

# Long-Term Regional Control and Survival in Patients With “Low-Risk,” Early Stage Oral Tongue Cancer Managed by Partial Glossectomy and Neck Dissection Without Postoperative Radiation

## The Importance of Tumor Thickness

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**BACKGROUND:** The objectives of this study were to determine the incidence of locoregional failure in patients with low-risk, early stage oral tongue squamous cell cancer (OTSCC) who undergo partial glossectomy and ipsilateral elective neck dissection without receiving postoperative radiation. **METHODS:** A combined database of patients with OTSCC who received treatment at Memorial Sloan-Kettering Cancer Center and Princess Margaret Cancer Center from 1985 to 2005 was established. In total, 164 patients with pathologic T1-T2N0 OTSCC who underwent partial glossectomy and ipsilateral elective neck dissection without postoperative radiation were identified. Patient-related, tumor-related, and treatment-related characteristics were recorded. Local recurrence-free survival, regional recurrence-free survival, and disease-specific survival were calculated by the Kaplan-Meier method. Predictors of outcome were analyzed by univariate and multivariate analysis. **RESULTS:** At a median follow-up of 66 months (range 1-171 months), the 5-year rates of local recurrence-free survival, regional recurrence-free survival, and disease-specific survival were 89%, 79.9%, and 85.6%, respectively. Regional recurrence was ipsilateral in 61% of patients and contralateral in 39% of patients. The regional recurrence rate was 5.7% for tumors <4 mm and 24% for tumors ≥4 mm. Multivariate analysis indicated that tumor thickness was the only independent predictor of neck failure (regional recurrence-free survival, 94% vs 72% [ $P = .02$ ] for tumors <4 mm vs ≥4 mm, respectively). Patients who developed recurrence in the neck had a significantly poorer disease-specific survival compared with those who did not (33% vs 97%;  $P < .0001$ ). **CONCLUSIONS:** Patients with low-risk, pathologic T1-T2N0 OTSCC had a greater than expected rate of neck failure, with contralateral recurrence accounting for close to 40% of recurrences. Failure occurred predominantly in patients who had primary tumors that were ≥4 mm thick. *Cancer* 2013;119:1168-76. © 2012 American Cancer Society.

**KEYWORDS:** oral tongue cancer, tumor thickness, outcome, prognostic factors.

## INTRODUCTION

The incidence of oral tongue squamous cell carcinoma in the United States has increased over the past 3 decades and is currently estimated at 3.0 per 100,000 population.<sup>1</sup> In patients with early stage disease (clinical tumor classification [cT] cT1-T2N0), the outcome generally is good, with 5-year survival rates between 75% and 89%.<sup>2-5</sup> The standard of care for those with early stage oral tongue cancer is partial glossectomy and elective neck dissection unless the primary tumor is small and superficial (ie, ≤2 mm), in which case, patients may undergo observation of the neck.

The decision for adjuvant postoperative radiation (PORT) in early stage oral tongue cancer is determined by adverse pathology features of the primary tumor and of the neck lymph nodes. These include close/positive margins, lymphovascular invasion, perineural invasion, and positive lymph nodes. Tumor thickness is generally not used as a criteria for PORT, despite evidence that this is a strong predictor for occult metastatic neck disease.<sup>2-5</sup> Patients without these adverse features (pathologic tumor classification [pT] pT1-T2N0 disease) are considered low risk and, thus, do not receive PORT. However, there are no long-term locoregional control or survival data on patients with pT1-T2N0 oral tongue cancer. The objectives of the current study were 3-fold; 1) to determine the incidence of local and regional failure in patients with pT1-T2N0 oral tongue cancer who undergo surgery without receiving PORT, 2) to determine which factors

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are predictive of local and regional recurrence, and 3) to determine the impact of local and regional recurrence on disease-specific survival.

## MATERIALS AND METHODS

### *Patient Inclusion Criteria*

A combined database of patients with oral tongue squamous cell cancer was created between the head and neck surgery divisions at Memorial Sloan-Kettering Cancer Center (New York, NY) and the Department of Otolaryngology-Head and Neck Surgery at the Princess Margaret Cancer Center (Toronto, Ontario, Canada). Approval of the institutional review boards of both institutions was obtained, and a deidentified database was then created. From this database, 164 patients with early stage pT1-T2N0 squamous cell cancer of the oral tongue were identified between the years 1985 and 2005. Patients were included if they had newly diagnosed, previously untreated squamous cell carcinoma of the oral tongue. Patients were excluded if they received PORT, if their oral tongue cancer was a second primary, or if they had distant metastases at the time of presentation. Patients were managed with partial glossectomy and neck dissection. Both hospitals are tertiary/quaternary care oncology hospitals that have a similar approach to managing oral cavity cancer with primary surgery and adjuvant PORT for high-risk pathologic features. Indications for PORT at both centers were close or positive margins, multiple lymph node metastases, extracapsular extension, lymphovascular invasion, and perineural invasion in select patients.

The details of patient and tumor characteristics are provided in Table 1. Of the 164 patients, 132 (81%) underwent supraomohyoid neck dissection, 15 (9%) underwent modified radical neck dissection, and 12 (7%) underwent bilateral neck dissection. The median patient age was 55 years (range, 25-82 years), 55% were men, 59% were smokers, and 51% were drinkers of alcohol. Pathology of the primary tumors revealed that 53% were pT2, 74% were  $\geq 2$  mm thick, and 59% were  $\geq 4$  mm thick. Tumor thickness, rather than depth of invasion, was used as the variable for analysis. This was recorded from a retrospective review of patient pathology forms. We chose tumor thickness as the variable because tumor thickness was consistently reported in all pathology forms at both institutions. In contrast, depth of invasion was not consistently recorded. The definition of tumor thickness was according to that proposed by Moore et al<sup>6</sup> as the deepest invasion of tumor into tissue from the mucosal surface. Twenty-five patients (15%) had close ( $n = 22$ ) or positive ( $n = 3$ ) margins.

**TABLE 1.** Patient and Tumor Characteristics

| Characteristic                  | No. of Patients | %  |
|---------------------------------|-----------------|----|
| Age, y                          |                 |    |
| <60                             | 98              | 60 |
| $\geq 60$                       | 66              | 40 |
| Sex                             |                 |    |
| Men                             | 90              | 55 |
| Women                           | 74              | 45 |
| Tobacco                         |                 |    |
| None                            | 49              | 30 |
| Yes                             | 96              | 59 |
| Not recorded                    | 19              | 11 |
| Alcohol                         |                 |    |
| None                            | 50              | 30 |
| Yes                             | 83              | 51 |
| Not recorded                    | 31              | 19 |
| Clinical tumor classification   |                 |    |
| cT1                             | 52              | 32 |
| cT2                             | 100             | 61 |
| cT3                             | 12              | 7  |
| Neck dissection                 |                 |    |
| SOHND                           | 132             | 81 |
| MRND                            | 15              | 9  |
| Bilateral ND                    | 12              | 7  |
| Not recorded                    | 5               | 3  |
| Tumor thickness, mm             |                 |    |
| <2                              | 9               | 6  |
| $\geq 2$                        | 122             | 74 |
| Not recorded                    | 33              | 20 |
| Tumor thickness, mm             |                 |    |
| <4                              | 35              | 21 |
| $\geq 4$                        | 96              | 59 |
| Not recorded                    | 33              | 20 |
| Margin status                   |                 |    |
| Negative                        | 133             | 81 |
| Positive/close                  | 25              | 15 |
| Not recorded                    | 6               | 4  |
| Histologic grade                |                 |    |
| Well differentiated             | 53              | 32 |
| Moderately differentiated       | 97              | 59 |
| Poorly differentiated           | 2               | 1  |
| Not recorded                    | 12              | 7  |
| Pathologic tumor classification |                 |    |
| pT1                             | 76              | 46 |
| pT2                             | 88              | 54 |
| Perineural invasion             |                 |    |
| No                              | 124             | 76 |
| Yes                             | 22              | 13 |
| Not recorded                    | 18              | 11 |
| Vascular invasion               |                 |    |
| No                              | 141             | 86 |
| Yes                             | 5               | 3  |
| Not recorded                    | 18              | 11 |

Abbreviations: MRND, modified radical neck dissection; ND, neck dissection; SOHND, supraomohyoid neck dissection.

### *Statistical Analysis of Outcomes*

Local recurrence-free survival, neck recurrence-free survival, and disease-specific survival were determined by using the Kaplan-Meier method. To identify which factors were predictive of survival, the following variables were analyzed by univariate analysis using the log-rank

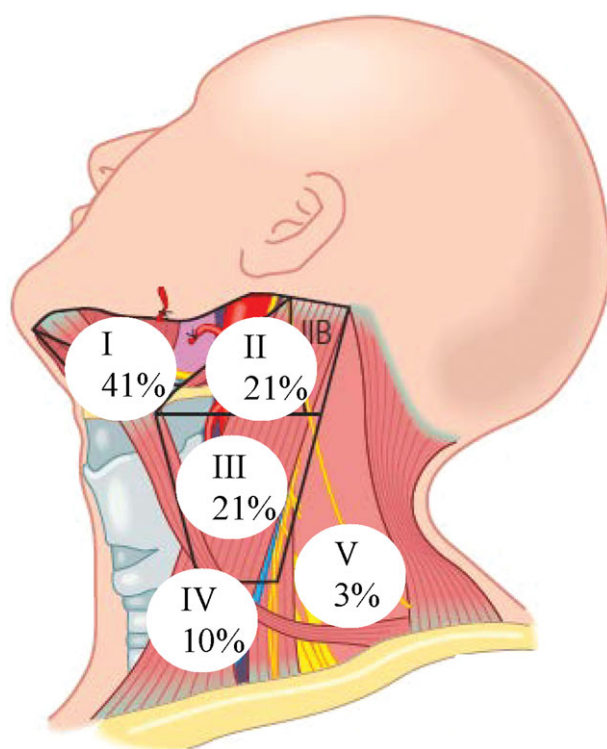
test: age, sex, tobacco and alcohol status, cT-classification, pT-classification, tumor differentiation, margin status, tumor thickness, and perineural and lymphovascular invasion. Clinical and pathologic factors that were significant on univariate analysis were then assessed by multivariate analysis using a Cox regression model and the log-rank test.

### **Pathologic Review of Neck Dissection Specimens for Micrometastases**

To determine whether neck recurrences were caused by micrometastases (defined as  $>0.2$  mm and  $\leq 2$  mm) that were not detected in the original pathology review, neck dissection specimens from Memorial Sloan-Kettering Cancer Center were reviewed by a single pathologist who specialized in head and neck pathology (D.L.C.). Of 70 patients from Memorial Sloan-Kettering Cancer Center, paraffin blocks from 52 neck dissection specimens were available for further analysis. Lymph nodes in each neck dissection specimen were reanalyzed using a sentinel lymph node technique. From each specimen, 4-micron-thick sections were recut from each lymph node at intervals of 20  $\mu$ m between each slide. At each level, the slides were stained with hematoxylin and eosin and also were assessed for metastases using immunohistochemistry with an antibody against cytokeratin 34BE12 to detect squamous cell cancer cells (mouse monoclonal antibody; Dako, Carpinteria, Calif; 1:400 dilution). Lymph nodes that were positive for hematoxylin-and-eosin staining or immunohistochemistry were then coded as positive for micrometastases. Any association between neck recurrence and the presence of micrometastases was determined using a Fisher exact test. Statistical analysis was carried out using SPSS for Windows (version 11.01; SPSS Inc., Chicago, Ill) and JMP (version 4.0; SAS Institute Inc., Cary, NC).

## **RESULTS**

With a median follow-up of 66 months (range, 1-171 months), 16 patients (10%) developed local recurrence, and 29 (18%) patients developed regional recurrence. Of the 29 patients with regional recurrence, 23 occurred in isolation without any local recurrence, whereas 6 patients had synchronous locoregional recurrence. Regional recurrence was ipsilateral in 61% of patients and contralateral in 39% of patients. The time to neck recurrence was 7.5 months (range, 2.3-29 months) for ipsilateral recurrences and 8.9 months (range, 5-58 months) for contralateral neck recurrences. The level of neck recurrence was level I in 41% of patients, level II in 21% of patients, level III in 21% of patients, level IV in 10% of patients, and level V



**Figure 1.** The sites and levels of neck recurrence are illustrated in patients with pathologic T1-T2N0 oral tongue cancer who underwent partial glossectomy and ipsilateral elective neck dissection without postoperative radiation.

in 3% of patients (Fig. 1). The chi-square test of association indicated that there were no statistically significant differences in pathologic features between patients with and without local recurrence (Table 2). The chi-square test of association also indicated that patients who had neck recurrence were more likely to have tumors  $\geq 4$  mm thick compared with patients with no neck recurrence (Table 2).

The 5-year rates of local recurrence-free survival, regional recurrence-free survival, and disease-specific survival for all patients were 89%, 79.9%, and 85.6%, respectively. Factors that were predictive of local and regional recurrence-free survival in univariate and multivariate analyses are listed in Tables 3 and 4. There were no factors that were predictive for local recurrence-free survival. However, tumor thickness  $\geq 4$  mm was an independent factor predictive for neck recurrence-free survival when the analysis was controlled for tumor grade and pT-classification on multivariate analysis. Patients who had tumors  $\geq 4$  mm thick were almost 5 times more likely to have a neck recurrence compared with patients who had tumors  $<4$  mm thick (regional recurrence-free survival rate, 94% vs 72%;  $P = .02$ ). The rate of regional recurrence at 2 years stratified by tumor thickness was 5.7% for

**TABLE 2.** Pathologic Factors Predictive of Local and Regional Recurrence

| Factor                          | Local Recurrence |     |                       | Neck Recurrence |     |                       |
|---------------------------------|------------------|-----|-----------------------|-----------------|-----|-----------------------|
|                                 | No               | Yes | <i>P</i> <sup>a</sup> | No              | Yes | <i>P</i> <sup>a</sup> |
| Pathologic tumor classification |                  |     |                       |                 |     |                       |
| pT1                             | 70               | 6   |                       | 66              | 10  |                       |
| pT2                             | 78               | 10  | .46                   | 69              | 19  | .16                   |
| Tumor thickness, mm             |                  |     |                       |                 |     |                       |
| <2                              | 8                | 1   |                       | 9               | 0   |                       |
| ≥2                              | 112              | 10  | .76                   | 97              | 25  | .13                   |
| Tumor thickness, mm             |                  |     |                       |                 |     |                       |
| <4                              | 33               | 2   |                       | 33              | 2   |                       |
| ≥4                              | 87               | 9   | .5                    | 73              | 23  | .02 <sup>b</sup>      |
| Margin status                   |                  |     |                       |                 |     |                       |
| Negative                        | 120              | 13  |                       | 109             | 24  |                       |
| Positive/close                  | 22               | 3   | .74                   | 21              | 4   | .8                    |
| Histologic grade                |                  |     |                       |                 |     |                       |
| Well differentiated             | 47               | 6   |                       | 47              | 6   |                       |
| Moderately differentiated       | 90               | 7   |                       | 79              | 18  |                       |
| Poorly differentiated           | 3                | 1   | .38                   | 2               | 2   | .11                   |
| Perineural invasion             |                  |     |                       |                 |     |                       |
| No                              | 111              | 13  |                       | 101             | 23  |                       |
| Yes                             | 21               | 1   | .56                   | 19              | 3   | .83                   |
| Vascular invasion               |                  |     |                       |                 |     |                       |
| No                              | 127              | 14  |                       | 116             | 25  |                       |
| Yes                             | 5                | 0   | .61                   | 4               | 1   | .97                   |

<sup>a</sup> The chi-square test was used to calculate *P* values.

<sup>b</sup> This was a statistically significant *P* value.

patients who had tumors <4 mm thick and 24% for patients who had tumors ≥4 mm thick (Fig. 2).

The impact of neck recurrence on disease-specific survival is illustrated in Figure 3. Patients who recurred in the neck had a significantly poorer disease-specific survival compared with those who did not (33% vs 97%; *P* < .0001). This indicated that approximately 66% of patients who had a neck recurrence could not be salvaged.

Pathologic review of lymph nodes in 52 neck dissection specimens revealed that 7 patients had micrometastases, including 2 of 13 patients with neck recurrence and 5 of 39 patients without neck recurrence (Fig. 4). The Fisher exact test revealed no statistically significant association between the presence of micrometastases and recurrence status (Table 5)

## DISCUSSION

Patients with early stage oral tongue cancer generally have an excellent prognosis.<sup>2-4</sup> We recently reported our own results with 5-year disease-specific and overall survival rates of 86% and 79%, respectively.<sup>5</sup> The decision for adjuvant PORT in early stage oral tongue cancer is determined by adverse pathologic features of the primary tumor and cervical lymph nodes. These include close/positive margins, lymphovascular invasion, perineural invasion, and positive lymph nodes. There is evidence

that tumor thickness is a strong predictor of occult metastatic neck disease,<sup>7-14</sup> but tumor thickness is not generally used as a criterion for PORT in patients who undergo elective neck dissection and have histopathologically negative lymph nodes. Patients without these adverse features are considered low risk (pT1-T2N0 disease) and, thus, typically do not receive PORT. However, there are no long-term locoregional control or survival data on patients with pT1-T2N0 oral tongue cancer. By using a bi-institutional collaboration, we present the outcome results from the largest series of patients to date with *low-risk*, pT1-T2N0 squamous cell cancer of the oral tongue. By combining data sets from 2 large head and neck institutions with similar management philosophy for treating oral tongue cancer, we were able to create a sample size of patients sufficient to have enough statistical power to address the objectives of the study. This study illustrates the strength of carrying out collaborative projects to create large patient numbers for the analysis of diseases with small patient numbers.

We report rather surprising results that 29 of 164 patients (approximately 18%) develop neck recurrence. It is likely that the cause of neck recurrence is either failure to remove subcentimeter occult metastases at the time of neck dissection or failure to detect micrometastases on pathologic examination in the original neck dissection specimens. To investigate this further, we reanalyzed 52

**TABLE 3.** Prognostic Factors for Local Recurrence-Free Survival

| Covariate                       | No. of Patients | 5-Year LRFS, % | <i>P</i>            |                       |
|---------------------------------|-----------------|----------------|---------------------|-----------------------|
|                                 |                 |                | Univariate Analysis | Multivariate Analysis |
| Age, y                          |                 |                |                     |                       |
| <60                             | 98              | 88.9           |                     |                       |
| ≥60                             | 66              | 88.7           | .56                 | —                     |
| Sex                             |                 |                |                     |                       |
| Men                             | 90              | 89.8           |                     |                       |
| Women                           | 74              | 88.1           | .83                 | —                     |
| Tobacco                         |                 |                |                     |                       |
| None                            | 49              | 87.2           |                     |                       |
| Yes                             | 96              | 91.4           | .80                 | —                     |
| Alcohol                         |                 |                |                     |                       |
| None                            | 50              | 89.5           |                     |                       |
| Yes                             | 83              | 90.6           | .87                 | —                     |
| Clinical tumor classification   |                 |                |                     |                       |
| cT1                             | 52              | 92.5           |                     |                       |
| cT2                             | 100             | 87.5           |                     | —                     |
| cT3                             | 12              | 85.7           | .36                 |                       |
| Tumor thickness, mm             |                 |                |                     |                       |
| <2                              | 9               | 87.5           |                     | —                     |
| ≥2                              | 122             | 90             | .83                 |                       |
| Tumor thickness, mm             |                 |                |                     |                       |
| <4                              | 35              | 92.6           |                     | —                     |
| ≥4                              | 96              | 88.7           | .41                 |                       |
| Margin status                   |                 |                |                     |                       |
| Negative                        | 133             | 89.4           |                     | —                     |
| Positive/close                  | 25              | 84.4           | .85                 |                       |
| Histologic grade                |                 |                |                     |                       |
| Well differentiated             | 53              | 88.1           |                     | —                     |
| Moderately differentiated       | 97              | 91.9           |                     |                       |
| Poorly differentiated           | 2               | 66.7           | .23                 |                       |
| Pathologic tumor classification |                 |                |                     |                       |
| pT1                             | 76              | 89             |                     | —                     |
| pT2                             | 88              | 89.1           | .52                 |                       |
| Perineural invasion             |                 |                |                     |                       |
| No                              | 124             | 87.5           |                     | —                     |
| Yes                             | 22              | 94.4           | .65                 |                       |
| Vascular invasion               |                 |                |                     |                       |
| No                              | 141             | 88             |                     |                       |
| Yes                             | 5               | 100            | .67                 |                       |

Abbreviations: LRFS, local recurrence-free survival.

neck dissection specimens from Memorial Sloan-Kettering Cancer Center. All lymph nodes were recut and reanalyzed by both hematoxylin-and-eosin staining and immunohistochemistry against cytokeratin 34EB12. Only 2 of 13 patients who developed a neck recurrence had micrometastases, and 5 of 39 patients with no neck recurrence had micrometastases. The Fisher exact test revealed no statistically significant association between the presence of micrometastases and neck recurrence status. The 5 patients who had micrometastases yet did not have neck recurrences require further analysis. This finding was extremely surprising, because several studies have reported improved regional control, disease-specific survival, and overall survival among patients with T1-T2N1 oral

tongue cancer who received PORT compared with those who underwent surgery alone. For example, Byers et al<sup>15</sup> reported that the neck recurrence rate among patients who had pN1 disease and did not receive PORT was high as 35.7% compared with 1.9% among patients who had pN0 disease. In the current study, the follow-up intervals for the 5 patients who had micrometastases but no neck recurrences were 1 month, 9 months, 12 months, 91 months, and 98 months, respectively. Because the majority of neck recurrences occurred in the first 24 months, it is possible that the 3 patients who had <24 months of follow-up may have been censored before a recurrence developed. It is also important to mention that all metastases were detected in a solitary lymph node, and there was no

**TABLE 4.** Prognostic Factors for Neck Recurrence Free Survival

| Covariate                       | No. of Patients | 5-Year NRFS, % | <i>P</i>            |                       |
|---------------------------------|-----------------|----------------|---------------------|-----------------------|
|                                 |                 |                | Univariate Analysis | Multivariate Analysis |
| Age, y                          |                 |                |                     |                       |
| <60                             | 98              | 78.4           |                     |                       |
| ≥60                             | 66              | 81.6           | .43                 | —                     |
| Sex                             |                 |                |                     |                       |
| Men                             | 90              | 75.6           |                     |                       |
| Women                           | 74              | 84.9           | .23                 | —                     |
| Tobacco                         |                 |                |                     |                       |
| None                            | 49              | 82.6           |                     |                       |
| Yes                             | 96              | 79.8           | .78                 | —                     |
| Alcohol                         |                 |                |                     |                       |
| None                            | 50              | 83.2           |                     |                       |
| Yes                             | 83              | 79.8           | .68                 | —                     |
| Clinical tumor classification   |                 |                |                     |                       |
| cT1                             | 52              | 84.8           |                     |                       |
| cT2                             | 100             | 77.3           |                     |                       |
| cT3                             | 12              | 82.5           | .73                 | —                     |
| Tumor thickness, mm             |                 |                |                     |                       |
| <2                              | 9               | 100            |                     |                       |
| ≥2                              | 122             | 76.2           | .14                 | —                     |
| Tumor thickness, mm             |                 |                |                     |                       |
| <4                              | 35              | 93.5           |                     | Reference             |
| ≥4                              | 96              | 71.9           | .015 <sup>a</sup>   | .037 <sup>a,b</sup>   |
| Margin status                   |                 |                |                     |                       |
| Negative                        | 133             | 79.3           |                     |                       |
| Positive/close                  | 25              | 82.2           | .75                 | —                     |
| Histologic grade                |                 |                |                     |                       |
| Well differentiated             | 53              | 86.3           |                     |                       |
| Moderately differentiated       | 97              | 79.4           |                     |                       |
| Poorly differentiated           | 2               | 33.3           | .07                 | NS                    |
| Pathologic tumor classification |                 |                |                     |                       |
| pT1                             | 76              | 85.1           |                     |                       |
| pT2                             | 88              | 75.7           | .24                 | NS                    |
| Perineural invasion             |                 |                |                     |                       |
| No                              | 124             | 78.8           |                     |                       |
| Yes                             | 22              | 83.3           | .85                 | —                     |
| Vascular invasion               |                 |                |                     |                       |
| No                              | 141             | 79.6           |                     |                       |
| Yes                             | 5               | 80             | .96                 | —                     |

Abbreviations: NRFS, neck recurrence-free survival; NS, nonsignificant.

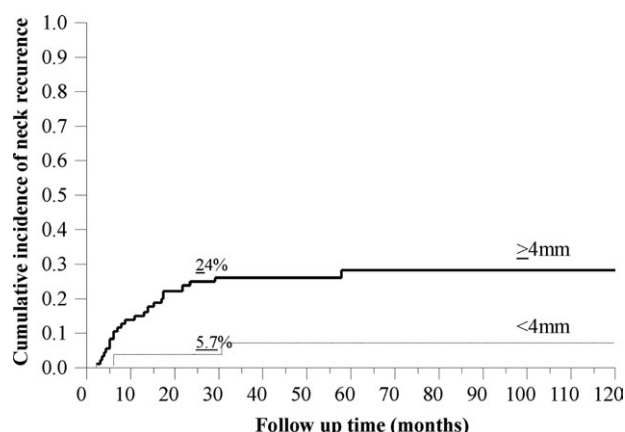
<sup>a</sup>This was a statistically significant *P* value.<sup>b</sup>In multivariate analysis, the relative risk for tumors ≥4 mm in thickness was 4.7 (95% confidence interval, 1.1-20.1).

extracapsular spread. Therefore, it is also possible that such microscopically pathologically positive lymph nodes may not be of such significance in terms of the risk for recurrence compared with lymph nodes that have larger metastatic deposits and extracapsular spread. Indeed, we recently presented data from Memorial Sloan-Kettering Cancer Center<sup>16</sup> on 35 patients with pN1 necks who were managed without PORT; these patients had a 5-year neck recurrence-free survival rate of 84% and a disease-specific survival rate of 83%. The good outcome in such patients may be related to the lack of extracapsular extension of the affected lymph node (only 2.9% incidence of extracapsular extension).

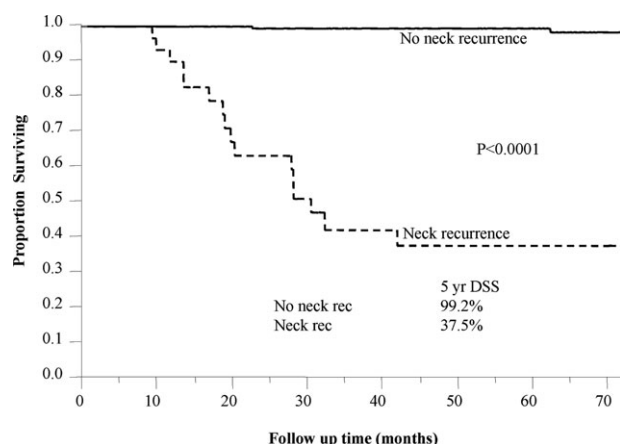
Another possible explanation for neck recurrence in these patients may be reseeding of the lymphatics of the neck secondary to a synchronous local recurrence. However, of the 29 patients who developed neck recurrences, 23 (14%) were isolated neck recurrences, and only 6 patients had a synchronous local and neck recurrence, suggesting that reseeding of the neck from local recurrence is not the reason for the neck recurrences we observed.

The rate of recurrence was highest in patients who had tumors that were ≥4 mm thick. The importance of tumor thickness is well documented in the literature for oral tongue cancer. Several studies have demonstrated that tumor thickness is a strong predictor of both occult



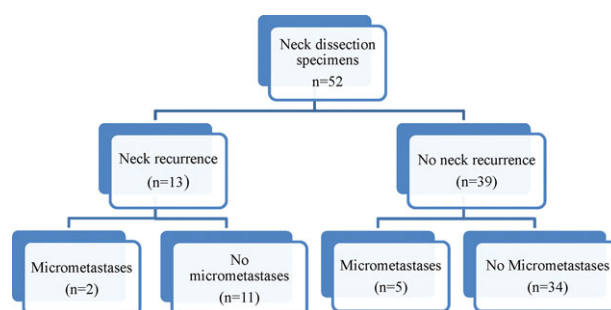


**Figure 2.** The rate of neck recurrence is illustrated in patients who had pathologic T1-T2N0 oral tongue cancer stratified according to thickness of the primary tumor ( $\geq 4$  mm vs  $< 4$  mm).



**Figure 3.** Disease-specific survival (DSS) is illustrated for patients who had pathologic T1-T2N0 oral tongue cancer stratified by neck recurrence (rec).

metastases and neck recurrence,<sup>5,7-14</sup> and a meta-analysis by Huang et al<sup>14</sup> has suggested that  $\geq 4$  mm tumor thickness is the cutoff for risk. In our current study, we report that, even in patients who are deemed to be at low risk for neck recurrence, those with pT1-T2N0 oral tongue tumors that are  $\geq 4$  mm thick also have an increased rate of neck recurrence. These findings further emphasize the importance of tumor thickness on neck recurrence and outcome. It is noteworthy that 40% of our patients had a recurrence in the undissected contralateral neck. The median time to recurrence was similar for ipsilateral and contralateral recurrences (8.9 months vs 7.5 months, respectively), suggesting that this was because of micrometastases. Another possible explanation may be the location of the primary tumor close to the midline. However,



**Figure 4.** This pathologic review of lymph nodes from 52 neck dissection specimens is illustrated according to neck recurrence status. The presence of micrometastases was detected by hematoxylin-and-eosin staining and immunohistochemistry for cytokeratin 34EB12.

**TABLE 5.** The Presence of Lymph Node Micrometastases on Pathologic Review of 52 Neck Dissection Specimens Stratified by Neck Recurrence Status

| Recurrence Status          | Presence of Lymph Node Micrometastases: No. of Patients (%) |          | <i>P</i> <sup>b</sup> |
|----------------------------|---|----------|-----------------------|
|                            | Positive <sup>a</sup>                                       | Negative |                       |
| Neck recurrence, n = 13    | 2 (15)  | 11 (85)  | 1.00                  |
| No neck recurrence, n = 13 | 5 (13)  | 34 (87)  |                       |

<sup>a</sup>Lymph node micrometastases were coded as positive if cancer cells were detected by hematoxylin-and-eosin staining or by immunohistochemistry against cytokeratin markers.

<sup>b</sup>The Fisher exact test was used to calculate *P* values.

because our study was a retrospective analysis of patient charts, it was not possible to clearly identify how close tumors were to the midline. Finally, tumor thickness may explain these findings; ie, once oral tongue cancers reach a certain depth, the rich network of lymphatic pathways in the well vascularized and muscular tongue may favor contralateral spread of disease.

This study raises several important questions. First, should tumor thickness  $\geq 4$  mm be used as an inclusion criteria for PORT, even when other traditional adverse risk factors, such as positive margins and perineural invasion, are absent? This is a rather contentious issue, because the decision to irradiate the neck and oral cavity in these patients is not without morbidity. Unpublished data from Memorial Sloan-Kettering Cancer Center indicate that, in patients who have tumors  $> 4$  mm thick, neck recurrence-free survival is superior among those who receive PORT versus no PORT for patients who have pathologically positive lymph node status (94% vs 50%) and also

for those with pN0 disease (78% vs 71%). A recent analysis using the Surveillance, Epidemiology, and End Results database<sup>17</sup> of 1539 patients who had T1-T2N1 oral cavity cancer (both oral tongue and floor of mouth) indicated that adjuvant radiotherapy improved survival (both disease-specific survival and overall survival) in patients with T2N1 tongue and floor of mouth cancer (52% vs 38% [ $P = .002$ ] and 40% vs 18% [ $P = .003$ ], respectively).

However, the question regarding whether or not PORT can reduce the incidence of neck recurrence in low-risk patients with tumors  $>4$  mm thick can be answered successfully only with a randomized controlled trial. In fact, such patients are relatively rare; thus, a multi-institutional trial would be required. However, such a trial may prove difficult, because there may be problems with crossover and noncompliance when randomizing patients to receive PORT in 1 arm and no treatment in the other arm. In addition, it would require the agreement of head and neck surgeons to volunteer their patients for this study when there may be an inherent reluctance to do so because of the potential morbidity that patients may endure from PORT. There is also the question regarding whether tumor thickness should be used as a criterion for bilateral neck dissection. The traditional teaching is to recommend bilateral neck dissection when the tumor encroaches or goes past the midline. Again, a larger study would be needed in patients who have tumors  $\geq 4$  mm thick to determine the incidence of bilateral neck disease.

Another question is whether or not more strict scrutiny of the neck should be carried out during the postoperative period in these patients. Because the majority of neck recurrences developed in the first 2 years, it may be beneficial to have close imaging surveillance every 3 months during this period. The use of positron emission tomography and computed tomography imaging appears to be an expensive method for this kind of surveillance. An equally sensitive and less expensive method would be to obtain 3 monthly ultrasound images and fine-needle aspirations of any suspicious lymph nodes. This method of follow-up is used in many European centers and has been reported as a highly sensitive and specific method for detecting metastatic disease in the neck.<sup>18-20</sup> However, the technique is highly operator dependent, and consistent, reliable results may only be possible in centers with experienced ultrasonographers and large patient volumes.

Finally, should lymphoscintigraphy be carried out in patients who have early stage oral tongue cancer to identify the few patients who harbor a sentinel lymph node in the contralateral neck? The use of sentinel lymph node biopsy has been well reported in the literature for

oral cavity cancer.<sup>21-24</sup> The use of lymphoscintigraphy to identify patients with a contralateral sentinel lymph node would allow us to identify the small number of patients who may benefit from bilateral selective neck dissection. A clinical trial to assess the incidence of contralateral sentinel lymph node in early stage T1-T2N0 tongue cancers would allow us to determine whether this approach is justified.

In conclusion, our current study demonstrates that patients with low-risk pT1-T2N0 squamous cell cancer of the oral tongue who undergo partial glossectomy and elective neck dissection without PORT have a greater than expected rate of neck failure, with contralateral recurrence accounting for close to 40% of cases. Failure occurs predominantly in patients who have primary tumors that are  $\geq 4$  mm thick. Only approximately 33% of patients who develop a neck recurrence are successfully salvaged. A randomized clinical trial for PORT in patients with pT1-T2N0 oral tongue cancer who have tumors  $\geq 4$  mm thick may answer the question of whether tumor thickness  $\geq 4$  mm may be an indication for PORT in these patients.

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