

# Primary Tumor Thickness as a Risk Factor for Contralateral Cervical Metastases in T1/T2 Oral Tongue Squamous Cell Carcinoma

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**Objectives/Hypothesis:** Contralateral cervical metastases represent an avoidable source of failure in squamous cell carcinoma (SCCa) of the oral tongue. We sought to identify risk factors for the development of contralateral cervical metastases in T1/T2 oral tongue SCCa.

**Study Design:** Retrospective review.

**Methods:** We reviewed the medical records of 50 sequential cases of Stage I/II SCCa of the oral tongue treated with surgery between 1983 and 2003 at Loyola University Medical Center and Hines VA Hospital. Clinical staging, primary tumor thickness, results of neck dissection, adjuvant treatment, site and date of recurrence, and final outcome were recorded. Follow-up ranged from 0.2 to 17 years, with a mean of 5 years. Data were analyzed using multivariate logistic, Cox regression analysis, and a classification and logistic regression tree analysis.

**Results:** The odds ratio for risk of developing contralateral neck metastasis was 5% for each 1 mm increase in tumor thickness ( $P = .68$ ). The risk did not change when controlling for the presence of ipsilateral metastasis. There was a significant relationship between contralateral cervical metastases and the development of recurrent disease at any site ( $P = .005$ ). Classification tree analysis determined the risk for contralateral metastases and was greatest for patients with tumors  $>3.75$  mm thick and  $\leq 9.5$  mm thick.

**Conclusions:** This report is the first to our knowledge that evaluates thickness as a risk factor for contralateral cervical metastasis in oral tongue SCCa. We recommend consideration be given to treating the contralateral neck in cases where the primary tumor is  $>3.75$  mm thick.

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## INTRODUCTION

The identification of patients who present with SCCa of the oral tongue and are at risk for cervical nodal metastases is a topic of interest for head and neck surgeons. Many groups have studied the incidence of ipsilateral nodal metastases in an attempt to more accurately identify those patients at risk. There is evidence to support various risk factors, notably thickness of the primary tongue SCCa,<sup>1–5</sup> double DNA aneuploidy,<sup>1</sup> and less differentiated pathology.<sup>1,3</sup> In addition to tumor thickness, Sparano's group found through a multivariate analysis that perineural invasion, infiltrating-type invasion front, poorly differentiated tumors, and T2 stage were also associated with an increased likelihood of cervical metastases in N0 early-stage tongue cancer patients.<sup>4</sup> Similarly, Lim et al. studied risk factors for late cervical metastases in 56 patients with early-stage oral tongue cancer.<sup>5</sup> Multivariate analysis revealed that tumor thickness  $> 4$  mm, mode of invasion grade 3 or 4, and low E-cadherin expression were independent factors predicting for late cervical metastases.

It is important to identify those at risk of regional disease, since evidence points to worse survival in patients with positive regional metastases,<sup>6</sup> especially those with + extracapsular spread (ECS) and/or multiple positive nodes.<sup>7</sup> Though therapeutic neck dissection is an option in those cases when regional metastases develop, there is evidence of benefit on survival from treatment of the clinical N0 neck with a prophylactic neck dissection simultaneous with resection of the primary.<sup>8,9</sup> The study by Lim found that late cervical metastasis was the only prognostic factor for overall survival ( $P = .002$ ).<sup>5</sup> In those patients who recur, survival is

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TABLE I.  
Clinical Characteristics and Treatment Information.

	Number of Cases (%)
Sex	
Male	40 (80)
Female	10 (20)
T stage	
1	21 (42)
2	29 (58)
N stage (clinical)	
Negative	38 (76)
Positive (1, 2a, or 2b)	12 (24)
Neck dissection	
None	19 (38)
Ipsilateral	25 (50)
Ipsilateral and contralateral	6 (12)
Adjuvant treatment	
Radiation therapy	
Primary	4 (8)
Primary & ipsilateral neck	5 (10)
Primary & bilateral neck	11 (22)
Chemotherapy	2 (4)

better in those with a local recurrence versus a regional recurrence.<sup>10</sup>

The majority of work in this area has focused on ipsilateral nodal metastases since the oral tongue is felt to have primarily an ipsilateral lymphatic drainage pattern, unlike the base of the tongue, which is known to have a rich and bilateral lymphatic drainage pattern. Experience demonstrates that a small group of patients with oral tongue SCCa will metastasize to the contralateral neck. Predicting who is at risk for this is also important, though at least as difficult as predicting those patients who are at high risk to harbor ipsilateral metastases. In fact, contralateral neck node metastasis has been identified as a significant factor in neck failures in those patients undergoing simultaneous prophylactic neck dissection.<sup>8</sup> There has been some work to show that the status of the ipsilateral neck is important in assessing the risk to the contralateral neck. Notably, when the ipsilateral side of the neck was involved, the contralateral side had a 22% false-negative assessment.<sup>11</sup> Furthermore, patients with ECS in neck dissection specimens obtained at the time of primary resection were at a higher risk of regional recurrence compared to those with no nodes positive or positive nodes without ECS.<sup>12</sup>

In our practice, we have noted a small but significant group of patients who developed contralateral regional metastases from T1 or T2 oral tongue squamous cell carcinoma. We initiated a retrospective review of our 20-year experience at a tertiary care program that includes a university-based practice as well as a veterans administration hospital to investigate those factors that may predict the presence of contralateral metastatic disease in patients with oral tongue SCCa. Our goal is

to identify those patients that may harbor micrometastases at presentation so that treatment of the contralateral neck may be reserved for those with a higher likelihood of contralateral failure.

## MATERIALS AND METHODS

Patients who underwent surgical resection of a T1 or T2 SCCa of the oral tongue during the period of 1983 through 2003 at Loyola University Medical Center or the Hines VA Hospital were identified. Fifty cases were identified. Patients were excluded if the primary surgery was not performed at either Loyola University Medical Center or Hines VA Hospital, if the pathology specimen was not available for review, and the desired information was not in the original pathology report, or if the status of the contralateral neck disease could not be determined due to insufficient follow-up. Permission to perform the study was granted by the institutional review board at both institutions. A retrospective review was performed on the patients' charts and pathology specimens to obtain the following information: patient gender, original stage of tumor, neck dissection results if done, primary tumor thickness, details of postoperative radiation therapy when performed, and status of disease during follow-up. Statistical analysis was accomplished using STATA 10.0 (StataCorp, College Station, TX) and CART (Salford Systems, San Diego, CA) statistical software.

## RESULTS

Fifty patients were identified who fit our inclusion criteria. The clinical stage and treatment characteristics of the patients are listed in Table I. Average follow-up was 5 years (range 0.2–17 years). In patients who are still alive, average follow-up was 5.9 years (range 0.6–13 years). One patient harbored a clinically occult contralateral metastasis noted on prophylactic neck dissection and developed further contralateral metastases during follow-up, and four other patients developed a contralateral metastasis during the follow-up period. The summary of patients grouped by status of cervical metastases is listed in Table II.

Tumor thickness was assessed in each of the cases. Table III shows the range and average thickness in the subjects based on the status of neck disease. Notably, three subjects suffered from bilateral cervical metastases; one had an ipsilateral micrometastasis on presentation and developed a contralateral metastasis,

TABLE II.  
Breakdown of Cervical Metastasis by Site and Presentation.

	Number of Cases (%)
Clinical metastases at presentation	
Ipsilateral	12 (24)
Contralateral	0 (0)
Micrometastases at presentation	
Ipsilateral (n = 20 ipsi ND, clin N0)	6 (12)
Contralateral (n = 6 contra ND)	1 (2)
Development of cervical metastases	
Ipsilateral	4 (8)
Contralateral	5 (10)

ipsi = ipsilateral; ND = neck dissection; clin = clinical; contra = contralateral.

TABLE III.

Thickness of Primary Tumors in Subjects Based on Status of Neck Disease.

	Number of Subjects	Thickness	
		Range	Average
No cervical metastases	28	0.6–16 mm	4.3 mm
Ipsilateral metastases on presentation or during f/u *	20	0.5–18 mm	7.95 mm
Contralateral metastases on presentation or during f/u	5	4–9 mm	6.8 mm

f/u = follow-up.

\*This includes one patient with a primary tumor thickness of 0.5 mm who was staged clinically as N1 but did not undergo neck dissection. The subject died 2 months after resection of the primary surgery with no evidence of disease. If that value is removed, the range of thickness in this group is 3–18 mm, and the average thickness is 8.3 mm.

and two subjects developed bilateral cervical metastases during follow-up. There was a significant relationship between thickness and the presence or development of ipsilateral metastases ( $P = .002$ ). There was also noted to be a relationship between thickness and the presence or development of contralateral metastases. Though this result did not achieve significance statistically, this analysis suggests that for each 1 mm increase in thickness, there is an approximate 5% increase in the risk for contralateral metastases (hazard ratio = 1.05,  $P = .68$ ). When this was controlled for the presence of ipsilateral metastasis, the relationship was similar (hazard ratio = 1.03,  $P = .98$ ).

We were also interested in risk factors for recurrent disease. There was a statistically significant relationship between thickness and recurrence. For every 1-mm increase in thickness, there was a 15% increase in the risk of recurrence (hazard ratio = 1.15,  $P = .007$ ). We also examined the relationship between the presence or development of contralateral cervical metastases and the risk of recurrence and found a significant relationship between the presence or development of contralateral cervical metastases and the development of recurrent disease at any site ( $P = .005$ ).

The survival data in these patients are shown in Figures 1 and 2. We found a significant difference in disease-free survival based on thickness such that subjects with a primary tumor  $>3.75$  mm in thickness were more likely to suffer a recurrence (Fig. 1). In fact, the risk of recurrence in the group of subjects with tumors  $>3.75$  mm thick showed an incidence rate of 9/100 patient-years versus an incidence rate of 3/100 patient-years in those with thin ( $\leq 3.75$  mm thick) tumors (one-sided,  $P = .04$ ). Overall survival based on the status of cervical metastases is shown in Figure 2. These differences did not reach statistical significance ( $P = .14$ ).

To assist with a clinically applicable view of these data, we performed a classification tree analysis. As noted in Figure 3, node 1 separates tumors initially into groups with primary tumor thickness  $\leq 3.75$  mm and another group with tumors  $>3.75$  mm. In the former group, there were no instances of contralateral metastasis. Node 2 separates the tumors again based on thickness, with tumors  $>9.5$  mm also showing no instan-

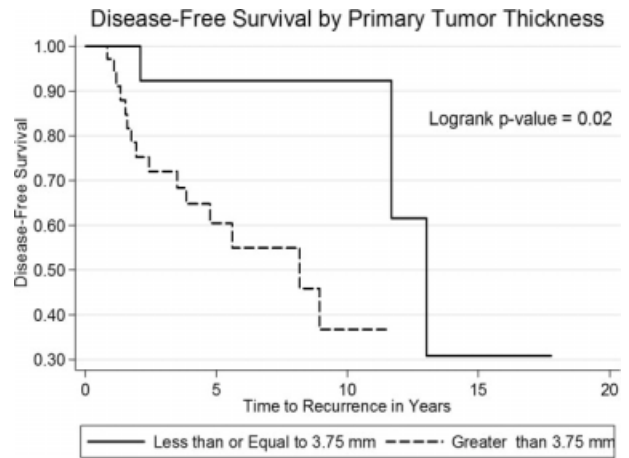


Fig. 1. Disease-free survival based on primary tumor thickness.

ces of contralateral metastasis. We hypothesized that this curious finding may be explained in that all patients with thick tumors ( $>9.5$  mm) may have undergone prophylactic treatment of the neck with surgery and/or radiation therapy. Indeed, of the seven patients in the group with tumors thicker than 9.5 mm, all but one (6/7, 86%) underwent treatment of the contralateral neck with surgery and/or full course radiation therapy. In contrast, of the 28 patients with tumors  $>3.75$  mm but  $\leq 9.5$  mm, only seven had the contralateral neck treated with a neck dissection or radiation therapy (7/28, 25%).

## DISCUSSION

The risk of presenting with or developing contralateral cervical metastases in patients diagnosed with SCCa of the oral tongue is low but real. In our study, the incidence was 10%. This corresponds to the findings of Mukherji and others who found that oral tongue and floor-of-mouth cancers have an expected drainage to contralateral nodal basins in up to 9% of cases.<sup>13</sup> The site of oral tongue cancers may play a factor in the risk of contralateral metastases since the lymphatic drainage may differ in different areas of the oral tongue, but the

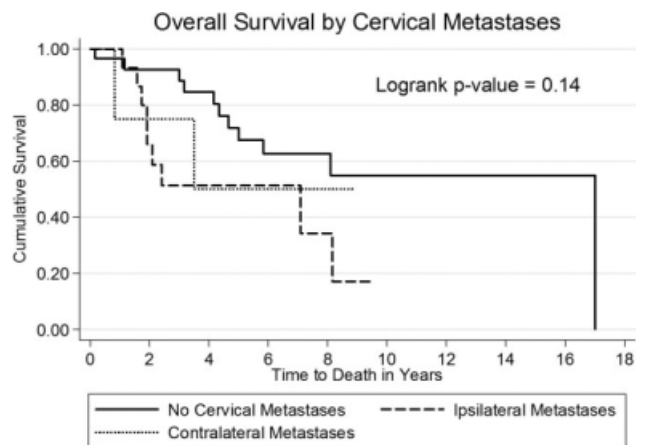


Fig. 2. Overall survival based on the presence or development of cervical metastases.

### Classification Tree Analysis Based on Thickness of Primary Tumor

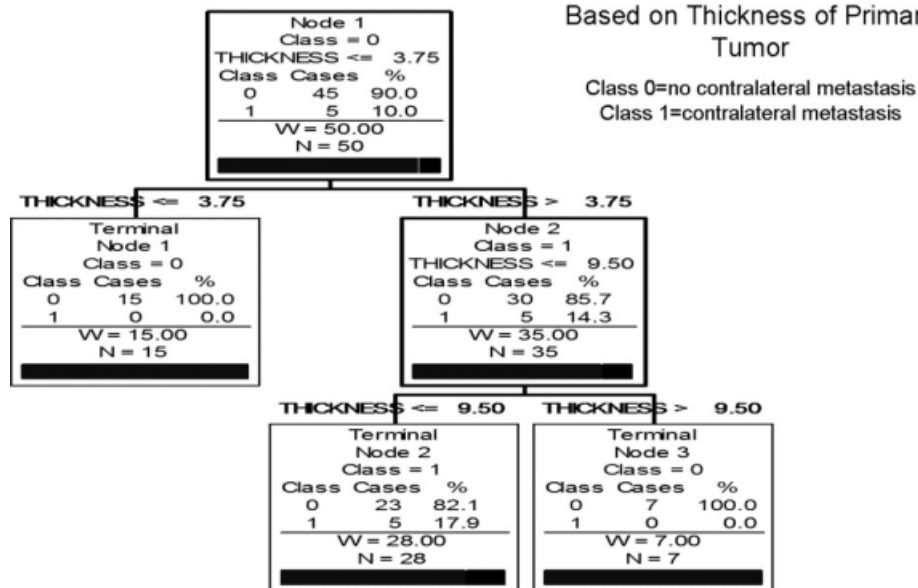


Fig. 3. Classification tree analysis for outcome 1 (presence or development of contralateral cervical metastases) based on thickness of the primary tumor.

numbers in the current study are too small to draw conclusions. The work of Mukherji and others also suggests that tongue and floor-of-mouth tumors have a similar risk of contralateral nodal involvement. Approximately 2/3 of tumors in the current study were described as posterior or lateral, and 1/3 of tumors were described as anterior, ventral, and/or involving the floor of mouth. Three of the five subjects who developed contralateral nodal metastases had tumors described as anterior or ventral, and two of the five subjects who developed contralateral metastases had tumors described as lateral.

Though relatively uncommon, it is important to identify individuals who are at risk for the development of contralateral cervical metastases since others have shown that disease-free survival for oral tongue SCCa is improved if positive nodes are identified on prophylactic neck dissection compared to those patients who undergo therapeutic neck dissection.<sup>8</sup> In addition to neck dissection, further adjuvant treatment may be indicated for those patients who harbor contralateral cervical metastases, particularly those in whom there is extracapsular spread. Myers et al. found that ECS was the most important predictor of regional recurrence, distant metastatic spread, and thus overall survival in a group of patients with SCCa of the oral tongue.<sup>12</sup> They recommend aggressive adjuvant therapy for this group. It is not practical or advisable to perform routine bilateral neck dissection in all patients with SCCa of the oral tongue, nor is it feasible to treat all of these patients with postoperative adjuvant therapy. Because of this, we were interested in identifying factors that would allow for tailored treatment of the contralateral neck in patients who present with early stage oral tongue SCCa.

Other groups have examined risk factors for cervical metastases in oral tongue SCCa, and this has been recently reviewed in the paper by Sano and Myers.<sup>14</sup> The most well-studied risk factor is tumor thickness. Many groups have examined tumor thickness as it

relates to risk of cervical metastases,<sup>1-5</sup> but this work has centered on the risk and treatment of ipsilateral nodal metastases. Though the cut-off thickness varies from study to study, there is a significant relationship between thicker tumors and the risk of ipsilateral cervical metastases. Our findings from this study agree with these groups. We found a statistically significant relationship between thickness of the primary tumor and ipsilateral cervical metastases, both at presentation and those metastases that developed during follow-up.

Recently, others have looked at the risk of contralateral cervical metastases in early SCCa of the oral tongue.<sup>15,16</sup> Lim et al. examined 54 patients with early stage SCCa of the oral tongue.<sup>15</sup> The goal of this study was to determine if there was an outcome difference between patients who underwent observation of the contralateral neck (29 patients) versus the 25 patients who underwent bilateral elective neck dissection. Notably, 7 patients in the "observation" group underwent radiation therapy that included the contralateral neck. The incidence of recurrence at any site in this study was 17/54 (31%) with no recurrences in the contralateral neck. There was only 1 of 25 (4%) contralateral neck dissections that showed occult malignancy. There was no significant difference in the disease-free survival between those who underwent observation of the contralateral neck and those who underwent contralateral elective neck dissection, even when those in the observation group who received radiation therapy were excluded.

The series by Gonzales-Garcia et al.<sup>16</sup> looked at a series of 203 patients with oral tongue SCCa. This study included all T and N stages of oral tongue SCCa. Of the total group of 203 patients, there were nine occurrences of contralateral lymph neck node relapse (CLNR). One of the nine had an initial neck dissection and 37.6% of the entire group of 203 patients received postoperative radiation therapy. Only histopathological grading and

peritumoural inflammation were found to be significantly related to CLNR. One of the nine CLNRs occurred in a tumor <2 mm thick, eight of the nine occurred in tumors >2 mm thick.

Our study is the only one to our knowledge that has examined the relationship between thickness of the primary tumor and occurrence of contralateral cervical metastases in T1 and T2 SCCa of the oral tongue. We found an approximately 5% increased risk of contralateral nodal metastasis for every 1-mm increase in tumor thickness by a Cox proportion hazards analysis. Though this was not found to be statistically significant, our study is limited due to the relatively small sample size. A power calculation assuming an overall incidence of 10% for contralateral metastases and a distribution of 1/3rd of primary tumors <3.75 mm and 2/3 of primary tumors ≥3.75 mm would require approximately 1000 patients to detect a two-fold difference (hazard ratio ≥2.0) in the risk of developing contralateral metastases between the two thickness groups with an alpha error of 0.05 and a power of 80%. A study of this size, though by this model predicted to be definitive, would require a multicenter approach over several years, and may not be feasible. The association we noted, though not statistically significant, appears clinically relevant since it agrees with the finding by us and others that ipsilateral nodal metastases are related to the thickness of the primary tumor.

Our classification tree analysis offers a way to approach the treatment of the contralateral neck in patients with T1 or T2 SCCa of the oral tongue. If the primary tumor has a thickness <3.75 mm, there were no cases of contralateral nodal metastases. This is compatible with the findings of others, in which the risk of ipsilateral nodal metastasis is increased in tumors thicker than 4-5 mm.<sup>1-3,5</sup> Our analysis also revealed that there were no instances of contralateral metastases in patients with tumors >9.5 mm thick. When this group of seven patients is examined, however, it is notable that in every case except one, the contralateral neck had been dissected and/or was included in the field of postoperative radiation therapy. All of the instances of contralateral metastases occurred in the group of 28 patients with primary tumors >3.75 mm and ≤9.5 mm. Only seven of this group (25%) had any treatment to the contralateral neck by neck dissection or radiation therapy.

Though it may be impractical to dissect both necks for every T1 or T2 oral tongue cancer, it should be considered in those patients who are felt to be at risk in the neck. Tumor characteristics as described in this paper are one way to attempt to identify patients who are at risk for contralateral nodal disease. Identification of an imaging study that would assist in the identification of occult cervical metastasis, ipsilateral, or contralateral is another area of intense interest. Because of the length of time over which the subjects in this study were treated, over half of them did not have imaging of the neck recorded. Of those who did have imaging, computed tomography (CT) scans were performed, and none showed evidence of occult contralateral nodal disease. The use of

ultrasonography has been studied as a means to follow the status of the cervical lymph nodes in patients treated for SCCa of the tongue,<sup>17</sup> but it is not clear whether this shows an advantage over CT of the neck. The use of sentinel node biopsy for SCCa of the oral tongue has been described<sup>18</sup> and may represent, after additional study, a useful way to assess the status of the contralateral neck in this disease.

## CONCLUSION

Our results indicate that consideration should be given to observation of the contralateral neck for tumors <3.75 mm, treatment of the contralateral neck with surgery and/or radiation therapy if the tumor is >9.5 mm thick, and neck dissection to the contralateral neck for tumors >3.75 mm thick.

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