Muscle Invasion in Oral Tongue Squamous Cell Carcinoma as a Predictor of Nodal Status and Local Recurrence: Just as Effective as Depth of Invasion?

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Received: 7 June 2011 / Accepted: 19 August 2011 / Published online: 4 September 2011
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Abstract Tumor depth of invasion (DOI) is a histologic feature that consistently correlates with lymph node metastasis; however, there are many difficulties with accurately assessing DOI. The aim of this study was to identify a simpler and more reproducible method of determining DOI, by using skeletal muscle invasion as a surrogate marker of depth. Oral tongue squamous cell carcinoma American Joint Committee on Cancer (AJCC) stage T1 cases were identified in the Emory University Department of Pathology database. 61 cases, with a minimum of 2 years of follow-up, were included in the study. Cases were examined histologically to assess muscle invasion and DOI. The two methods of measurement were analyzed to determine the positive predictive value (PPV) of DOI or muscle invasion for both nodal disease and local recurrence. Cases with muscle invasion had a 23.3% PPV of occult lymph node metastasis. Cases with DOI of greater than 3 mm had a 29.7% PPV of occult lymph node metastasis. Cases with muscle invasion had a 43.7% PPV of local tumor recurrence. Cases with maximum DOI of greater than 3 mm had a 40.4% PPV of tumor recurrence. Although the PPV of muscle invasion in regards to nodal status was slightly less than DOI, it represents a more easily reproducible parameter which could guide surgeons in determining if the case warrants an elective neck dissection in a cN0 (clinically negative) neck. Interestingly, the PPV of local recurrence was higher with muscle

invasion than DOI, and may represent an important indicator for extent of resection.

Keywords Oral squamous cell carcinoma · Tongue · Depth of invasion · Muscle invasion · Oral cancer

Introduction

Head and neck squamous cell carcinoma (HNSCC) is currently the 7th most common cancer, with 260,000 cases new cases diagnosed yearly and around 128,000 deaths annually worldwide [1]. In the United States, the overall burden is about 35,000 new cases a year with 7,600 deaths [2]. While significant advancements have been made in diagnostics, treatment strategies, and prevention, only modest progress has been made in improving the survival rates in patients with advanced and metastatic disease over the last 20 years [2–4].

The most significant prognostic factor in HNSCC is the presence of metastatic disease in the cervical lymph nodes, with a 50% decrease in 5-year survival in patients with nodal disease [5–8]. The ability to determine lymph node status represents an issue of paramount importance in the treatment of HNSCC. Currently, patients with clinical and/or radiographic evidence of lymph node metastasis (N+) will receive a lymph node dissection at the time of surgical resection of their tumor. Despite clinical or radiographic “evidence” of lymph node metastasis, 10–20% of these patients were actually metastasis-free upon histologic examination (N0). Conversely, approximately 20–40% of patients staged clinically as N0 actually had metastatic disease [9]. These statistics highlight the inaccuracies in clinical staging of lymph node status in oral tongue squamous cell carcinoma (SCC).

This material was presented in part at the 2011 USCAP Meeting in San Antonio, Texas.

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Neck dissections are associated with significant morbidity, discouraging the use of elective neck dissections to determine nodal status in subclinical disease; therefore, another method is needed to detect subclinical lymph node metastasis. Currently, many studies have demonstrated a good correlation between depth of tumor invasion and the presence of occult lymph node metastasis, prompting many institutions to adopt depth of invasion as an indicator for necessity of lymph node dissection. However, these aforementioned studies have used several different cut-off points for depth of invasion, ranging from 1.5 to 10 mm [10–25]. The studies also report differing methods of measurement, thus further complicating the issue.

Additionally, even if a consensus can be reached about a cut-off point, unfortunately, there are many other difficulties associated with determining an accurate depth of invasion. These include histologic parameters, such as degree of surface erosion or ulceration (Fig. 1), and hyperkeratosis, which make it problematic to determine exactly where to begin measuring from the “surface”. Furthermore, depth can be difficult to ascertain due to obscuring inflammation surrounding the invasive front of the lesion. These problems are magnified during an intra-operative consultation when tissue sections are frequently maloriented with tissue folds (Fig. 2) and fraught with frozen section artifact, such as blade chatter and freezing artifact (Fig. 3). Formalin fixation also leads to an overall shrinkage of the specimen, which may result in an artifactually diminished measurement.

Fig. 1 Histologic section demonstrating complete ulceration of surface epithelium with replacement by a fibrinopurulent membrane. Since no overlying epithelium is present, ulceration makes accurate measurements of depth of invasion problematic since the normal anatomic landmarks where measurements are taken from are no longer present

Fig. 2 Histologic section obtained in the frozen section room demonstrating artifactual folding of the tissue which is a common issue in the performance and interpretation of frozen sections. The overlapping tissue makes depth of invasion measurements problematic

Fig. 3 Histologic section obtained by frozen section processing demonstrating frozen “chatter artifact” from the frozen tissue skipping across the blade. This is another artifact common with frozen section preparations that makes accurate depth of invasion measurements difficult

The presence of muscle invasion is another simple histologic landmark that is measurable within the oral tongue (Fig. 4). Skeletal muscle invasion would be more straight-forward to ascertain in specimens, as compared to DOI, and would likely have greater inter-observer

Fig. 4 Histologic section demonstrating islands of malignant epithelium infiltrating the underlying skeletal muscle

reproducibility. Additionally, muscle invasion would be simpler to determine in the frozen section setting, which is where DOI is frequently needed to determine if the surgery should proceed to lymph node dissection. In this paper, we propose using muscle invasion as a surrogate marker for DOI. Our hypothesis, therefore, maintains that muscle invasion should correlate similarly for likelihood of occult lymph node metastasis.

Materials and Methods

After obtaining IRB approval, 74 cases of oral tongue SCC American Joint Committee on Cancer (AJCC) stage T1 cases resected at Emory University Hospital from 1999 to 2008 were identified by searching the Emory University Department of Pathology database. The patient clinical histories were then reviewed via electronic medical records. Among these, 61 cases were identified that had clinically negative lymph nodes, negative margins of resection (tumor ≥ 0.1 cm from margin of resection), and possessed at least 2 years of clinical follow-up, and were therefore included in the study. The remaining 13 cases were excluded due to insufficient clinical follow-up. The H&E stained slides for these 61 cases were retrieved from archives and examined histologically to assess presence of skeletal muscle invasion and perineural invasion, as well as greatest depth of invasion. Depth of invasion was measured via a micrometer and rounded to the closest 0.5 mm according to the method recommended by the 2010

Fig. 5 The *dark lines* demonstrate where our measurements were taken—from below the keratin layer to the deepest point of invasion

American Joint Committee on Cancer Staging [26]. Measurements were made from the deepest point of invasion into the underlying tissue to the granular layer of the overlying epithelium. The keratin layer was not included in the measurements (Fig. 5). In cases where the overlying epithelium was ulcerated, the depth was measured from the surface of the ulcer. Of note, the AJCC also uses the term *tumor thickness* to refer to this method of measurement. We prefer the term *depth of invasion* to avoid confusion with other possible measurements of thickness. The medical records were evaluated to record clinical nodal status, as well as local recurrence, metastatic recurrence, or death from disease. The data was then analyzed to determine the PPV of DOI for both nodal disease and local recurrence, as well as muscle invasion with both of the same parameters. The PPVs of DOI and muscle invasion were compared.

Results

Of the 61 cases included in the study, 43 demonstrated muscle invasion. Among the 43 cases with muscle invasion, 10 cases had evidence of lymph node metastasis at the time of surgery. One case with positive nodal disease failed to demonstrate muscle invasion. This represents a 23.3% PPV of muscle invasion with respect to positive lymph nodes (Table 1). Comparatively, 37 of the 61 cases demonstrated DOI greater than or equal to 3 mm. Of these 37 cases, 11 had lymph node metastasis which represents a 29.7% PPV (Table 2).

Table 1 This 2 × 2 table correlates the presence of muscle invasion with the presence of lymph node metastasis (positive lymph nodes)

Positive nodes	Muscle invasion			
	Yes	No		
Yes	10	1	11	PPV = 23.3%
No	33	17	50	LR = 1.36
	43	18	61	

Of the 11 cases that were positive for lymph node metastasis, only 1 case failed to exhibit muscle invasion

Table 2 This 2 × 2 table correlates the measurement of depth of invasion (greater than or equal to 3 mm vs. less than 3 mm) with the presence of lymph node metastasis

Positive nodes	Depth of invasion (≥ 3 mm)			
	Yes	No		
Yes	11	0	11	PPV = 29.7%
No	26	24	50	LR = 1.92
	37	24	61	

All 11 cases with positive lymph nodes had tumor invasion to at least 3 mm in depth. (PPV Positive predictive value, LR Likelihood ratio)

Table 3 This 2 × 2 table correlates the presence of muscle invasion with clinical recurrence of disease, either locally or distantly

Recurrence	Muscle invasion			
	Yes	No		
Yes	19	5	24	PPV = 43.7%
No	24	13	37	LR = 1.22
	43	18	61	

Of the 24 cases that recurred, only 5 cases failed to exhibit muscle invasion

In regards to recurrence, 19 cases out of the 43 with muscle invasion had either local disease recurrence or locoregional metastasis within their course of follow-up. This confers a 43.7% PPV for muscle invasion in reference to disease recurrence (Table 3). Of the 37 cases with depth greater than or equal to 3 mm, 15 recurred. This calculates to a DOI having a 40.4% PPV for recurrence (Table 4).

Two cases were found with a DOI ≥ 3 mm that did not demonstrate muscle invasion. One of these cases, in fact, also had lymph node metastasis (depth of invasion = 5.0 mm). Alternately, there were 8 cases with muscle invasion present that had a depth of invasion less than 3 mm (all measured either 2.0 or 2.5 mm). None of these cases had positive lymph nodes.

Table 4 This 2 × 2 table correlates the measurement of depth of invasion (greater than or equal to 3 mm vs. less than 3 mm) with clinical recurrence

Recurrence	Depth of invasion (≥ 3 mm)			
	Yes	No		
Yes	15	9	24	PPV = 40.4%
No	22	15	37	LR = 1.06
	37	24	61	

Of the 24 cases that recurred, 9 cases measured less than 3 mm at maximum depth of invasion

Discussion

With all of the inherent difficulties in obtaining an accurate depth of invasion measurement, a simple histologic landmark that could determine which patients with a clinically negative neck (cNO) warranted a neck dissection would be valuable for both pathologists and surgeons. In this paper, we examined the presence of muscle invasion in relation to lymph node status in the hope of finding a simpler and more reproducible parameter.

As mentioned earlier, numerous studies have analyzed depth of invasion with relation to lymph node status and these studies have recommended a wide variety of cut-off values for warranting a lymph node dissection using differing measuring techniques. In this study, we used 3 mm as our study cut-off, which is on the conservative end of the proposed depths from previous research and is the value used at our institution by our head and neck surgeons. Furthermore, while some authors advocate measuring depth of invasion from the basement membrane, the measurements included in this study were obtained using the method recommended by the AJCC [26].

The PPVs of DOI and muscle invasion in relation to lymph node metastasis were 29.7 and 23.3%, respectively. While this data supports that DOI has a slightly higher predictive value, we demonstrated that muscle invasion has above a 20% PPV for lymph node metastasis. This is clinically significant since the current standard of care contends that a 20% likelihood of occult lymph node metastasis warrants a neck dissection [27, 28]. As mentioned previously, using muscle invasion as the criteria is a much easier parameter to access, especially in the frozen section room where many of the decisions must be made as to whether or not to perform a neck dissection.

Interestingly, the PPV of muscle invasion in relation to recurrence was marginally higher than with a DOI ≥ 3 mm (43.7% vs. 40.4%). This could potentially serve as an important indicator for the extent of resection warranted to assure that complete surgical resection is obtained. Moreover, evidence of muscle invasion may also facilitate

decision-making by radiation oncologists as to the extent of field requiring treatment.

In this study, case numbers were limited due to our desire to have at least 2 years of clinical follow-up available for each patient. Therefore, the difference in predictive values is largely attributed to a single case that did not demonstrate muscle invasion but had positive lymph nodes. A larger study could help elucidate the applicability of muscle invasion as an indicator of lymph node positivity. While more exploration into this topic is needed, these results hold promise for the utility of the use of muscle invasion in clinical decision-making as compared to the more problematic depth of invasion.

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