Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma

Hans C. Brockhoff II, DDS, MD,[1]* Roderick Y. Kim, DDS, MD,[1] Thomas M. Braun, PhD,[2] Christos Skouteris, DMD, PhD,[1] Joseph I. Helman, DMD,[1] Brent B. Ward, DDS, MD[1]

[1]Oral and Maxillofacial Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan, [2]Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan.

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ABSTRACT: *Background.* The purpose of this study was to investigate the critical primary tumor depth of invasion in oral squamous cell carcinoma that would lead to a 20% or greater risk of nodal metastasis.

Methods. An institutional review board approved retrospective review of our head and neck database was performed from 2009 to 2014 and the data were statistically analyzed.

Results. Two hundred eighty-six patients with a diagnosis of oral squamous cell carcinoma who met our inclusion criteria underwent primary excision and neck dissection. For a depth of invasion of 1 mm or less, there were no patients with a positive node. From 1.1 mm to 2 mm of depth of invasion, there was 1 of 11 patients (9%) who had at least 1 positive node. At 2.1 mm to 3 mm, 5 of 25 patients (20%) had at least 1 positive node.

Conclusion. Depth of invasion and the location of the tumor are 2 important variables to consider when making treatment recommendations to patients with clinical N0 disease. © 2017 Wiley Periodicals, Inc. *Head Neck* **39:** 974–979, 2017

KEY WORDS: oral squamous cell carcinoma, nodal metastasis, depth of invasion, N0 neck, elective neck dissection

INTRODUCTION

An estimated 45,780 new cases and 8650 deaths because of oral cavity and oropharyngeal cancers are expected in the United States during 2015.[1] The 5-year and 10-year relative survival rates are 63% and 51%, respectively.[1] Regional metastatic disease to the lymph nodes remains an important clinical prognostic factor. Decision-making in regard to management of the neck has generated a tremendous amount of investigation and effort. Even with the aid of multiple imaging modalities, the detection of early microscopic disease to the lymph nodes remains difficult. When considering all stages of oral squamous cell carcinoma, occult nodal metastasis has been reported in up to 50% of cases.[2,3] Additionally, it is clear that not every patient, more specifically the clinically N0 neck, carries the same risk for nodal metastasis, and, thus, it would not be reasonable to consider every patient for an elective neck dissection because of the morbidity associated with the procedure.[4,5] A neck dissection is generally offered to those patients who harbor at least a 20% risk for occult nodal metastasis.[6]

Investigations of the histopathological features of oral squamous cell carcinoma are numerous in order to help better characterize which patient's pose the greatest risk for harboring occult disease.[7–15] One of the more recognized indicators of placing a patient at risk for lymph node metastasis is the depth of tumor invasion. Kane et al[12] reviewed 48 previously untreated patients with a T1/T2 N0 squamous carcinoma of the oral cavity who underwent a primary excision of the tumor and elective neck node dissection and concluded that depth of invasion was the most significant histologic predictor of subclinical node metastasis. Discovering what the precise value for the depth of invasion that would substantiate an elective neck dissection has continued to be a point of debate. Authors have advocated for various depths of thicknesses as a predictor, and current studies give a wide range from 2 mm to greater than 5 mm.[10–15] Warburton et al[14] reported on 29 patients with T1NOM0 or T2N0MO oral squamous cell carcinoma of the tongue or floor of the mouth that on statistical analysis showed that a tumor thickness of 2.2 mm is the optimal cutoff point with a statistically significant association with delayed neck metastasis. Huang et al[24] performed a meta-analysis involving 16 studies yielding a pooled total of 1136 patients. They looked at tumor thickness and its predictive value for cervical lymph node involvement. Their conclusion was that tumor thickness was indeed a strong predictor for cervical lymph node involvement and that the optimal cutoff point was 4 mm.

***Corresponding author:** H. C. Brockhoff II, Oral and Maxillofacial Surgery, University of Michigan, Department of Surgery, 1500 E. Medical Center Drive, Ann Arbor, MI 48109. E-mail: hans.brockhoff@gmail.com

Within the current literature, there is still a wide range of variability and conflicting data, which has led to the lack of consensus in regard to the depth of invasion. Many of the studies are small in size, which further add to the challenge. The purpose of this study was to review the experience at our institution and investigate what the critical depth of invasion would be, leading to a 20% or greater risk of nodal metastasis.

MATERIALS AND METHODS

We completed an institutional review board approved, retrospective, single institution review of all patients from 2009 to 2014. Our institutional review board consists of an established committee that reviews and approves research involving human subjects. This ensures that all human subject research is conducted in accordance with federal, institutional, and ethical guidelines. Our inclusion criteria consisted of all patients who had received any form of neck dissection with resection of a primary oral cavity squamous cell carcinoma completed by 1 of our 4 attending oral/head and neck surgeons. Patients were excluded from our study if they had previously been treated with a neck dissection, previous resection of an oral cancer, previous treatment with radiotherapy, and/or chemotherapy specifically for head and neck cancer. The data collected included: age, sex, race, pathologic staging (TNM classification), location of primary tumor, depth of invasion, type of surgery performed, and presence of lymph node involvement.

The information regarding tumor characteristics, including depth of invasion, was obtained from pathology reports of the final specimen. At our institution, measured depths of invasion are standardized and read as the depth of the tumor that extends vertically beyond the basement membrane into the underlying tissue not the total tumor thickness.

Descriptive statistics were used to summarize the clinical characteristics of the sample of patients. The strength of the association of tumor size and depth of invasion with node positivity was assessed using logistic regression. The diagnostic ability of depth of invasion for nodal involvement was also summarized with empirical estimates of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve; the bootstrap statistical analysis was used to compute 95% confidence intervals for those quantities.

RESULTS

Over a period of 6 years, a total of 303 patients with a diagnosis of oral squamous cell carcinoma in need of a primary excision and neck dissection presented to our institution at the University of Michigan. Of these patients, 286 met both our criteria and, thus, were analyzed. One hundred sixty-nine patients (59%) were men and 117 (41%) were women with average age at the time of surgery being 63 years (+/-12.5 years; range, 18–95 years). The majority of patients (270; 94%) were white.

Location

The number of tumors presenting in anatomic location were as follows: oral tongue 105 (37%), alveolus/hard palate 91 (32%), floor of the mouth 39 (14%), retromolar trigone 25 (9%), and other 24 (8%).

TABLE 1. Pathologic staging (no. of patients = 286).

Overall stage	TNM	No. of patients	Overall percentage
1	T1N0M0	66 (23.1%)	23.1
2	T2N0M0	54 (18.9%)	18.9
3	T1N1M0	16 (5.6%)	13.5
	T2N1M0	17 (5.9%)	
	T3N0M0	5 (1.7%)	
	T3N1M0	1 (0.3%)	
4	T1N2M0	8 (2.8%)	44.3
	T2N2M0	24 (8.4%)	
	T3N2M0	5 (1.7%)	
	T4N0M0	47 (16.4%)	
	T4N1M0	9 (3.1%)	
	T4N2M0	34 (11.9%)	

Pathologic staging

There were 66 patients (23%) with stage I disease, 54 (19%) with stage II, 39 (14%) with stage III, and 127 (44%) with stage IV. The average size of the tumors was 2.7 cm (SD +/- 1.1) with a range 0.1 cm to 6.9 cm (Table 1).

Node positivity

One hundred fifteen patients (40%) had at least 1 positive lymph node on the final pathology report, whereas 171 (60%) were negative.

Association of tumor size and depth of invasion with node positivity

Three logistic regression models were created, 1 with size of tumor predicting node positivity (model A), 1 with depth of invasion predicting node positivity (model B), and 1 with both size of tumor and depth of invasion predicting node positivity (model C). In model A, the size of the tumor was significantly associated with node positivity (odds ratio, 1.9; p value $< .001$). In model B, the depth of invasion was significantly associated with node positivity (odds ratio, 1.3; p value $= .002$). In model C, only depth of invasion was statistically significant ($p < .001$). Thus, although both the size of the tumor and the depth of invasion were associated with node positivity, depth of invasion was a stronger predictor and remained significant after controlling for tumor size, whereas the converse was not true.

Thresholding depth of invasion for predicting node positivity

Table 2 displays the percentage of necks with positive nodes measured at 1-mm increments of depth of invasion. Each neck was individually assessed such that among our 286 patients, we found that there were a total of 390 neck specimens (104 patients required a bilateral neck dissection). At 1-mm depth of invasion, we found that there were 7 necks in our dataset and none of them had a positive node. At 2-mm depth of invasion, there were 12 patients with negative node necks and 3 with positive node necks for an overall percentage of 20%. Increasing

TABLE 2. Percentage of necks with positive nodes measured at 1-mm increments of depth of invasion.

Depth of invasion	No. of necks with negative nodes ($N = 223$)	No. of necks with positive nodes ($N = 167$)	Percentage of necks with positive nodes
1 mm	7	0	0
2 mm*	12*	3*	20*
3 mm	23	7	23
4 mm	25	9	26
5 mm	22	6	21
6 mm	11	5	31
7 mm	7	5	42
8 mm	14	7	33
9 mm	14	12	46
10 mm	12	13	52
>10 mm	76	100	57

*Shows the shallowest depth of invasion (in millimeters) in which 20% or greater of the necks dissected demonstrated positive lymph nodes.
Note: Each neck was treated independently.

depth of invasion beyond 2 mm consistently demonstrated a greater than 20% node positivity rate reaching a rate higher than 50% at 10 mm.

This same methodology was applied to various anatomic sites. Only those anatomic sites for which we had sufficient data to make statistical inference were included in this analysis. Table 3 shows the first recorded depth of invasion (the shallowest depth) in which at least 20% of the necks had positive lymph nodes on final pathology report.

Twenty percent cutoff

Table 4 displays what we called our 20% cutoff point. These descriptive data identify the precise value for the depth of invasion in which 20% of all patients at that depth and shallower would present with positive lymph nodes. We found this point to be significant at 4 mm. In other words, at 4-mm depth of invasion, we know that the collective sum of patients with 1 mm, 2 mm, 3 mm, and 4 mm depth of invasion there is a 22% incidence of positive disease in the neck. This analysis differs from the data presented in Table 2, which looked at nodes that were positive at isolated depths.

This same methodology was applied to various anatomic sites. Only those anatomic sites for which we had sufficient data to make statistical inference were included. Table 5 shows the cutoff points where 20% of all patients at that depth and shallower would present with positive lymph nodes. The tongue was 2 mm, the floor of the mouth was 3 mm, the retromolar trigone was 4 mm, and the alveolus/hard palate was 4 mm.

TABLE 3. Various anatomical sites showing the shallowest depth of invasion where at least 20% of the necks had positive lymph nodes.

Anatomic site	Depth of invasion
Tongue	2 mm
Floor of mouth	3 mm
Retromolar trigone	3 mm
Alveolus/hard palate	4 mm

TABLE 4. Twenty percent cutoff points in which 20% of all necks at that depth and shallower would present with positive lymph nodes.

Depth of invasion	No. of necks with negative nodes ($N = 223$)	No. of necks with positive nodes ($N = 167$)	Percentage of necks with positive nodes
1 mm	7	0	0
2 mm	12	3	14
3 mm	23	7	19
4 mm*	25*	9*	22*
5 mm	22	6	22
6 mm	11	5	22
7 mm	7	5	24
8 mm	14	7	25
9 mm	14	12	28
10 mm	12	13	30
>10 mm	76	100	42

*Indicates the 20% cuoff point. This is the level (in millimeters) in which 20% of all the necks at that depth and shallower demonstrated positive lymph nodes.

Diagnostic operating characteristics of depth of invasion

The diagnostic operating characteristics of depth of invasion (mm) for predicting nodal involvement are listed in Table 6. In our analysis, we focused on the NPV at the various depths representing patients in whom if a neck dissection was not performed, would truly be negative for disease. In this analysis, at 4-mm depth of invasion, 80% of patients would not have received a neck dissection and would be negative for disease, which means that only 20% of patients who did not receive a neck dissection would be positive for disease. Thus, 4 mm was the critical value in this analysis.

This same methodology was applied to various anatomic sites. Only those anatomic sites for which we had sufficient data to make statistical inference were included. Table 7 shows the critical values for depth of invasion in which the NPVs were 80% or greater. This translates to the depth of invasion in which, if a patient did not receive a neck dissection, then only less than or equal to 20% of patients would be harboring nodal disease.

T1 Lesions

In our final analysis (Table 8), we looked only at T1 lesions because T2 lesions have historically undergone neck dissection in general. There were a total of 111 necks analyzed from our data. At 2-mm depth of invasion, the descriptive data yielded 30% of patients had positive lymph nodes, the NPV was 80%, and the 20% cutoff point resided there as well. Therefore, the descriptive data, NPV, and

TABLE 5. Twenty percent cutoff points for various anatomic sites with 95% confidence intervals among all sites.

Anatomic site	Depth of invasion (95% CI)
Tongue	2 mm (2–14 mm)
Floor of the mouth	3 mm (1–10 mm)
Retromolar trigone	4 mm (2–10 mm)
Alveolus/hard palate	4 mm (3.5–25 mm)

Abbreviation: CI, confidence interval.

TABLE 6. Diagnostic operating characteristics of depth of invasion (mm) for predicting nodal involvement.

Tumor depth	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
1 mm	100% N/A	3% (0% to 6%)	41% (35% to 47%)	100% N/A	0.68 (0.61–0.74)
2 mm	98% (95% to 100%)	9% (5% to 13%)	42% (36% to 48%)	89% (75% to 100%)	
3 mm	94% (90% to 98%)	21% (15% to 27%)	44% (38% to 50%)	84% (73% to 95%)	
4 mm	88% (82% to 94%)	33% (26% to 40%)	47% (40% to 54%)	80% (71% to 89%)	
5 mm	83% (76% to 90%)	43% (36% to 50%)	50% (43% to 57%)	80% (72% to 88%)	
6 mm	81% (74% to 88%)	48% (41% to 55%)	51% (44% to 58%)	79% (71% to 87%)	

Abbreviations: CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; N/A, not applicable.

20% cutoff point all indicate that a neck dissection should be performed at 2 mm if the surgeon accepts a 20% risk for occult nodal metastasis.

DISCUSSION

Performing a neck dissection will ultimately enable correct staging of the patient, lend insight into prognosis, and aid in determination of adjuvant treatments. Shah et al[20] performed a retrospective review of pathology reports of 501 consecutive patients at Memorial Sloan Kettering Cancer Center (New York, NY) with primary oral cavity squamous cell carcinoma. They found 192 patients were N0 at presentation and underwent an immediate elective radical neck dissection. Clinically occult metastatic disease was present in 34% of the patients.[20] A more recent study from that same institution from 1985 to 2005 looked at 216 patients with early-stage (cT1T2N0) squamous cell carcinoma of the oral tongue. Importantly, in their multivariate analysis, the main independent predictor of disease-free survival and overall survival was the status of the neck. Those patients who had occult nodal metastasis had a 5-fold increased risk of dying of the disease compared with patients who did not have metastatic disease. Furthermore, in this same study, the incidence of occult nodal metastases was 28%.[21] Additionally, Pimenta Amarel et al[22] and Kligerman et al[23] reported an incidence of 23% and 21%, respectively, for occult metastasis in oral squamous cell carcinoma. Despite nonuniformity with decision-making in regard to the management of the neck and what the appropriate risk for nodal metastasis warranting a neck dissection, the evidence supporting a value of 20% has been accepted by many.

TABLE 7. Negative predictive values at various anatomic sites predicting a 20% nodal involvement.

Anatomic site	NPV
Tongue	2 mm
Floor of mouth	2 mm
Retromolar trigone	3 mm
Alveolus/hard palate	3 mm

Abbreviation: NPV, negative predictive value.

Discovering the precise value for depth of invasion that would substantiate the need for an elective neck dissection has continued to be a point of debate. Many studies have advocated for various depths of invasion as a predictor, and current studies give a wide range from 2 mm to greater than 5 mm. Most of these studies are small in size and/or look at a single site, which further adds to the challenge. To date, our study is one of the largest studies attempting to answer the question on depth of invasion and its correlation with occult nodal metastasis. Additionally, it is one of the only studies with adequate data to explore site-specific behaviors of tumors. It has long been understood that there are variations in the lymphatic patterns and lymphatic risk throughout the oral cavity, yielding certain sites to be a higher risk for nodal metastasis. However, there is little information on how this affects clinical outcomes. This article identifies common oral cavity sites and results in various recommendations on when to consider offering a patient a neck dissection versus observation at a specific depth of invasion.

After logistic regression confirming correlation between depth of invasion and lymph node positivity, we analyzed our data using 3 separate methods with a focus on specific depths with a 20% positive rate, overall cutoff of depths with 20% positive rate, and NPVs of 80%. We expected that slightly different answers would result from these various analyses that could be combined into an overall set of recommendations based on our data.

A number of important limitations to our specific study should be considered. First, it is retrospective in nature and suffers from all the normal limitations of this type of study. Pathology reports were accepted as written and no effort was made to review the findings in a more scientific fashion. The patient pool was also limited to those who underwent neck dissection. At our institution, surgeons vary in recommending neck dissection for patients with T1N0 disease based on the depth of invasion of the initial biopsy confirmed on frozen section for patients of shallower depths. The recommendation ranges from 2 mm or 3 mm depth of invasion in standard cases depending on the surgeon. Aging patients or those with significant comorbidities

TABLE 8. T1 Lesions (no. of necks = 111).

Depth of invasion	No. of necks with negative nodes	No. of necks with positive nodes	Percentage of necks with positive nodes	Sensitivity	Specificity	PPV	NPV
1 mm	5	0	0	100%	6%	31%	100%
2 mm*	7*	3*	30*	91%*	15%*	31%*	80%*
3 mm	16	5	24	76%	36%	33%	78%
4 mm	17	3	15	67%	58%	40%	80%
5 mm	13	3	19	57%	74%	48%	81%
6 mm	5	2	29	51%	81%	53%	80%
7 mm	3	4	57	39%	85%	52%	78%
8 mm	5	4	44	27%	91%	56%	75%
9 mm	4	1	20	24%	96%	73%	75%
10 mm	2	2	50	18%	99%	86%	74%
>10 mm	1	6	86	0	100%	n/a	70%

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.
* Shows the shallowest depth of invasion (in millimeters) in which 20% or greater of the necks dissected demonstrated postive lymph nodes and the NPV is 80% or less.

may be offered greater depth thresholds before dissection. Therefore, patients who did not undergo neck dissection because of not reaching the cutoff recommendations were not included in this study. We used patients who received neck dissections to explore data estimating what the results would have been if "watch-and-wait" had been undertaken at the various depths, which is obviously not the same as comparing treatment outcomes with neck dissection versus "watch-and-wait." Finally, for purposes of this study, we utilized 20% risk of occult metastasis as a threshold to recommend neck dissection. Although this is the most standard recommendation, if a surgeon accepted a higher or lower rate, then our recommendations would not be applicable.

The utility of depth of invasion has been questioned because of a number of limitations that were not study specific, per se, but deserve mention and discussion. One of the critiques to using depth is biopsy-sampling error. Holmstrup et al[16] reported on 101 lesions with initial biopsy followed by complete excision, on average, 10.4 months after biopsy. Although the study compared histologic diagnosis and not depth of invasion, only 49% of lesions matched raising questions regarding both the possibilities of sampling error and pathologist variability. At our institution, we overcome this challenge by basing final decisions for neck dissection on patients with "close decisions" to frozen-section pathology with multiple sampling where indicated. Thus, we rely not only on the initial biopsy but information at the time of resection. In addition, in cases in which the depth of invasion is the decision-maker, the attending surgeon views the frozen section slides with the pathologist as depth measurements are made. The limitations of this methodology are patient uncertainty before the operation of the final plan and allotment of operating room time for patients who ultimately do not qualify for neck dissection. Despite these limitations, this practice has been well received by patients and successful in assisting with final decisions with comprehensive and standardized reviews of specimens.

Another potential error in depth of invasion assessment may stem from known discrepancies of various sites in regard to mucosal shrinkage after resection, which has been explored by a number of authors with variable discrepancies reported from the low 20% to a high upward of 71.90%.[17,18] Again, although these studies do not directly assess the depth of invasion question, they should be considered. One of the advantages of our study was the adequate sample size for subsite analysis, which takes into consideration the variety of tissues in the oral cavity adding a level of credence to our study not available to many others.

Finally, a recent prospective clinical trial examined elective treatment of the neck versus therapeutic (watch-and-wait), demonstrating a statistically significant overall and disease-free survival benefit in patients undergoing elective neck dissection. In this study, using logistic regression in the elective group depth of invasion was the only factor that was significantly associated with node positivity for the 72 patients with positive nodes demonstrating a marked increase in cumulative lymph node positivity with increasing depth of invasion from 3 mm (5.6%) to 4 mm (16.9%). Despite this finding, the authors conclude that, given lack of statistical significance, the result was hypothesis generating at best. It should be noted that depth of invasion was not the primary endpoint of the study nor was the study powered to answer the question of depth of invasion. In addition, because the study included both patients with T1 and T2 disease, it is not generalizable to the T1-only population for which depth of invasion is most commonly used

TABLE 9. Summary of pertinent findings at specific anatomic sites and recommendations for the appropriate depth to offer a neck dissection.

Site	Descriptive data	20% cutoff	NPV	Recommendation for neck dissection
Tongue	2 mm	2 mm	2 mm	2 mm
Floor of mouth	3 mm	3 mm	2 mm	2–3 mm
Retromolar trigone	3 mm	4 mm	3 mm	3–4mm
Alveolus/hard palate	4 mm	4 mm	3 mm	3–4 mm
All sites	2 mm	4 mm	4 mm	2–4 mm

Descriptive data: Precise value for the depth of invasion where the percentage of necks with positive nodes measured at 1mm increments reached a value of 20%.
20% Cutoff: Precise value for the depth of invasion where 20% of all patients at that depth and shallower would present with positive lymph nodes.
NPV: Negative predictive value represents the depth of invasion in a patient whom if a neck dissection was not performed, would truly be negative for disease.
Recommendation: Given all data collected, we are recommending a neck dissection at this depth.

as an indicator for treatment decisions; given the patients with T2 disease and above receive elective neck dissection regardless of depth.[19]

Despite the stated study specific and general limitations above, we believe our data represents a significant contribution to the literature on the subject because of the large numbers, statistical validity of the findings, and the fact that depth of invasion was the most statistically significant predictor of neck metastasis. Although certainly these data are not adequate on which to base all clinical decisions, it does provide a level of evidence that can guide surgeons as they treat individual patients particularly with clinical T1N0 disease. Table 9 summarizes the treatment recommendations based on the data of the study. Recommendations are based off of the descriptive data of 20% rates at various levels, 20% cutoff points considering all levels, and the NPVs of 80%. We found that the tongue and floor of the mouth were our highest risk sites and, thus, had a more aggressive approach to offering a neck dissection. If the primary lesion is on the tongue, then the data suggest neck dissection at 2 mm depth of invasion. At the floor of the mouth, then 2 to 3 mm is the recommendation. The retromolar trigone and alveolus/hard palate are slightly lower risk sites and with recommendations in the 3- to 4-mm range.

In analysis of our T1 lesions independently (Table 8), we found that our data indicated that 2 mm would be an appropriate threshold for offering a neck dissection to patients with T1 disease. We noted that this number is influenced by the fact that a large percentage of our T1 lesions were primarily in the tongue and the floor of the mouth, thus influencing our data toward a more aggressive treatment regimen overall for these regions.

CONCLUSION

We conclude that depth of invasion remains an important variable to consider when making treatment recommendations to patients with clinical T1N0 disease. The recommendations should also take both depth and location of tumor into account. We have additionally suggested methods that help to diminish some of the limitations of this technique, including standardization of depth measurements with surgeon and pathologist, and frozen section analysis to diminish sampling error. We believe depth of invasion remains as an important factor to consider for future prospective studies.

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