Editorial Commentary

Depth of invasion for prognostic stratification in oral cavity cancer: do we need further validation?

Cesare Piazza[1], Lorenzo Bresciani[1,2], Lorenzo Giannini[1,3]

[1]Department of Otorhinolaryngology, Maxillofacial and Thyroid Surgery, Fondazione IRCCS National Cancer Institute of Milan, University of Milan, Milan, Italy; [2]Department of Otorhinolaryngology, Head and Neck Surgery, Fondazione IRCCS, Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [3]Department of Otorhinolaryngology, Head and Neck Surgery, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy

Correspondence to: Cesare Piazza. Department of Otorhinolaryngology, Maxillofacial and Thyroid Surgery, Fondazione IRCCS National Cancer Institute of Milan, Via Giacomo Venezian 1, 20133 Milan, Italy. Email: Cesare.piazza@istitutotumori.mi.it; ceceplaza@libero.it.

Comment on: Kano S, Sakashita T, Tsushima N, *et al.* Validation of the 8th edition of the AJCC/UICC TNM staging system for tongue squamous cell carcinoma. Int J Clin Oncol 2018;23:844-50.

Submitted Mar 24, 2019. Accepted for publication Apr 04, 2019.
doi: 10.21037/atm.2019.04.19
View this article at: http://dx.doi.org/10.21037/atm.2019.04.19

Introduction

The tumor-node-metastasis (TNM) staging system of the American Joint Cancer Committee (AJCC)/Union for International Cancer Control (UICC) is a tool originally conceived for description of disease extent, aimed at providing prognostic information and making useful "post hoc" comparisons possible between different centers/series and/or therapeutic strategies. Nevertheless, in everyday clinical practice, it is frequently (and inappropriately) employed "upfront" in choosing primary and/or complementary treatment(s) for a given patient. To correctly assign outcomes categories and possibly (de-) escalate treatment accordingly, a staging system should identify distinct prognostic stratifications that must be internally homogeneous, while at the same time differing from one another. Moreover, when aiming towards more finely-tuned staging accuracy, TNM should remain relatively simple, user friendly, and reproducible.

Oral cavity squamous cell cancer (SCC) is the most common head and neck neoplasm, and in some countries still represents one of the leading causes of cancer-specific mortality, with the tongue the most frequently encountered localization. Despite numerous improvements in treatment, the prognostic landscape of tongue SCC remains poor, with nodal metastasis occurring frequently, and representing the most important prognosticator in terms of loco-regional control and survival (1-3). Thus, a reliable criterion in distinguishing lesions with a low or high risk of nodal metastasis could greatly help in shaping the prognostic outcomes of patients and provide information of paramount importance when choosing the type and extent of primary or complementary treatment(s).

The 7th Edition of the AJCC/UICC TNM staging system, based on a crude two-dimensional definition of the T category, was lacking adequate prognostic performance when applied to tongue SCC, since it failed to distinguish "early" lesions that can potentially develop nodal metastases, from true early tumors without such regional spread (4,5). The 8th Edition was therefore recently updated, and staging for oral cavity SCC has changed significantly. In fact, in response to growing evidence, a well-known pathological feature, namely depth of invasion (DOI), was introduced as a fundamental staging criterion to define T1, T2, and T3 categories as it shows significant correlation with disease specific survival (DSS) (6,7). Moreover, DOI correlates well with the risk of nodal metastasis and loco-regional recurrence, especially in tongue SCC (1,2,6,8,9). Extranodal extension was also added to the N classification of every non-viral related tumor of the upper aero-digestive tract, given its profound negative effect on prognosis in terms of not only regional, but also local and distant relapses (7).

The first validation studies of the last edition of the AJCC/UICC TNM staging system demonstrated good prognostic distinction between early- and advanced-stage

tongue SCC compared to the 7th Edition (7). However, the actual efficacy of such a new tool and its impact on stage distribution of tongue cancer remains a matter of debate, and should be addressed by a larger number of prospective and retrospective studies from different centers.

Validation?

The prognostic performance of the 8th Edition of the TNM applied to tongue SCC has been already tested by many authors. In a recent validation study, Kano and coworkers (10) observed that the T3 category was internally homogeneous, since DSS curves of patients formerly belonging to the T2, T3, and T4a categories according to the 7th Edition, and then reclassified on the base of the DOI parameter, were almost overlapping when grouped together in the 8th Edition T3 category. Moreover, in the latter TNM version, the T2 category showed significantly improved DSS, in line with what is routinely observed in clinical practice. Indeed, tongue tumors with a superficial diameter between 2 and 4 cm (former T2) frequently have a DOI >10 mm (and are therefore now reclassified as T3). Removing from the T2 group this kind of tumors, now leaves in such category those with a better prognosis (DOI in between 5 and 10 mm), consistent with the concept of T2 itself. On the other hand, no significant change was observed in DSS for T1 and T3 lesions, indicating that the 7th Edition had already adequately identified, on the basis of two-dimensional criterion (<2 cm for T1 and >4 for T3), most tumors with a DOI <5 or >10 mm, respectively.

Conversely, Kano and colleagues found that DSS for tongue SCC was not significantly different between T1 and T2 diseases (10). Similarly, other authors observed an improvement in discriminating between early-stage (T1/T2N0) and advanced-stage diseases considering both overall survival (OS) and DSS, while stratification proved unsatisfactory when trying to differentiate T1 from T2N0 disease (4,10-12). The stage migration effect previously described can partially justify the results herein observed. Moreover, this phenomenon was more significant when restaging was performed according to pathological DOI (measured from the level of the basement membrane adjacent to normal mucosa to the deepest point of tumor invasion) rather than on the basis of clinical DOI (12).

The present data reinforce the concept that DOI correlates well with the risk of nodal metastasis in oral cavity SCC (2,8,9,13), with a risk of loco-regional recurrence that increases for any DOI, in a clinically negative neck, with a sharp cumulative risk from 2 to 6 mm (2,8). As noted many years ago, nodal metastasis has a profound and dismal impact on prognosis, with a 50% reduction of 5-year DSS in patients showing positive neck nodes (1). DSS for tongue SCC decreases, passing from T2 to T3N0 disease, as the prevalence of loco-regional recurrence greatly increases for an infiltration deeper than 10 mm (10,14-16). According to many studies, in fact, 10 mm is the threshold of DOI predicting a decline in both DSS and disease-free survival (DFS) for tongue cancer (10,13-15). This is also favorably explained on the basis of anatomical considerations, taking into account that at around 10 mm from the mucosal surface the complex array of extrinsic tongue muscles becomes even more represented than in the superficial layers of the organ, and may be thus responsible for unpredictable distant tumor progression along the muscular fibers and neurovascular bundles contained in the paramedian and lateral lingual connective septa (5).

By contrast, retrospective validation studies showed a similar DSS for T1 and T2N0 disease as identified by the last edition of the TNM staging system (4,10-12). This was another effect of the staging migration described above: since survival of T2N0 tongue SCC improved as more invasive cancers were clustered in Stage III disease, the existent gap between T1 and T2N0 scenarios was reduced in a parallel way (4,10-12,17). At the same time, small cancers (<2 cm), infiltrating in depth more than 5 mm, migrated from T1 to T2. Interestingly, according to Kano *et al.* (10), no significant difference was found between tongue SCC prognostic groups separated by a DOI of 5 mm, while such a distinction proved real when the groups were separated by a DOI of 10 mm, thus reinforcing the anatomical concepts of tongue compartmentalization (5,10,18).

Prognosis of early-stage cancers of the tongue and oral cavity is quite good, with a mean OS and DSS of 75% and 89%, respectively. The most important predictor of survival for early-stage tongue SCC with a clinically negative neck is the presence of occult nodal metastasis, with a prevalence in the literature that ranges from 8.2% to 46.3% (1-3). In fact, patients with occult nodal metastasis have a 5-fold increased risk of dying for disease (1). Therefore, correct assessment of the risk of nodal metastasis is crucial in deciding whether the patient could benefit from upfront or staged elective neck dissection and to correctly define the ensuing prognosis (17). According to every current risk-decision tree analysis, prophylactic neck dissection in cN0 patients is considered cost-effective when the risk of nodal metastasis exceeds 20% (17). DOI was found to be an excellent

predictor of occult nodal metastasis from oral cavity SCC with a clinically negative neck (9,13) and therefore it is potentially an extremely powerful instrument to predict the incidence of nodal spread and, hence, prognosis. Unfortunately, a robust enough threshold to predict which patient may harbor occult nodal metastasis, and display the related prognostic decrease, is still unknown. According to the literature, the optimal DOI cut-off used to establish the need for elective neck dissection can be extremely heterogeneous, ranging from 3 to 10 mm among different series (2,9,13). On top of this, the frequency of occult nodal metastasis in early-stage oral cavity SCC greatly varies depending on the primary subsite. For example, nodal metastasis occurs in 11.2% of tongue SCC with a thickness between 2 and 4 mm, while cancer of the floor of the mouth with an identical DOI has a frequency of metastasis that is significantly higher by 41.7% (19). Therefore, it is unlikely that a DOI cut-off of 5 mm can predict the risk of occult nodal metastasis for SCC of the entire oral cavity or for any of its subsites. The difference between the DOI threshold chosen for upstaging oral cavity SCC from T1 to T2 (5 mm), and to decide for elective neck dissection (which is usually set around 4 mm), brings a relevant risk of occult nodal metastasis for both T1 and T2 disease (9,13). Therefore, T1 disease frequently behaves similarly to T2, showing nodal metastasis and worse prognosis. Lowering the DOI cut-off used to upstage T1 to T2 probably would not significantly improve the distinction between Stage I and II diseases. In a recent work, in fact, Almangush *et al.* reclassified 311 early-stage tongue SCC, suggesting a 2 mm DOI cut-off to upstage to T2 and a 4 mm threshold for upstaging to T3. According to their proposal, T3 disease had an even worse DSS, but the difference between T1 and T2N0 was still not significant (11).

Open questions

As the two-dimensional criterion previously applied in the 7th Edition, the DOI parameter introduced in the last one also falls short if one uses it as the only histopathologic characteristic predicting node metastasis or DSS. From this observation, it directly derives that other factors should be taken into account when studying prognosis of oral cavity and, particularly, tongue SCC, as they all might play a role, heavily influencing the risk of nodal metastasis and survival. Nomograms and prediction models, developed using large (but retrospective) cohorts, showed excellent accuracy for predicting 5-year OS or determining the probability of nodal metastasis (8,20,21). These models use many other clinically-relevant variables such as age, pattern of invasion, perineural and lympho-vascular involvement, or primary site of cancer occurrence to correlate with OS or nodal metastasis (8,20,21). It might be that these factors could obfuscate the role played by DOI and tumor size in separating T1 from T2 diseases. On the other hand, prediction scores and nomograms often show a higher degree of inherent complexity, demanding elaborated histopathologic evaluations that severely limit their overall applicability and reproducibility, especially from the cT and cN point of view.

At the same time, clinical DOI assessment should be refined since it is of crucial importance in the treatment-planning phase. So far it is usually ascertained through clinical examination and imaging, mostly magnetic resonance (MR) (10): measurements of the size and DOI of a given tumor allow to precisely refine clinical staging and thus help in choosing the extent of resection, need for compartmental surgery, possible reconstruction, and/or neck dissection (18,22). Previous studies, although retrospective, supported the employment of MR in the clinical assessment of DOI (23,24) underlying a good correlation between tumor thickness by MR and histologic DOI, even though imaging usually overestimates the latter, probably due to the coexistence of at least two phenomena: peritumoral edema on one hand, and shrinkage of the specimen after surgical resection and fixation on the other (23,24). Notably, imaging accuracy may be reduced when evaluating T1 lesions, as neither clinical nor MR measurements correlated well with a pathological DOI less than 5 mm (24).

Another limit of the current imaging modalities is represented by the impossibility to preoperatively detect nodal micro-metastases. Therefore, once surgery of the primary site has been completed and DOI pathologically demonstrated to be above a given alert threshold, neck dissection should be prophylactically performed with staging purposes within 40 days from resection of the oral cancer. However, management of the cN0 neck in tongue SCC is still controversial: occult nodal metastasis in such a clinical scenario may range between 20% and 44% and, therefore, neck dissection would cause unnecessary morbidity for 56–80% of patients who probably will not harbor nodal metastases (17). Moreover, regional recurrence can occur in 10% of cases even after prophylactic neck dissection, mainly in undissected nodal levels, since selective neck dissection of levels I-III is usually performed (13,17). Therefore, a

strategy of active surveillance by ultrasonography and/or computed tomography (CT) followed by therapeutic neck dissection in case of clinically-positive nodes has been proposed as an alternative to upfront elective neck dissection. The literature on this topic is frequently based on retrospective and small series, while the number of prospective trials is limited and often present critical issues or methodological biases (3,17,25). Nevertheless, recent prospective trials and meta-analyses show that prophylactic neck dissection still significantly reduces regional recurrence and improves DSS in Stage I-II tongue SCC (3,13). While the benefit is evident in patients undergoing follow-up without routine CT examination, it is substantially lacking in case of close follow-up with imaging (17). Therefore, prophylactic selective neck dissection remains the preferred treatment policy when managing a cN0 neck in tumors at high-risk of occult nodal metastasis. Nevertheless, clinical decisions should be always taken based on the evaluation of risks and benefits, as a watchful surveillance strategy can be beneficial, especially in the elderly and fragile patients.

Conclusions

The 8th Edition of the AJCC/UICC TNM staging system performs better than the previous one when applied to tongue SCC, showing overall improved prognostication for each stage. However, while the difference between early- and advanced-staged diseases is solid, the distinction between the T1 and T2 categories remains unsatisfactory. One reason might be that in early-stage tongue SCC more ancillary clinical and histopathologic factors, in addition to size and DOI of the primary tumor, have an influence on prognosis, while the impact of DOI on DSS is strong enough to separate early from advanced tongue SCC. Prognostication based on pathologic staging (using predictive models like nomograms) is definitively much more informative, even though not applicable in the preoperative setting and more complex than every TNM staging system. However, the probability of nodal metastasis in a clinically negative neck is definitely influenced by DOI, even though there is uncertainty regarding the magnitude of the phenomenon itself. Conversely, the employment of TNM staging for choosing treatment, or whether to proceed to neck dissection, should be discouraged, as staging per se does not adequately separate T1 and T2N0 patients according to the risk of occult nodal metastasis. Further high-quality prospective randomized trials are needed to obtain information useful in treatment planning of these clinical scenarios.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ganly I, Patel S, Shah J. Early stage squamous cell cancer of the oral tongue - Clinicopathologic features affecting outcome. Cancer 2012;118:101-11.
2. Shinn JR, Wood CB, Colazo JM, et al. Cumulative incidence of neck recurrence with increasing depth of invasion. Oral Oncol 2018;87:36-42.
3. Abu-Ghanem S, Yehuda M, Carmel NN, et al. Elective neck dissection vs observation in early-stage squamous cell carcinoma of the oral tongue with no clinically apparent lymph node metastasis in the neck. A systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2016;142:857-65.
4. Amit M, Tam S, Takahashi H, et al. Prognostic performance of the American Joint Committee on Cancer 8th edition of the TNM staging system in patients with early oral tongue cancer. Head Neck 2019;41:1270-6.
5. Piazza C, Montalto N, Paderno A, et al. Is it time to incorporate "depth of infiltration" in the T staging of oral tongue and floor of mouth cancer? Curr Opin Otolaryngol Head Neck Surg 2014;22:81-9.
6. Ebrahimi A, Gil Z, Amit M, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: An international multicenter retrospective study. JAMA Otolaryngol Head Neck Surg 2014;140:1138-48.
7. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-37.
8. Chang B, He W, Ouyang H, et al. A prognostic nomogram incorporating depth of tumor invasion to predict long-term overall survival for tongue squamous cell carcinoma with R0 resection. J Cancer 2018;9:2107-15.
9. Huang SH, Hwang D, Lockwood G, et al. Predictive value of tumor thickness for cervical lymph-node involvement in

squamous cell carcinoma of the oral cavity: A meta-analysis of reported studies. Cancer 2009;115:1489-97.
10. Kano S, Sakashita T, Tsushima N, et al. Validation of the 8th edition of the AJCC/UICC TNM staging system for tongue squamous cell carcinoma. Int J Clin Oncol 2018;23:844-50.
11. Almangush A, Mäkitie AA, Mäkinen LK, et al. Small oral tongue cancers (≤ 4 cm in diameter) with clinically negative neck: From the 7th to the 8th edition of the American Joint Committee on Cancer. Virchows Archiv 2018;473:481-7.
12. Cramer JD, Reddy A, Ferris RL, et al. Comparison of the seventh and eighth edition American Joint Committee on Cancer oral cavity staging systems. Laryngoscope 2018;128:2351-60.
13. D'Cruz AK, Vaish R, Kapre N, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015;373:521-9.
14. Matos LL, Dedivitis RA, Kulcsar MAV, et al. External validation of the AJCC Cancer Staging Manual, 8th edition, in an independent cohort of oral cancer patients. Oral Oncol 2017;71:47-53.
15. Matos LL, Manfro G, Dos Santos RV, et al. Tumor thickness as a predictive factor of lymph node metastasis and disease recurrence in T1N0 and T2N0 squamous cell carcinoma of the oral tongue. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118:209-17.
16. Faisal M, Abu Bakar M, Sarwar A, et al. Depth of invasion (DOI) as a predictor of cervical nodal metastasis and local recurrence in early stage squamous cell carcinoma of oral tongue (ESSCOT). PLoS One 2018;13:e0202632.
17. Hanai N, Asakage T, Kiyota N, et al. Controversies in relation to neck management in N0 early oral tongue cancer. Jpn J Clin Oncol 2019;49:297-305.
18. Piazza C, Grammatica A, Montalto N, et al. Compartmental surgery for oral tongue and floor of the mouth cancer: Oncologic outcomes. Head Neck 2019;41:110-5.
19. Balasubramanian D, Ebrahimi A, Gupta R, et al. Tumour thickness as a predictor of nodal metastases in oral cancer: Comparison between tongue and floor of mouth subsites. Oral Oncol 2014;50:1165-8.
20. Arora A, Husain N, Bansal A, et al. Development of a new outcome prediction model in early-stage squamous cell carcinoma of the oral cavity based on histopathologic parameters with multivariate analysis: The Aditi-Nuzhat Lymph-node Prediction Score (ANLPS) System. Am J Surg Pathol 2017;41:950-60.
21. De Silva RK, Siriwardena BSMS, Samaranayaka A, et al. A model to predict nodal metastasis in patients with oral squamous cell carcinoma. PLoS One 2018;13:e0201755.
22. Calabrese L, Bruschini R, Giugliano G, et al. Compartmental tongue surgery: Long term oncologic results in the treatment of tongue cancer. Oral Oncol 2011;47:174-9.
23. Preda L, Chiesa F, Calabrese L, et al. Relationship between histologic thickness of tongue carcinoma and thickness estimated from preoperative MRI. Eur Radiol 2006;16:2242-8.
24. Alsaffar HA, Goldstein DP, King EV, et al. Correlation between clinical and MRI assessment of depth of invasion in oral tongue squamous cell carcinoma. J Otolaryngol Head Neck Surg 2016;45:61-5.
25. Kamali A, Gahm C, Palmgren B, et al. Regional recurrence in early stage I–II oral tongue cancer: A single institutional study and review of the literature. Acta Otolaryngol 2017;137:755-61.

Cite this article as: Piazza C, Bresciani L, Giannini L. Depth of invasion for prognostic stratification in oral cavity cancer: do we need further validation? Ann Transl Med 2019;7(Suppl 3):S84. doi: 10.21037/atm.2019.04.19

