useful to know especially when there is no clinical lymph node metastasis on presentation. This issue has not been addressed in the literature. Current surgical and radiotherapeutic guidelines for treatment of the contralateral neck lack the benefit of large studies that examine the factors predictive of contralateral lymph node metastasis and survival.

The objectives of this study are to use a population-based cancer registry to examine the effect of various clinicopathological factors, including extension to the midline, T classification, grade, gender, race, and age, on the rate of contralateral lymph node metastasis for oral tongue squamous cell carcinoma and to examine the effects of these factors on survival.

Materials and Methods

We collected cases of oral tongue SCC from the Surveillance, Epidemiology, and End Results (SEER) program database from 1988 to 2004 for the following primary sites (site codes in parentheses): Dorsal surface of tongue NOS (C02.0), Border of tongue (C02.1), Ventral surface of tongue (C02.2), and Anterior 2/3 of tongue NOS (C02.3). Squamous cell carcinoma histological subtypes included squamous cell carcinoma NOS, keratinizing, large cell, small cell, spindle cell, micro-invasive, clear cell type, papillary and basaloid squamous cell carcinoma, as well as Bowen disease and verrucous carcinoma.

We used SEER “Extent of Disease” codes to identify midline involvement for patients diagnosed between 1988 and 2002. For the oral tongue, SEER provides a value for the furthest extent of disease applicable to the case. The potential values are as follows: 10 = invasive tumor on one side confined to lamina propria or submucosa; 20 = musculature, intrinsic or NOS; 30 = Localized, NOS; 40 = tumor crosses midline; 50 = base of tongue, gingival, or floor of mouth; 60 = lateral pharyngeal wall or inferior surface of soft palate; 70 = mandible or maxilla; and 80 = extrinsic musculature. For years 2003 and 2004, SEER provides a “Collaborative Staging Extension” code that functions similarly and has similar values. One exception is that a “midline tumor” is coded as having less extension than a tumor that crosses midline. These midline tumors are given the same extension code as tumors listed as localized, NOS and this is considered less extension than crossing the midline. Because of this, for two of the 16 years of our study, a minority of midline arising tumors may not be counted as midline crossing in our analyses. Tumors centered exactly on the midline are uncommon and an analysis of contralateral lymph node metastasis would be nonsensical for these tumors since they presumably do not arise from one side. In summary, we included all tumors assigned an extent of disease value of 40 as involving the midline and all tumors with lesser values as being lateral only. Tumors assigned an extent of disease value greater than 40 are not included in analyses assessing the prognostic significance of midline crossing and because of this, we are only able to examine T1-3 tumors that did not extend beyond the oral tongue in these analyses as outlined below.

We excluded patients from the study if they had previous primaries of the head and neck (393 cases). We also excluded cases if the nodal status was unknown (822 cases) in all analyses. In our analysis of the predictors of contralateral lymph node metastasis, we excluded the abovementioned cases as well as those coded in such a way that the laterality of the nodes was not explicitly stated as unilateral or contralateral (75 cases). In our Cox proportional hazards model, we excluded the cases in the two abovementioned categories as well as those coded in such a way that the number of ipsilateral nodes was not explicitly stated (383 cases). All survival analyses included only those patients who were treated with primary cancer directed surgery. The median follow-up was 5 years, 2 months.

All staging data includes the information available from imaging and/or pathology within four months of diagnosis or up to the time of the first primary tumor directed surgery. We refer to the staging done in this time period as the stage “at presentation” throughout this manuscript. Staging was assigned according to the Seventh Edition of the AJCC Staging System according to extent of disease and tumor size, extent of nodal involvement and presence or absence of distant metastasis as given in SEER. We used the Chi-square statistic for univariable analysis of categorical variables and binary logistic regression for multivariable analysis. Survival was analyzed with Kaplan-Meier curves and a Cox proportional hazards model. All statistics were calculated on SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

Our final dataset consisted of 5430 cases of squamous cell carcinoma of the oral tongue. The mean age at diagnosis was 61 years with a standard deviation of 14.9 years. 3194 (58.8%) patients were male and 2236 (41.2%) were female. 4584 (84.4%) patients were listed as Caucasian, 342 (6.3%) were listed as African American and 461 (8.5%) were listed as other races.

One hundred and thirty-five (2.5% of all patients) had contralateral lymph node metastasis. This represented 14.6% of the 922 patients in the study with any lymph node involvement. Most patients listed as not having contralateral lymph node metastasis were staged clinically. T1 tumors as well as T2 and T3 tumors that didn't cross the midline or extend beyond the oral tongue were very unlikely to present with contralateral lymph node metastasis with rates ranging from 0.7 to 0.9% (Table 1). Conversely, T4 tumors and lateral T2 and T3 tumors that extended across the midline but not beyond the oral tongue had rates ranging from 8.3 to 13.0%. T2 and T3 tumors that crossed the midline were 10.6 and 18.0 times more likely to go to the contralateral lymph nodes than strictly lateral tumors respectively. Anatomical position and grade were not as powerful in predicting the presence of contralateral nodes. Contralateral nodes were involved more frequently in dorsal surface tumors than in ventral surface tumors (3.2% versus 2.2%) and more frequently in high-grade tumors than in low-grade tumors (3.6% versus 2.7%). Neither of these differences was statistically significant. Furthermore, verrucous carcinoma and papillary SCC subtypes never metastasized across the midline and only 2 of 80 had ipsilateral nodal involvement.

Extension across the midline retained its significance in predicting contralateral lymph node metastasis while holding other factors constant in logistic regression. Tumors that extend across the midline were more likely to involve the contralateral nodes with an odds ratio of 9.61 ($p < 0.001$). No other clinicopathological factor was statistically significant except the number of nodes examined, which was included as a control for the extent of neck dissection performed. The other factors examined included grade, T classification, race, age, and gender. 2433 cases were included in the analysis.

Patients with tumors that cross the midline had a significantly decreased survival (Figure 1). Crossing the midline decreased mean survival by more than one half (9 years 0.6 months and 4 years 1.0 months respectively). We separated patients by T classification and again examined the survival of patients whose tumors crossed the midline versus those whose tumors did not. This was done in order to test the hypothesis that the effect of crossing the midline on survival is confounded by tumor size. Mean survival was lower for tumors that crossed the midline for T1 and T3 tumors and there was not a statistically significant difference for T2 tumors, although the trend remained.

There were significant differences in survival among nodal groups (Figure 2). Specifically, any nodal disease at presentation decreased survival compared to patients with no nodal metastasis. Also, when a single ipsilateral node was detected, mean survival was longer than when contralateral node(s) were detected. The difference between one ipsilateral node and multiple ipsilateral nodes, and the difference between multiple ipsilateral nodes and contralateral node(s) were not statistically significant.

When the analysis of the effect of crossing the midline on survival was broken down into nodal involvement groups, this survival advantage remained especially pronounced for patients who were node negative at presentation (8 years 9.9 months and 4 years 9.3 months respectively). For patients with a single or multiple ipsilateral nodes or patients with contralateral nodes there was no difference in mean survival. The survival for patients with contralateral lymph node metastasis on presentation was similar to the survival of N0 patients with tumors that crossed the midline.

While controlling for other clinicopathological factors in a Cox proportional hazards model, tumors that cross the midline had statistically significant decreased survival with a hazard ratio of 2.18 (Table 2). Other factors that conferred decreased survival were positive ipsilateral or contralateral nodes, T2 stage, male gender, older age, and high-grade tumors. Lymph node dissection as defined by pathological examination of 4 or more nodes was associated with increased survival.

As determined by the site-specific cause of death recode data in SEER, patients who died were almost three times more likely to die from oral tongue cancer when the tumor crossed the midline (36.2% vs. 12.4%, p -value < 0.001 by Pearson chi-square test). The cause of death was also more likely to be attributed to the tongue in node positive patients, in patients with increasing T classification, in high-grade tumors, and in female patients as determined by univariable analysis.

Discussion

The importance of midline involvement on survival raises the question of whether contralateral lymph node metastasis is being identified and/or treated aggressively enough. In the case of the ipsilateral neck, prophylactic treatment generally improves locoregional control but the hypothesis that it improves survival has not been shown consistently in published analyses (10-14).

In patients with tongue SCC that does not cross the midline, it has been suggested that contralateral neck dissections are ineffective. In a study of stage I and II oral cavity SCC, Lim and colleagues found only one case of occult contralateral lymph node metastasis in 25 elective contralateral neck dissections (4%) (15). Patients were followed for a mean of 56.3 months and no cases of contralateral neck relapse were found. There was no survival benefit for contralateral prophylactic lymph node dissections. All patients had unilateral lesions that did not extend across the midline. In light of the results of the present study, the rate may be much higher in patients with tumors that involve the midline. In another retrospective review of oral cavity carcinomas, Koo and colleagues found that prophylactic contralateral neck dissection was more likely to reveal occult nodes when there was ipsilateral nodal involvement, or when the primary tumor crossed the midline (16). Five of eight patients (63%) had occult contralateral lymph node metastasis in midline crossing primaries and only 1/20 (5%) had occult contralateral lymph node metastasis in non-midline crossing primaries.

Prophylactic external beam radiation therapy of the contralateral N0 neck has been shown to decrease the rate of contralateral neck relapse for oral tongue SCC in some studies (17-19). Northrup and others reported that it occurred in only 1/22 (4.5%) patients treated with

elective contralateral neck dissection and irradiation or irradiation only compared to 8/30 (26.7%) patients treated with radical neck dissection only in cases of oral tongue (N1-2a) SCC (19). Doses from 3,000 centigray in 3 weeks to 5,000 centigray in 5 weeks were given to the subdigastric area of the contralateral neck.

In our study, patients with T1 tumors and those with T2 or T3 tumors that did not cross the midline had rates of contralateral lymph node metastasis ranging from 0.7 to 0.9%. Given these results and those cited above, it is probably safe to withhold contralateral neck dissection for these patients when there is no clinical evidence of cervical metastasis at presentation. However, close observation is advised and longitudinal data is needed to determine the rate of subsequent conversion in the contralateral neck. Many studies have found that recurrence in the contralateral lymph nodes occurs largely within 2 years of diagnosis (7, 20, 21) and close surveillance is thus mandatory during this time period.

Because of limitations in SEER data we were unable to tell which patients had clinically negative contralateral necks but were found to have contralateral disease at surgical neck dissection. The data are clear however, that midline involvement remains the biggest factor predicting contralateral lymph node metastasis independent of T classification while controlling for the number of nodes sampled. The patients whose management stands to change the most from these findings are those with T2 disease with lesions extending to the midline and who are clinically N0 because at many centers these patients would not be offered contralateral neck dissection or radiation therapy. Because of the association we have demonstrated between midline involvement and with contralateral lymph node metastasis, and perhaps more importantly, the significantly decreased overall survival, these patients may merit more aggressive treatment. Further prospective studies need to be undertaken to determine the benefit of prophylactic neck dissection and/or radiation therapy in these patients.

Among the few studies that have examined the clinicopathological risk factors for contralateral lymph node metastasis, results have been inconsistent. Kowalski and colleagues also found a higher risk for T4 tumors but there was no statistical relationship on multivariable analysis (5). Our study revealed an increased risk for T4 tumors on univariable analysis. In our multivariable analysis, we excluded cases in which the tumor extended beyond the oral tongue, i.e. T4 tumors, so T4 classification may still be important. In a small series by Gonzalez-Garcia histopathologic grading and peritumoral inflammation were the only factors that were associated with contralateral lymph node relapse in the nine patients in whom it occurred (7).

We found an incidence of contralateral lymph node metastasis of 2.5% at presentation (135 of 5430 patients). This is slightly below the rate found in other studies, which ranges from 3.0 to 9.2% (5, 6, 9, 22, 23). In contrast to the present study, many of these studies included only patients who received a contralateral neck dissection. The data in our analysis likely includes many cases in which post-operative radiation therapy to the neck is planned and for this reason providers have foregone a neck dissection that would have likely revealed positive nodes.

Lymphatic metastasis from the tongue can follow different patterns depending on the location of the primary tumor. It has been shown by Feind and others that more anterior tumors are at a higher risk for contralateral neck involvement (6). In the present study there was an increased rate in patients with dorsal tongue tumors compared to ventral tongue tumors. The explanation for this may be similar to that of the anterior tongue effect in that metastases must travel longer through the tongue, and longer through the lymphatics, giving rise to more chance of crossover.

Contralateral lymph node metastasis can only occur if the tumor involves or crosses the midline either clinically or sub-clinically or if the tumor comes close enough to the midline for small lymphatic structures that themselves cross the midline in the tongue are utilized. Lymphatic capillaries and collecting trunks that cross the midline exist and are utilized more frequently the more centrally located the primary lesion (6). Vascular and perineural infiltration are two sub-clinical factors that may provide an anatomically rational explanation for increased contralateral neck involvement (5). The propensity for vascular and neural structures to aid in spread across the midline can be expected to rise the closer the tumor is to the midline however.

In SEER data when contralateral metastasis is found no information is given on the presence or extent of ipsilateral metastasis. Therefore, we were unable to examine the effect of ipsilateral lymph node metastasis on contralateral lymph node metastasis. This association has been shown in several studies (4-6, 8, 9) and this has led to the general practice of radiotherapeutic treatment of the contralateral neck when the ipsilateral neck is node positive (15). We also did not include tumors arising directly on the midline because of the difficulty of assigning laterality to metastases.

Conclusions

For SCC of the oral tongue, contralateral lymph node metastasis is rarely found at presentation in T1 tumors and T2-3 tumors that do not extend across the midline. Special attention must be paid to the contralateral neck for patients with T2 or T3 tumors that cross the midline and for all T4 tumors. T classification is not a significant predictor of contralateral lymph node metastasis in tumors that do not extend beyond the oral tongue while primary midline involvement is extremely important. Contralateral lymph node metastasis is extremely unlikely for lateral verrucous or papillary SCC subtypes. When the oral tongue SCC crosses the midline it portends significantly decreased survival, particularly in clinically N0 patients. Midline involvement is thus important in predicting the pattern of nodal spread as well as providing prognostic information about survival. A prospective, randomized trial would be more suitable to determine if a survival advantage exists for elective treatment of the contralateral neck with surgical neck dissection and/or radiation therapy in these patients.

Acknowledgments

Funding for this project was provided by CTSA Grant Number UL1 RR024139 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH roadmap for Medical Research.

Shane Lloyd had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- [1]. Kowalski LP, Bagietto R, Lara JR, et al. Prognostic significance of the distribution of neck node metastasis from oral carcinoma. *Head Neck*. 2000; 22:207–14. [PubMed: 10748442]
- [2]. Puri SK, Fan CY, Hanna E. Significance of extracapsular lymph node metastases in patients with head and neck squamous cell carcinoma. *Curr Opin Otolaryngol Head Neck Surg*. 2003; 11:119–23. [PubMed: 14515090]
- [3]. Lawrence KB, Murray JE, Friedman P. Influence of Cervical Lymph Node Metastases on Therapy and Prognosis of Lingual Cancer. *Am J Surg*. 1964; 108:461–4. [PubMed: 14211430]
- [4]. Martin H, Del Valle B, Ehrlich H, et al. Neck dissection. *Cancer*. 1951; 4:441–99. [PubMed: 14839606]

- [5]. Kowalski LP, Bagietto R, Lara JR, et al. Factors influencing contralateral lymph node metastasis from oral carcinoma. *Head Neck*. 1999; 21:104–10. [PubMed: 10091977]
- [6]. Feind CR, Cole RM. Contralateral spread of head and neck cancer. *Am J Surg*. 1969; 118:660–5. [PubMed: 5347082]
- [7]. 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. [PubMed: 17331706]
- [8]. 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. [PubMed: 15380167]
- [9]. Woolgar JA. Histological distribution of cervical lymph node metastases from intraoral/oropharyngeal squamous cell carcinomas. *Br J Oral Maxillofac Surg*. 1999; 37:175–80. [PubMed: 10454023]
- [10]. Yuen AP, Ho CM, Chow TL, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck*. 2009; 31:765–72. [PubMed: 19408291]
- [11]. Capote A, Escorial V, Munoz-Guerra MF, Rodriguez-Campo FJ, et al. Elective neck dissection in early-stage oral squamous cell carcinoma--does it influence recurrence and survival? *Head Neck*. 2007; 29:3–11. [PubMed: 17103411]
- [12]. Keski-Santti H, Atula T, Tornwall J, et al. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol*. 2006; 42:96–101. [PubMed: 16256414]
- [13]. Haddadin KJ, Soutar DS, Oliver RJ, et al. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head Neck*. 1999; 21:517–25. [PubMed: 10449667]
- [14]. Veness MJ, Morgan GJ, Sathiyaseelan Y, et al. Anterior tongue cancer and the incidence of cervical lymph node metastases with increasing tumour thickness: should elective treatment to the neck be standard practice in all patients? *ANZ J Surg*. 2005; 75:101–5. [PubMed: 15777383]
- [15]. Lim YC, Lee JS, Koo BS, et al. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. *Laryngoscope*. 2006; 116:461–5. [PubMed: 16540910]
- [16]. Koo BS, Lim YC, Lee JS, et al. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. *Head Neck*. 2006; 28:896–901. [PubMed: 16721743]
- [17]. Spaulding CA, Korb LJ, Constable WC, et al. The influence of extent of neck treatment upon control of cervical lymphadenopathy in cancers of the oral tongue. *Int J Radiat Oncol Biol Phys*. 1991; 21:577–81. [PubMed: 1869456]
- [18]. Fletcher GH. Elective irradiation of subclinical disease in cancers of the head and neck. *Cancer*. 1972; 29:1450–4. [PubMed: 5031239]
- [19]. Northrop M, Fletcher GH, Jesse RH, et al. 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. [PubMed: 5007385]
- [20]. Snow GB, Annyas AA, van Slooten EA, et al. Prognostic factors of neck node metastasis. *Clin Otolaryngol Allied Sci*. 1982; 7:185–92. [PubMed: 7105450]
- [21]. Weber PC, Johnson JT, Myers EN. The impact of bilateral neck dissection on pattern of recurrence and survival in supraglottic carcinoma. *Arch Otolaryngol Head Neck Surg*. 1994; 120:703–6. [PubMed: 8018320]
- [22]. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. *Head Neck Surg*. 1988; 10:160–7. [PubMed: 3235344]
- [23]. Droulias C, Whitehurst JO. The lymphatics of the tongue in relation to cancer. *Am Surg*. 1976; 42:670–4. [PubMed: 949139]

Overall Survival by the Laterality of the Primary Tumor by T Classification

Figure 1.

All curves are Kaplan-Meier survival curves and patients alive at last follow up are censored. The X-axis is months and the Y-axis is proportion of patients surviving. P-Values are for the Log Rank (Mantel-Cox) test comparing the two curves. Ips: Ipsilateral. Contr: Contralateral.

Figure 2.

All curves are Kaplan-Meier survival curves and patients alive at last follow up are censored. The X-axis is months and the Y-axis is proportion of patient surviving. P-Values are for the Log Rank (Mantel-Cox) test comparing the two curves.

Table 1

Frequency of Contralateral Lymph Node Metastasis in Selected Clinicopathological Groups.

Clinicopathological Characteristic (P-Value)*	Patients with Contr. LN Met. / Patients in Group	% CLNI (95% C.I.)
Laterality (P < 0.001)		
Lateral	20 / 2654	0.8 (0.4-1.1)
Crosses Midline	8 / 87	9.2 (3.1-15.3)
T Classification (P < 0.001)		
T1	17 / 2391	0.7 (0.4-1.1)
T1 & Lateral	11 / 1544	0.7 (1.3-1.1)
T1 & Crosses Midline	0 / 12	0.0
T2	27 / 1408	1.9 (1.2-2.6)
T2 & Lateral	5 / 641	0.8 (0.1-1.5)
T2 & Crosses Midline	3 / 36	8.3 (-0.7-17.4)
T3	47 / 1321	3.6 (2.6-4.6)
T3 & Lateral	4 / 469	0.9 (0.0-1.7)
T3 & Crosses Midline	5 / 39	12.8 (2.3-23.3)
T4	29 / 223	13.0 (8.6-17.4)
Anatomical Site (P < 0.001)		
Dorsal Surface	13 / 409	3.2 (1.5-4.9)
Border	39 / 2471	1.6 (1.1-2.1)
Ventral Surface	26 / 1171	2.2 (1.4-3.1)
Ant 2/3, NOS	57 / 1379	4.1 (2.3-4.9)
Grade (P = 0.068)		
Grade I or II	93 / 3767	2.5 (2.0-3.0)
Grade III or IV	30 / 835	3.6 (2.3-4.9)
Histological Sub-type (P = 0.136)		
Papillary or Verrucous	0 / 86	0.0
Other SCC Sub-types	135 / 5344	2.5 (2.1-3.0)

* P-value for Chi Square analysis testing for differences in rates of contralateral lymph node metastasis among groups. C.I.: Confidence Interval of the proportion. "Contr. LN Met." = contralateral lymph node metastasis.

Table 2Cox Proportional Hazards Model. $N = 2196$.

	H.R.	C.I.	P-Value
Lymph Nodes			< 0.001
Single Ipsilateral	2.02	(1.50-2.71)	0.001
Multiple Ipsilateral	3.81	(2.86-5.08)	< 0.001
Contralateral	5.73	(2.91-11.29)	< 0.001
Tumor Crosses Midline	2.18	(1.46-3.25)	< 0.001
T Classification (Compared to T1)			< 0.001
T2	1.57	(1.33-1.86)	< 0.001
T3	1.03	(0.84-1.26)	0.776
Male Gender	1.16	(1.00-1.35)	0.046
Age	1.03	(1.02-1.03)	< 0.001
High Grade (Compared to Low-Grade)	1.48	(1.23-1.79)	< 0.001
Lymph Node Dissection	0.70	(0.58-0.84)	< 0.001

* "Nodal Dissection" includes those cases documented as a dissection or those cases with 4 or more nodes examined by pathology. No cases in this analysis had distant metastasis. Only those cases that had surgery to the primary site are included. $-2 \text{ Log Likelihood} = 10452.843$. Change from model of constant only: $\text{chisquare } 287.178 \text{ with } 13 \text{ d.f., Sig. } < 0.001$.