Review Article

Tumor Infiltration Depth as a Prognostic Parameter for Nodal Metastasis in Oral Squamous Cell Carcinoma

Abstract

Oral squamous cell carcinoma (OSCC) has locoregional evolution, with frequent neck involvement. Significant number of studies have been undertaken to assess the parameters for treatment of N0 neck patients with a high likelihood of harboring occult node metastases. Many studies have indicated tumor infiltration depth (or tumor thickness) as one of the most important criteria in determining the further management. Growing evidence in the literature shows that tumor infiltration depth is a reliable parameter for predicting regional node involvement and patient survival in OSCC. The substantial agreement among authors, despite the lack of comparable study groups, of measurement techniques, and cutoff values paradoxically enforced its reliability. Further studies are clearly awaited to reach a consensus on these topics to develop therapy protocols that are also based on this parameter. This article is an attempt to substantiate the use of tumor infiltration depth as a prognostic factor for nodal metastasis in OSCC.

Keywords: *Lymphatic metastasis, oral cancer, squamous cell carcinoma, tumor infiltration depth, tumor invasion*

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Introduction

Oral mucosa squamous cell carcinoma (OSCC) has locoregional evolution. As it grows, it invades the surrounding tissue and metastasizes to regional neck nodes, but it rarely develops distant metastases. With reference to the Tumor, Node, Metastasis staging system,[1] when dealing with large lesions (T3 and T4) or preoperative N-positive neck nodes, there is a substantial agreement in recommending treatment including the neck nodes. However, there are still many doubts concerning the best way to approach neck disease in the case of early-stage lesions (T1 and T2).

The treatment of patients with early-stage, clinically node-negative oral squamous-cell cancer has been a contentious issue spanning five decades.[2-8] Surgical options for addressing the neck include elective neck dissection at the time of the excision of the primary tumor or watchful waiting (or wait and see approach) with therapeutic neck dissection for nodal relapse. Proponents of elective neck dissection cite decreased relapse rates and better survival rates.[2-8] Part of the problem with a "wait and see'" approach is that patients affected by upper aerodigestive tract (UADT) squamous cell carcinoma (SCC) with negative nodes at the time of presentation (N0) have a high risk of harboring occult node metastases. In these cases, we can prove the presence of a metastasis only by postoperative histologic node examination; the clinical aspects and preoperative tests are not completely reliable. The presence of occult node metastases of early-stage tumors in the clinically negative neck has been reported in 20%–44% of cases.[9-18]

Elective neck dissection provides pathologic information on the status of neck nodes, thus helping to determine the need for additional therapy, and can also remove undetectable cancer cells lodged in the lymph vessels. However, many patients might not need such treatment, and furthermore, it does have an associated morbidity and may remove or destroy a natural barrier to cancer spread.[19]

The unpredictable behavior of UADT SCC has led clinicians to look for reliable parameters to be applied as predictors of neck node metastasis and prognosis. However, to date, management of the clinically negative neck in early SCC of the oral cavity is still a controversial issue.

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Recently, several studies evaluated tumor thickness (TT), which can be considered an objective parameter of the depth of invasion within the connective tissue. The increasing depth of invasion and the microvascular proliferation caused by neoplastic growth might determine proximity to blood vessels and lymphatics, thus facilitating the tumor's ability to metastasize.[20] Moreover, it has been observed that it is more difficult for tumor emboli to form in the small-caliber lymphatics of superficial areas than in the wider lymphatics of deeper tissue.[20]

With this article, we attempt to review and discuss the role of tumor infiltration depth as a prognostic parameter for the development of nodal metastases with OSCC.

Infiltration Depth and Thickness - Synonyms???

As stated by Moore *et al*.,[21] depth of invasion and TT are not the same, and a distinction has to be made, even though many authors use these two terms synonymously.[9,12] "Tumor Infiltration Depth" means the extent of cancer growth into the tissue beneath an epithelial surface. In cases in which the epithelium is destroyed, some investigators reconstruct a surface line and measure from this line.[22,23] However, the infiltration depth is sometimes expressed by referring to the microscopic, anatomic deep structures that are reached, rather than by referring to objective micrometer measurements in millimeters.[24,25,26] In this case, congruence among pathologists is less readily achieved because a series of subjective assessments are needed to determine the level of invasion.[22]

On the other hand, TT concerns the entire tumor mass; an objective parameter is needed, and it can be obtained using an ocular micrometer.[22,23] The proximity to blood vessels and lymphatics is what determines an increased risk of nodal metastases developing in as much as it facilitates the tumor's ability to expand.

Therefore, it might be better to take into consideration the actual mass that is present beneath the theoretical reconstruction of a basement membrane (Infiltration depth or depth of invasion) rather than the thickness of the entire tumor.

Breslow defined strict criteria for measuring cutaneous melanoma (i.e., from the deepest point of invasion to the top of the granular cell layer of the overlying epidermis, excluding keratin, parakeratin, and inflammatory exudates).[23] If the lesion is ulcerated, the ulcer base serves as the reference point. However, he reported two main problems: poor sampling and variation in apparent thickness because of the variable angle of sectioning. In articles concerning oral carcinoma, maximum TT was most often evaluated with an optical micrometer with various measurement techniques, depending on whether the mucosal surface, the tumor surface, or the ulcer base was chosen as the starting point [Figure 1].

Some authors adopted the technique developed by Breslow and measured vertically starting from the tumor surface or the base of the ulcer base [Figure 1 a-d]. In those cases in which the tumor was exophytic, the most perpendicular section was measured from the tip of the papilla to the maximal depth.[23] Other authors likely used the same technique, but it is not clear whether they excluded keratin, parakeratin, and inflammatory exudates.

Alternately, an imaginary line indicating the level of the adjacent intact mucosa [Figure 1 b-e] or of the basal membrane [Figure 1 c-f] can be considered the starting point for measuring the thickness of the tumor into the underlying tissue to the deepest point of invasion. Moore *et al*. used the technique proposed by Breslow, as well as a second measurement obtained from an imaginary "normal mucosal line" for comparison.[21] They found that longer survival of most patients with verrucous cancer correlated better with thickness as measured from the line of a "basement membrane constructed through the tumor" than with the entire thickness of the exophytic tumor. Analogously, Urist *et al*.[27] and Woolgar[16] and Woolgar and Scott[28] considered thickness as the entire tumor measurement and depth as the amount from the surrounding normal mucosa.

There is, of course, a great deal of difference in the concept of TT as expressed, for example, by Giacomarra *et al*.,[29] who affirm that "TT is commonly used as a synonym of depth of invasion and indicates the part of the tumor situated under the line of the basal membrane" compared with authors who adopted the technique proposed by Breslow that measures TT from either the tumor surface or

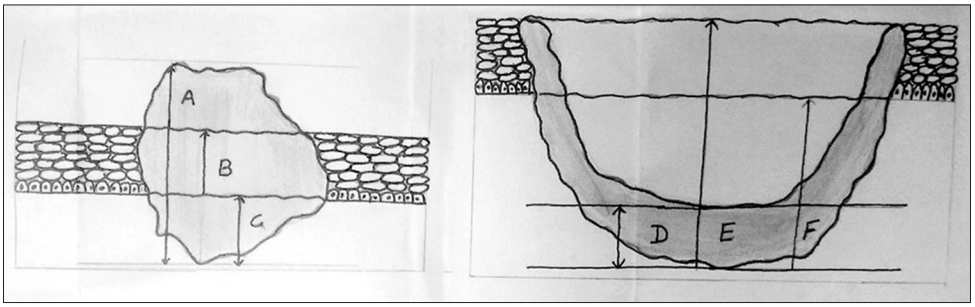

Figure 1: Original image methods of measuring tumor thickness. (A-D) Tumor surface/base of the ulcer – deepest point of invasion (B-E) adjacent intact mucosa – deepest point of invasion (C-F) basal membrane – deepest point of invasion

from the base of the ulcer. It must be pointed out that it is not always easy to distinguish the exact technique that was used in each study.

Furthermore, even when an apparently exhaustive explanation is given, there could be some misunderstanding. As previously stated, Moore *et al*.[21] reported the possibility of reconstructing a ''normal mucosal line'' as the basement membrane line in case of exophytic and/or verrucous tumors. Both Ambrosch *et al*.[30] and Woolgar *et al*.[28] used a measurement technique based on the ''normal mucosal line'' cited by Moore *et al*., but only thanks to the figures in these two articles is it clear that Ambrosch *et al*. alone interpreted it as the basement membrane line, whereas Woolgar *et al*. used the surface line of the surrounding healthy mucosa. It must be pointed out that no figures were used to clarify Moore *et al*.' s concept.

It must be said that the lack of standard sampling, measurement techniques, and cutoff values makes it quite impossible to compare the studies found in the literature. Although most authors substantially agree that TT is a significant parameter for predicting nodal metastasis development and for survival, the cutoff thickness is really quite variable, ranging from 1.5[31] to 10 mm.[32,33] It is unclear why the studies have reached such inconsistent results with reference to the cutoff measurement point. A possible explanation could be related to the different measurement techniques and methods that were adopted, as discussed previously. Alternately, some studies related the critical thickness to the site, but to date, there is no agreement about this. Woolgar and Scott reported different cutoff values for TT as related to the tumor site.[28] They found a higher incidence of nodal metastases in tumors that were 7.6-mm thick versus those that were 3.8-mm thick in the floor of the mouth (FOM), and 15.1-mm thick versus 9.6-mm thick in the tongue. A possible explanation might be related to the difference in the depth and caliber of the lymphatics at the two sites. Analogously, in 50 T2 SCC of the tongue, Woolgar found that the mean thickness of the lesions of the lateral tongue (13.6 mm) was significantly greater than the mean thickness of tumors of the ventral surface (9.1 mm).[16] Conversely, O'Brien *et al*. found no differences among 145 cancers from different oral cavity sites, with a median TT that was similar for the tongue (6.4 mm), the FOM (6.6 mm), and other sites (5.7 mm).[34]

Mohit-Tabatabai *et al*.[31] and Spiro *et al*.[15] were the first authors to apply Breslow's hypothesis regarding the link between nodal involvement and TT to OSCC. Mohit-Tabatabai *et al*. planned a retrospective study based on 84 patients with Stage I–II SCC of the FOM. All the histologic slides were blind reviewed by expert pathologists, who examined maximum TT, grading, and inflammatory reaction. The authors evaluated three thickness ranges (<1.5 mm, from 1.6 to 3.5 mm, and >3.6 mm) and found a metastases incidence of 2%, 35%, and 60%, respectively. Statistical analysis revealed a significant link between thickness and metastasis in tumors >1.5-mm thick. As a consequence, they suggested performing modified neck dissection in cases of TT >1.5 mm and with no clinical nodal evidence.[31]

Spiro *et al*. retrospectively analyzed ninety-two patients with T1–T2–T3 disease who had been surgically treated for carcinoma of the tongue/FOM and who had been followed up for at least 24 months.[15] Some of them also underwent elective neck dissection on clinically negative necks. Using univariate and multivariate analysis, they found a significant difference when they chose a cutoff thickness of 2 mm, both for locoregional recurrences and survival. Finally, they considered elective neck dissection appropriate for N0 oral cancer when the thickness of the primary tumor exceeded 2 mm because the risk of metastasis approached 40% in their study.[15]

Recent Studies on Infiltration Depth as Prognostic Factor

Keski-Säntti *et al*., in 2007 assessed the predictive value of histopathologic parameters in early OSCC in 73 patients. They concluded that depth of infiltration predicted occult nodal disease, but its value in clinical decision-making is limited because of poor specificity when using a cutoff value that offers reasonable sensitivity for finding the patients with occult nodal disease.[35]

In 2012, Melchers *et al*. did a classical study on 351 OSCC cases to explore infiltration depth as an independent prognostic factor and also recommend a cutoff depth for performing neck dissection. The analysis on pT1cN0 tumors resulted in an optimal cutoff for the prediction of the nodal status at a depth of 4.59 mm. They recommended an infiltration depth of P4 mm as an indication to perform a neck dissection in pT1cN0 OSCC.[36]

In 2014, Balasubramanian *et al*. compared the TT as a predictor of nodal metastases in cancers of tongue and FOM subsites. They concluded that thin FOM tumors (2.1–4 mm) have a high rate of nodal metastases. They also suggested neck dissection in FOM tumors >2 mm thick and tongue tumors of more than 4 mm thickness.[37]

In 2013, Süslü *et al*. did a case series analysis of 138 patients to identify factors affecting the clinical course and survival of patients with SCC of the tongue. Indicated that TT >8 mm and lymph node metastasis were independent predictors of worse survival in patients with SCC of the tongue. Because similar regional recurrence rates were observed in selective and radical neck dissections, supraomohyoid neck dissection was supported as a primary treatment for patients with clinical N0 tumor.[38]

A study done by Wermker *et al*. in 2015 aimed at identifying predictive factors for lymph node metastases

in Lip SCC. Regression analysis revealed tumor extent, tumor infiltration depth, and grading as the most important factors in the correct classification of Lymph Node Metastasis (LNM) in 94.2% of patients.[39]

Garzina-Demo *et al*., in 2016 assessed the parameters and outcomes in 525 patients operated on for OSCC. As standardized in previous studies, they considered 4 mm as a cutoff for tumor infiltration depth for deciding the need for neck treatment. Tumor infiltration depth was measured in 150 cT1 cases of tongue and FOM. In 102 of those patients with depth <4 mm, the 5-year DSS was observed to be 95.15%, while it dropped to 72.27% for the 48 patients with invasion of more than 4 mm.[40]

Tarsitano *et al*. in 2016 conducted a retrospective longitudinal study to identify the cutoff value of infiltration depth for predicting the risk of lymph node metastasis of the neck in a well-defined population of surgically treated patients affected by stage T1 to T2 oral SCC of the tongue. The mean infiltration depth of the N-negative group was found to be 2.4 mm which was substantially different from the mean value observed in the N-positive group at 5.5 mm. A meaningful cutoff was identified at an infiltration depth value of 4 mm.[41]

Studies of prognostic factors in patients with head and neck cancers almost invariably recommended that the staging system should be changed or that a prospective, randomized trial was needed to clarify the issue once and for all. Howaldt *et al*. proposed a modified pTumor, Node, Metastasis staging in which three cutoffs of TT (5, 10, and 20 mm) were combined with the greatest tumor dimension to obtain the pT classification.[42] They based their proposal on the findings in 806 patients in the large Do¨sak tumor registry in Germany.

After a considerable number of studies and consensus among oncologists and pathologists over the world, the most recent 8th Edition update on American Joint Committee on Cancer Cancer Staging Manual, introduced in September 2016, Tumor Infiltration depth has been included as a prognostic factor for tumor staging.[43] The update includes tumors with greatest dimension of ≤2 cm but <5 mm of infiltration depth as T1. According to the same, tumors ≤2 cm but >5 mm or tumors >2 cm and <4 cm with infiltration depth <10 mm has been upgraded as T2 tumors. Tumors with greatest dimension of >4 cm and depth >10 cm has been marked as T3.[43]

Radioimaging and Infiltration Depth

The reliability of high-resolution magnetic resonance imaging (MRI) in determining TT of carcinoma of the tongue was first investigated on resected specimens. In 2001, Tetsumura *et al*. found a strong correlation between the measurements obtained by MRI and histopathology, both for normal mucosa and for tumor lesions.[44] In 2002, Iwai *et al*. found a significant correlation between the TT measured on the histologic specimen and what was obtained by MRI in 30 lesions of the tongue.[45] They found significant results when they investigated the maximum TT from both the surface and from a hypothetical, reconstructed mucosal line. Analogously, in 2004, Lam *et al*. found a significant correlation between histologic samples and TT as measured by MRI in 18 lesions (at any stage) of the tongue. They pinned each specimen to a board to prevent shrinkage of the tissue caused by the formalin fixation and digitally measured the TT of both the MRI images and the histologic specimens by means of a computerized image analyzer.[46]

Taylor *et al*. did a study in 2009 to assess if preoperative ultrasound sonography (USG) is an accurate measure of tumor depth in oral carcinoma. Twenty-one consecutive patients with biopsy proven SCC of the tongue/floor of mouth were analyzed prospectively. There was a significant correlation between the preoperative ultrasonography and histological measures of tumor depth. They also suggested that TT is a significant predictor of nodal metastasis and elective neck dissection should be considered when this thickness is P5 mm.[47]

Yesuratnam *et al*. conducted a study on eighty-eight patients with tongue SCC to investigate the correlation between TT on intraoral ultrasound (US) and MRI with the histologically determined TT of tongue cancers. Preoperative TT as determined by USG demonstrated high correlation and MRI moderate correlation with histological TT. They suggested that USG could be considered as the initial modality of choice for preoperative assessment of TT.[48]

Conclusion

Growing evidence in the literature shows that TT is a reliable parameter for predicting regional node involvement and patient survival in OSCC. The substantial agreement among authors, despite the lack of comparable study groups, of measurement techniques, and cutoff values paradoxically enforced its reliability.

We have concluded that that infiltration depth is an independent predictor for the presence of nodal metastasis in pT1–2 OSCC. We have also established that applying infiltration depth as indication for elective neck dissection in patients currently treated by elective neck dissection would result in the correct treatment in comparison to case of overtreatment.

Our study also highlights the varied values of tumor infiltration depth being used as a cutoff for management of the neck. Further studies are clearly awaited to reach a consensus on these topics to develop therapy protocols that are also based on this parameter.

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Conflicts of interest

There are no conflicts of interest.

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