Review

Staging and grading of oral squamous cell carcinoma: An update

Alhadi Almangush[a,b,c,d], Antti A. Mäkitie[e,b,f], Asterios Triantafyllou[g], Remco de Bree[h],
Primož Strojan[i], Alessandra Rinaldo[j], Juan C. Hernandez-Prera[k], Carlos Suárez[l,m],
Luiz P. Kowalski[n,o], Alfio Ferlito[p], Ilmo Leivo[c,*]

[a] Department of Pathology, University of Helsinki, Helsinki, Finland
[b] Research Program in Systems Oncology, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[c] Institute of Biomedicine, Pathology, University of Turku, Turku, Finland
[d] Faculty of Dentistry, University of Misurata, Misurata, Libya
[e] Department of Otorhinolaryngology, Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Finland
[f] Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet and Karolinska Hospital, Stockholm, Sweden
[g] Department of Pathology, Liverpool Clinical Laboratories and School of Dentistry, University of Liverpool, Liverpool, UK
[h] Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands
[i] Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
[j] University of Udine School of Medicine, Udine, Italy
[k] Department of Pathology, Moffitt Cancer Center, Tampa, FL, USA
[l] Instituto de Investigacion Sanitaria del Principado de Asturias and (CIBERONC), ISCIII, Oviedo, Spain
[m] Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain
[n] Head and Neck Surgery and Otorhinolaryngology Department, A C Camargo Cancer Center, Sao Paulo, Brazil
[o] Head and Neck Surgery, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil
[p] Coordinator of the International Head and Neck Scientific Group, Padua, Italy

ABSTRACT

Oral squamous cell carcinoma (OSCC) is a common malignancy of the head and neck region. OSCC has a relatively low survival rate and the incidence of the disease is increasing in some geographic areas. Staging and grading of OSCC are established prerequisites for management, as they influence risk stratification and are the first step toward personalized treatment. The current AJCC/UICC TNM staging (8th edition, 2017) of OSCC has included significant modifications through the incorporation of depth of invasion in the T stage and extra-capsular spread/extranodal extension in the N stage. Further modifications for AJCC 8 have been suggested. On the other hand, the World Health Organization (WHO) classification (4th edition, 2017) still endorses a simple, differentiation-based histopathologic grading system of OSCC (despite its low prognostic value) and ignores factors such as tumor growth pattern and dissociation, stromal reactions (desmoplasia, local immune response), and tumor-stroma ratio. The various controversies and possible developments of the current staging and grading criteria of OSCC are briefly discussed in this update together with possible applications of artificial intelligence in the context of screening and risk stratification.

Introduction

Oral cancer is a significant health problem and regarded as the main cause of death from oral diseases in many countries. Recent global estimates have revealed 354,864 new cases and 177,384 deaths in 2018 [1]. Traditional risk factors of oral cancer include tobacco and alcohol abuse. Conventional oral squamous cell carcinoma (OSCC) is one of the most common cancers of the head and neck; the incidence of OSCC has increased in many countries, especially in younger age groups [2,3]. Whether or not young and old patients with OSCC have a different prognosis remains a controversial issue [4,5]. However, no significant differences were observed in the tumor stage or grade in recent studies that compared the characteristics of OSCC in young and old patients [4,6,7]. The oral tongue is the most common subsite and is associated

with higher mortality than OSCC in other subsites (e.g. floor of mouth, gingivae, and retromolar trigone) according to a recent analysis of Surveillance, Epidemiology, and End Results (SEER) database [8].

Management of OSCC is based on surgical resection with or without adjuvant treatment (e.g. radiotherapy or chemoradiotherapy). The indication for adjuvant treatment is influenced by features detailed in the standardized histopathology report of the resection, which include differentiation, growth pattern, depth of invasion, status of margins, vascular/neural invasion, bone involvement, nodal status (number of lymph nodes involved, size of largest metastasis, extracapsular spread (ECS)/extranodal extension (ENE)), and pTNM staging. Standardized histopathological reporting has been pioneered by the minimum data sets issued by the Royal College of Pathologists (United Kingdom) in 2005 [9]; and an international version has been published recently [10]. Because recent studies are centered on the role of immunotherapy with the use of immune checkpoint inhibitors, PDL-1 immunohistochemical staining of tumor biopsies becomes important in guiding patient selection for PD-1/PD-L1 inhibitor therapy [11].

TNM staging of OSCC

The TNM system of cancer staging reflects the extent of tumor growth in the whole body and is based on assessment of the size of the primary tumor (T), involvement of locoregional lymph nodes (N), and distant metastases (M). This classification is important for treatment planning, estimating risk of recurrence, and assessment of overall survival. However, this classification only considers the anatomic extension of the disease and not the other prognostic factors, such as co-morbidity or treatment [12].

The International Union Against Cancer (UICC) published the first edition of the TNM staging in 1968, whereas the American Joint Committee on Cancer (AJCC) published its first staging manual in 1977. Later editions were synchronized and effected updating. In 2017, the 8th edition of the UICC and AJCC (AJCC 8) staging manual was released [13,14]. It introduced two major changes for OSCC, namely incorporation of the tumor depth of invasion (DOI) in the T stage and incorporation of extracapsular spread (ECS) in the N stage. Several studies have examined the performance of AJCC 8 in independent cohorts of OSCC [15–18] and the need for further development is acknowledged.

DOI, also known as reconstructed tumor thickness, is different from clinical tumor thickness, particularly in exophytic and ulcerated lesions. DOI was originally envisaged as distance from a theoretical reconstructed normal mucosal surface line to the deepest extent of growth [19,20]. Recently, Müller et al. (2019) favored the level of the epithelial basement membrane zone instead of the normal mucosal surface [10], although the value of this is debatable. The AJCC 8 manual and UICC Atlas suggest that DOI can be reliably defined clinically, but DOI seems difficult to estimate by palpation only. An alternative to overcome these difficulties would be the use of preoperative imaging (e.g. magnetic resonance imaging (MRI) or ultrasound (US)) to assess the depth of invasion and tumor thickness. In a retrospective study, Dirven et al. found that the T category and the TNM stage prognostic performance of the AJCC 8 staging of oral cancer is similar regardless of whether DOI or tumor thickness was used as the T-category modifier [18].

A recent systematic review and a meta-analysis, including individual participant data of 240 patients, showed a high correlation of tumor thickness within this subgroup as measured by intraoral US and histopathology (r = 0.82, P < 0.001), with minor overestimation of 0.5 mm on US [21]. It was concluded that intraoral US is very accurate in determining tumor thickness in early oral tongue cancer [21]. This was confirmed in a more recent systematic review including 471 patients, in which a pooled correlation coefficient of 0.95 was observed [22]. Regarding preoperative imaging (CT or MRI), Weimar et al. [17] successfully used the measurements of tumor thickness as a modifier for T stage in AJCC 8; these results were corroborated by Dirven et al. [18].

Lwin et al. [23] compared radiological tumor thickness (RTT) with histological tumor thickness (HTT) for OSCC and reported that although RTT shows a somewhat predictable relationship with HTT, this varies between sub-sites with better results for tongue using axial MRI. These authors acknowledged the need for evaluating the role of biomarkers and US. In this context, Brouwer de Koning et al. [24] recently reported that tumor thickness for preoperative staging of OSCC can be more accurately measured with US than with MRI.

It has been emphasized that the modifications included in AJCC 8 have caused upstaging of many cases according to recently published studies [15,18,25]. In a recent analysis of a large cohort, Lee et al. [26] reported that upstaging has occurred in 12.4% of cases for pT stage, in 13.3% for the pN stage, and in 24.8% for the overall stage. Similarly, when DOI was incorporated for cT stage of early oral tongue cancer, upstaging was noted [15]. This would influence treatment planning, as OSCC cases that were early stage according to AJCC 7 are now upstaged as advanced lesions according to AJCC 8. In a series of 199 patients with AJCC 7 cT1-2N0 oral cancer subjected to sentinel node biopsy, a (pretreatment) clinical upstage (to T3) of 8% was found [27].

The implementation of AJCC 8 has been influenced by the multiple corrections made to the original printed edition and by the fact that the histopathological assessment of DOI in some cases is subject to uncertainty and inter-observer variability. For instance, according to the first version of AJCC 8, tumors > 4 cm or any tumor with DOI > 10 mm were considered T3. This statement contrasts with the latest version of the erratum, which defines T3 as tumors between > 2 cm and ≤ 4 cm with DOI > 10 mm or tumors > 4 cm with DOI ≤ 10 mm [28]. Therefore, it was not made clear until the third version that it is DOI *in conjunction* with tumor size that determines the T category. It is imperative to be aware of these corrections as these changes may affect the interpretation and conclusions of some clinical studies related to the performance of AJCC 8.

A suggestion has been made to lower the threshold of T stage. As an example, Almangush et al. suggested lowering the cutoff point (from 5 mm to 2 mm for T1 and from 10 mm to 4 mm for T2) to better categorize the risk groups of early oral tongue cancer cases [15]. Further, recent studies [16,29,30] have proposed considering the number of positive metastatic nodes to modify the N stage. Determining the ideal cutoff point of DOI and the number of positive nodes used as modifiers of T and N stages with adequate risk discrimination still requires further validation studies to examine these recently proposed modifications.

In an attempt to improve recognition of DOI and reconstructed thickness, Woolgar and Triantafyllou [19,20,31] used linear segments and curved lines on histopathological photomicrographs, a practice later endorsed by Lydiatt et al. [32] and Müller et al. [10]. It is observed that Lydiatt et al. [32] drew a horizontal line to the closest adjacent intact mucosa and dropped a "plumb" line perpendicular to it, but it appears that a study of the figures suffices. Obtaining slices of tissue perpendicular to the mucosal surface during macroscopical cutting is of paramount significance in establishing DOI. Such slices are often easier to obtain in segmental glossectomies, including the curvature of the lateral border of the tongue. Purported cases where DOI can be underestimated or overestimated include absence of adjacent intact mucosa, absence or only minimal residual tumor after biopsy, extratumoral perineural or vascular invasion, and a positive deep margin [33]. However, the absence of adjacent mucosa seems unlikely in resections. In cases of a positive deep margin, the pathologist should measure and report what has been available (resections are likely > 5.0 mm thick); hence, the tumor would be of an adversely prognostic thickness and precise measurement would not influence clinical decisions. More challenging is the case of perineurial invasion. If "satellites" are present ahead of the main front, the sensible action would possibly be to measure the DOI of the mass and also to include in the pathology report the distance of the perineurial invasion from the main tumor front (Fig. 1) [34]. If the tumor shows a dispersed growth pattern and
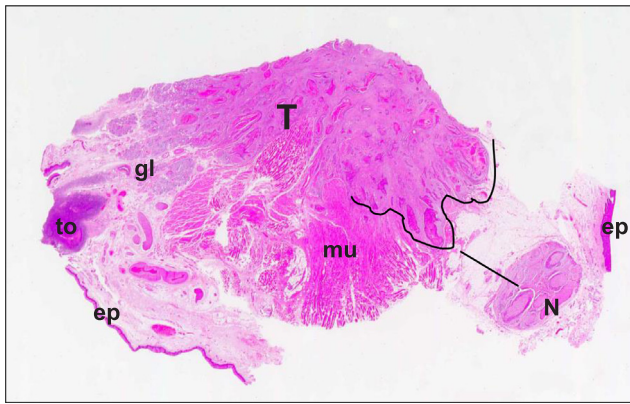
Fig. 1. SCC invades nerve fascicles ahead of its main front. Key: e, surface, epithelial; gl, glands; mu, muscle; N, nerves; T, tumor; to, tonsil. The curved line indicates the main front. The distance between invaded nerves and main front (straight line) should be measured (H & E). Modified from Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. Oral Oncol. 41:1034-43, 2005.

perineurial invasion [10], it would seem sensible to regard the distance between the mucosal surface and the nerve involved as DOI.

Histopathological grading of OSCC

Histopathological grading was first introduced by Broders for squamous cell carcinoma of the lip and was based on the differences in differentiation between tumors [35]. Later, more complex grading systems were suggested by Jakobsson et al. [36], Anneroth et al. [37], and Bryne et al. [38]. These multifactorial systems consider features of the tumor per se (e.g. differentiation), the tumor host interface (invasion patterns), and host reactions (inflammatory response). They influenced formulating the concept of favorable/cohesive and dys- and non-cohesive patterns of invasion in the minimum data sets of the Royal College of Pathologists (United Kingdom) [19,20], to which a dispersed pattern was recently added [10]. These systems should be updated by introducing the feature of myofibroblasts or cancer-associated fibroblasts, which often assessed with the use of immunohistochemistry for alpha smooth muscle actin [39,40].

Curiously, the World Health Organization (WHO) did not endorse such multifactorial systems and paid little attention to minimum data sets or standardized histopathological reporting. The current edition of the Classification of Head and Neck Tumors supports a simple grading system [41] based on the Broders criteria and merely recognizes well-, moderately-, and poorly-differentiated variants of conventional OSCCs, although they acknowledge that "*Grading alone does not correlate well with prognosis*" [41]. Many studies indicate minor or no prognostic

value of the WHO grading system [42,43]. The data sets of the Royal College of Pathologists (United Kingdom) [9] and sets from Müller et al. [10] would be the sensible alternative.

The dys-/non-cohesive and dispersed invasive patterns defined in the aforementioned sets also likely include tumor budding. Elseragy et al. [44] added tumor budding to the WHO differentiation criteria and showed a better prognostic value than the conventional WHO system in a series of early oral tongue SCC [44]. Further validation in large cohorts of OSCC would be desirable.

A different approach was based on tumor budding and the size of cell nests but was independent of the degree of cell differentiation [45]. Arora et al. assessed the prognostic significance of multiple features, including T stage, tumor grade, tumor budding, tumor thickness, depth of invasion, shape of tumor nests, lymphoid response at the tumor-host interface, and the pattern of invasion, eosinophilic reaction, foreign-body giant cell reaction, lymphovascular invasion, and perineural invasion [46]. They reported that on univariate and multivariate analyses, seven of these were independent variables for predicting lymph node metastasis. In descending order, these were depth of invasion ($P = 0.003$), pattern of invasion ($P = 0.007$), perineural invasion ($P = 0.014$), grade ($P = 0.028$), lymphovascular invasion ($P = 0.038$), lymphoid response ($P = 0.037$), and tumor budding ($P = 0.039$). It was observed that the pattern of invasion scores higher than tumor budding, but the relationship between these features should be clarified.

Whatever that relationship may be, "tumor budding" has become fashionable as a potential prognostic feature in OSCC [47–49]. Such a trend reflects an appealing terminology and the endorsement of the concept of tumor budding also in other cancers [50,51].

Assessing tumor and stromal features to improve risk stratification

Traditional approaches in histopathological grading are centered on the tumor per se (e.g. differentiation, mitotic activity, DOI) rather than stroma and host responses. The multifactorial systems suggested by Jakobsson et al.[36], Anneroth et al. [37], and Bryne et al. [38,52] attempted to make improvements. Currently, the role of the microenvironment in tumor progression spearheads cancer research [53]. The significance of myofibroblasts and cancer-associated fibroblasts was already mentioned above.

Stromal myofibroblasts are innate components of the so-called desmoplastic reaction (desmoplasia) in OSCC [19,20]. Except for myofibroblasts, stromal glycosaminoglycans (GAGs) are also involved in that reaction. Although usually assessed by mucosubstance histochemistry and immunohistocemistry, GAGs can also be studied by immunohistochemistry and visualized to some degree also in routine HE sections (Fig. 2) [19,20]. However, little attention has been paid to the role of GAGs as possible prognosticators in OSCC [54].

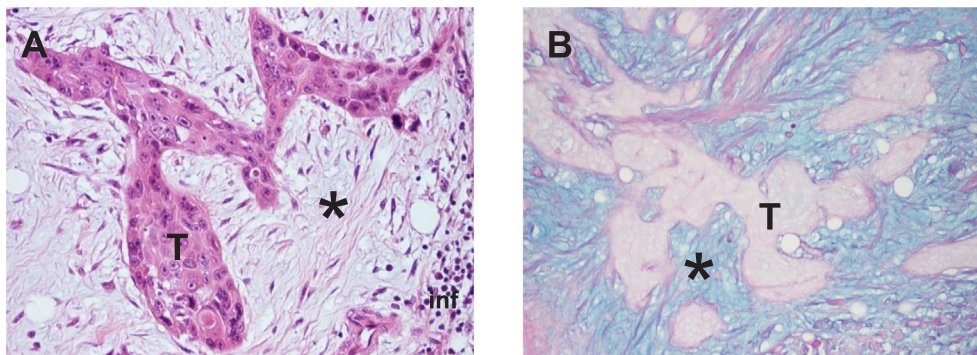The so-called immunoscore has been used to characterize various

Fig. 2. (A) GAGs (asterisk) in the stroma of SCC (T) (H & E). They are easily distinguished from tumor or the host inflammatory reaction (inf). Modified from (Woolgar and Triantafyllou 2011). (B) Histochemistry for mucosubstances demonstrates the Alcianophilia of GAGs (asterisk); the tumor cell aggregates (T) are unstained.
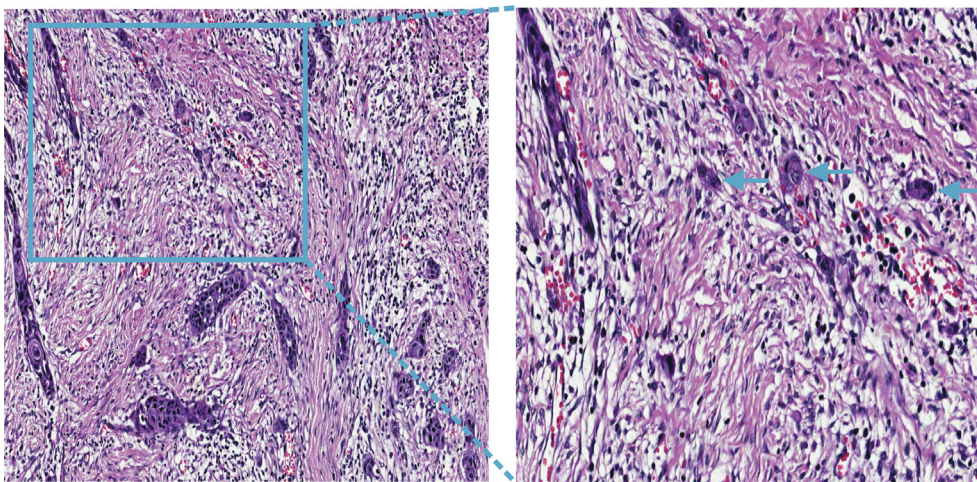
Fig. 3. SCC with stroma-rich tumor. The stroma includes areas of a fibrous appearance intermingled with lymphocytic infiltrates. The infiltrates are associated with loose matrix and they are often located around carcinomatous components of non-cohesive, dispersive, or budding (arrows) growth patterns.
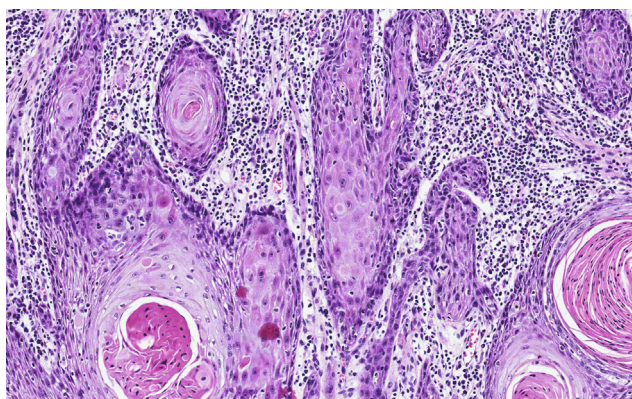

Fig. 4. In comparison with Fig. 3, this SCC shows stroma-poor tumor. The stroma shows widespread lymphocytic infiltration in a largely loose matrix; fibrous areas are inconspicuous.

cancers [55,56]. Zhou et al. have recently developed an immune-based prognostic score that includes seven features (such as CD 3 and CD 8) that has significant clinical relevance for survival [57]. Such assessment may be used to identify cases that could benefit from immunotherapy [58]. Endorsing a different approach, Heikkinen et al. suggested that an overall assessment of stromal tumor-infiltrating lymphocytes (TILs) allows risk stratification in early stage oral tongue SCC [59]. This assessment can be easily incorporated in routine histopathology reporting based on HE-stained sections (Figs. 3 and 4). At the same time, recent studies have used immunohistochemistry and reported the significance of different subtypes of lymphocytes and other immune cell components (e.g. dendritic cells) in the prediction of overall survival and disease-free survival [60–64]. Based on the accumulated evidence, recent meta-analyses have identified specific immune biomarkers (e.g. CD57+ and CD163+) for prognostication of OSCC [65,66].

Finally, the tumor-stroma ratio (TSR) was also examined in early-stage oral tongue SCC and may be of useful prognostic significance [67]. Stroma-rich tumors (Fig. 3) are associated with increased recurrence and mortality compared with stroma-poor tumors (Fig. 4) [67]. Again, the assessment of TSR is simple and easily performed on HE-stained slides. A recent meta-analysis indicated the importance of TSR in many cancers [68].

We would like to re-emphasize that the assessment of stromal myofibroblasts, GAGs, TILs, and TSR is cost-effective and can be included in the histopathology report with minimal effort.

Artificial intelligence to improve staging, grading and treatment planning

Treatment planning is a multifactorial process and many factors and parameters with a variable impact should be considered in the decision-making process for management of OSCC. Recently, artificial intelligence and machine-learning tools have been used to analyze factors that could influence the probability of survival, including TNM stage and WHO grade [69]. Regarding OSCC, Bur et al. [70] used machine learning and developed a predictive algorithm that consists of many prognostic factors (including tumor grade) to predict lymph node metastasis in early-stage tumors. Similarly, Kim et al. [71] used many clinicopathologic characteristics (including stage and grade) for deep learning prognostication that may improve prediction of survival after treatment of OSCC. Furthermore, Alabi et al. [72] used machine learning to construct an artificial neural network and also developed a web-based tool to allow for the assessment of several parameters (including stage and grade) to estimate the risk of recurrence in early oral tongue cancer [72].

Insights and perspectives

Possible improvements for TNM staging and WHO grading [15,16,29,30,44] may assist risk stratification of OSCC. The role of the anatomical sub-site should be considered and distinction between early- and advanced-stage OSCCs is important. Prospective studies are necessary. A recent review observes that due to the heterogeneity of methodological approaches, it is impossible to perform a satisfactory meta-analysis for the identification of biomarkers specific for OSCC [73]. Efforts to overcome these difficulties should be undertaken as the identification of biomarkers that allow the screening and identification of individuals who are at risk of developing a primary OSCC or predict relapse after treatment would be a clear way forward. Artificial intelligence has recently shown potential as a promising tool to analyze patient survival based on many factors, including staging and grading. Further research on OSCC should consider application of artificial intelligence in large multi-institutional studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Ng JH, Iyer NG, Tan MH, Edgren G. Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. Head Neck 2017;39:297–304.

[3] Du M, Nair R, Jamieson L, Liu Z, Bi P. Incidence trends of lip, oral cavity, and pharyngeal cancers: global burden of disease 1990–2017. J Dent Res 2020;99:143–51.

[4] Chen S, Lin Z, Chen J, Yang A, Zhang Q, Xie C, et al. Older age is a risk factor associated with poor prognosis of patients with squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 2020.

[5] Oliver JR, Wu SP, Chang CM, Roden DF, Wang B, Hu KS, et al. Survival of oral tongue squamous cell carcinoma in young adults. Head Neck 2019;41:2960–8.

[6] Xu Q, Wang C, Li B, Kim K, Li J, Mao M, et al. The impact of age on oral squamous cell carcinoma: A longitudinal cohort study of 2,782 patients. Oral Dis 2019;25:730–41.

[7] Bello IO, Almangush A, Heikkinen I, Haglund C, Coletta RD, Kowalski LP, et al. Histological characteristics of early-stage oral tongue cancer in young versus older patients: A multicenter matched-pair analysis. Oral Dis 2020.

[8] Farhood Z, Simpson M, Ward GM, Walker RJ, Osazuwa-Peters N. Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis. Laryngoscope 2019;129:1400–6.

[9] Helliwell TR, Woolgar JA. Minimum dataset for histopathology reports on head and neck carcinomas and salivary neoplasms. London: The Royal College of Pathologists; 2005.

[10] Muller S, Boy SC, Day TA, Magliocca KR, Richardson MS, Sloan P, et al. Data set for the reporting of oral cavity carcinomas: explanations and recommendations of the guidelines from the international collaboration of cancer reporting. Arch Pathol Lab Med 2019;143:439–46.

[11] Luo JJ, Young CD, Zhou HM, Wang XJ. Mouse models for studying oral cancer: impact in the era of cancer immunotherapy. J Dent Res 2018;97:683–90.

[12] Patel SG, Lydiatt WM. Staging of head and neck cancers: is it time to change the balance between the ideal and the practical? J Surg Oncol 2008;97:653–7.

[13] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th edition New York: Springer; 2017.

[14] Brieleyt JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors, 8th Edition. Willey Blackwell; 2017, 272p ISBN 978-1-119-26357-9.

[15] Almangush A, Makitie AA, Makinen LK, Kauppila JH, Pukkila M, Hagstrom J, 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 Arch 2018; 473: 481–7.

[16] Ho AS, Kim S, Tighiouart M, Gudino C, Mita A, Scher KS, et al. Metastatic lymph node burden and survival in oral cavity cancer. J Clin Oncol 2017;35:3601–9.

[17] Weimar EAM, Huang SH, Lu L, O'Sullivan B, Perez-Ordonez B, Weinreb I, Hope A, Tong L, Goldstein D, Irish J, de Almeida JR, Bratman S, Xu W, Yu E. Radiologic-pathologic correlation of tumor thickness and its prognostic importance in squamous cell carcinoma of the oral cavity: implications for the Eighth Edition tumor, node, metastasis classification. AJNR Am J Neuroradiol 2018;39(10):1896–902. https://doi.org/10.3174/ajnr.A5782.

[18] Dirven R, Ebrahimi A, Moeckelmann N, Palme CE, Gupta R, Clark J. Tumor thickness versus depth of invasion - Analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. Oral Oncol 2017; 74: 30–3.

[19] Woolgar JA, Triantafyllou A. Pitfalls and procedures in the histopathological diagnosis of oral and oropharyngeal squamous cell carcinoma and a review of the role of pathology in prognosis. Oral Oncol 2009;45:361–85.

[20] Woolgar JA, Triantafyllou A. Squamous cell carcinoma and precursor lesions: clinical pathology. Periodontol 2000;2011(57):51–72.

[21] Klein Nulent TJW, Noorlag R, Van Cann EM, Pameijer FA, Willems SM, Yesuratnam A, et al. Intraoral ultrasonography to measure tumor thickness of oral cancer: A systematic review and meta-analysis. Oral Oncol 2018;77:29–36.

[22] Tarabichi O, Bulbul MG, Kanumuri VV, Faquin WC, Juliano AF, Cunnane ME, et al. Utility of intraoral ultrasound in managing oral tongue squamous cell carcinoma: Systematic review. Laryngoscope 2019;129:662–70.

[23] Lwin CT, Hanlon R, Lowe D, Brown JS, Woolgar JA, Triantafyllou A, et al. Accuracy of MRI in prediction of tumour thickness and nodal stage in oral squamous cell carcinoma. Oral Oncol 2012;48:149–54.

[24] Brouwer de Koning SG, Karakullukcu MB, Lange CAH, Ruers TJM. The oral cavity tumor thickness: Measurement accuracy and consequences for tumor staging. Eur J Surg Oncol 2019.

[25] Matos LL, Dedivitis RA, Kulcsar MAV, de Mello ES, Alves VAF, Cernea CR. External validation of the AJCC Cancer Staging Manual, 8th edition, in an independent cohort of oral cancer patients. Oral Oncol 2017; 71: 47–53.

[26] Lee NCJ, Eskander A, Park HS, Mehra S, Burtness BA, Husain Z. Pathologic staging changes in oral cavity squamous cell carcinoma: Stage migration and implications for adjuvant treatment. Cancer 2019;125:2975–83.

[27] den Toom IJ, Janssen LM, van Es RJJ, Karagozoglu KH, de Keizer B, van Weert S, et al. Depth of invasion in patients with early stage oral cancer staged by sentinel node biopsy. Head Neck 2019;41:2100–6.

[28] UICC 8th Edition Errata – 28th of January 2019.

[29] Lee H, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY. Number of positive lymph nodes better predicts survival for oral cavity cancer. J Surg Oncol 2019.

[30] Rajappa SK, Maheshwari U, Jaipuria J, Singh AK, Goyal S, Batra U, et al. Number of positive nodes - Current relevance in determining prognosis of oral cavity cancer after the recent AJCC staging update. Oral Oncol 2019;90:1–5.

[31] Woolgar JA, Triantafyllou A, Glossectomy, In Volavsek m, (ed). Head and Neck Pathology, Encyclopedia of Pathology (Series ed. JHJM van Krieken). Springer International Publishing, Switzerland; 2016. p. 131–6.

[32] Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, 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.

[33] Berdugo J, Thompson LDR, Purgina B, Sturgis CD, Tuluc M, Seethala R, et al. Measuring depth of invasion in early squamous cell carcinoma of the oral tongue: positive deep margin, extratumoral perineural invasion, and other challenges. Head Neck Pathol 2019;13:154–61.

[34] Woolgar JA, Triantafyllou A. A histopathological appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. Oral Oncol 2005;41:1034–43.

[35] Broders AC. Squamous cell cancer of the lip: a study of five hundred and thirty-seven cases. JAMA 1920;74:656–64.

[36] Jakobsson PA, Eneroth CM, Killander D, Moberger G, Martensson B. Histologic classification and grading of malignancy in carcinoma of the larynx. Acta Radiol Ther Phys Biol 1973;12:1–8.

[37] Anneroth G, Batsakis J, Luna M. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. Scand J Dent Res 1987;95:229–49.

[38] Bryne M, Koppang HS, Lilleng R, Kjaerheim A. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 1992;166:375–81.

[39] Marsh D, Suchak K, Moutasim KA, Vallath S, Hopper C, Jerjes W, et al. Stromal features are predictive of disease mortality in oral cancer patients. J Pathol 2011;223:470–81.

[40] Thode C, Jorgensen TG, Dabelsteen E, Mackenzie I, Dabelsteen S. Significance of myofibroblasts in oral squamous cell carcinoma. J Oral Pathol Med 2011;40:201–7.

[41] El-Naggar AK, Chan J, Grandis J, Takata T, Slootweg P. WHO classification of head and neck tumours. 4th ed.; 2017. p. 105–111.

[42] Almangush A, Bello IO, Keski-Santti H, Makinen LK, Kauppila JH, Pukkila M, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. Head Neck 2014;36:811–8.

[43] Dik EA, Ipenburg NA, Kessler PA, van Es RJJ, Willems SM. The value of histological grading of biopsy and resection specimens in early stage oral squamous cell carcinomas. J Craniomaxillofac Surg 2018;46:1001–6.

[44] Elseragy A, Salo T, Coletta RD, Kowalski LP, Haglund C, Nieminen P, et al. A proposal to revise the histopathologic grading system of early oral tongue cancer incorporating tumor budding. Am J Surg Pathol 2019;43:703–9.

[45] Boxberg M, Jesinghaus M, Dorfner C, Mogler C, Drecoll E, Warth A, et al. Tumour budding activity and cell nest size determine patient outcome in oral squamous cell carcinoma: proposal for an adjusted grading system. Histopathology 2017;70:1125–37.

[46] Arora A, Husain N, Bansal A, Neyaz A, Jaiswal R, Jain K, 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.

[47] Almangush A, Pirinen M, Heikkinen I, Makitie AA, Salo T, Leivo I. Tumour budding in oral squamous cell carcinoma: a meta-analysis. Br J Cancer 2018;118:577–86.

[48] Yu P, Wang W, Zhuang Z, Xie N, Xu J, Wang C, et al. A novel prognostic model for tongue squamous cell carcinoma based on the characteristics of tumour and its microenvironment: iBD score. Histopathology 2019;74:766–79.

[49] Sakata J, Yamana K, Yoshida R, Matsuoka Y, Kawahara K, Arita H, et al. Tumor budding as a novel predictor of occult metastasis in cT2N0 tongue squamous cell carcinoma. Hum Pathol 2018;76:1–8.

[50] Jesinghaus M, Bruhl F, Steiger K, Klare P, Reiser M, Scheiter A, et al. Cellular dissociation grading based on the parameters tumor budding and cell nest size in pretherapeutic biopsy specimens allows for prognostic patient stratification in esophageal squamous cell carcinoma independent from clinical staging. Am J Surg Pathol 2019;43:618–27.

[51] Boxberg M, Kuhn PH, Reiser M, Erb A, Steiger K, Pickhard A, et al. Tumor budding and cell nest size are highly prognostic in laryngeal and hypopharyngeal squamous cell carcinoma: further evidence for a unified histopathologic grading system for squamous cell carcinomas of the upper aerodigestive tract. Am J Surg Pathol 2019;43:303–13.

[52] Bryne M, Koppang HS, Lilleng R, Stene T, Bang G, Dabelsteen E. New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. J Oral Pathol Med 1989;18:432–7.

[53] Giraldo NA, Sanchez-Salas R, Peske JD, Vano Y, Becht E, Petitprez F, et al. The clinical role of the TME in solid cancer. Br J Cancer 2019;120:45–53.

[54] Kosunen A, Ropponen K, Kellokoski J, Pukkila M, Virtaniemi J, Valtonen H, et al. Reduced expression of hyaluronan is a strong indicator of poor survival in oral squamous cell carcinoma. Oral Oncol 2004;40:257–63.

[55] Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, et al. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J Pathol 2014;232:199–209.

[56] Yomoda T, Sudo T, Kawahara A, Shigaki T, Shimomura S, Tajiri K, et al. The immunoscore is a superior prognostic tool in stages II and III colorectal cancer and is significantly correlated with programmed death-ligand 1 (PD-L1) expression on tumor-infiltrating mononuclear cells. Ann Surg Oncol 2019;26:415–24.

[57] Zhou C, Diao P, Wu Y, Wei Z, Jiang L, Zhang W, et al. Development and validation of a seven-immune-feature-based prognostic score for oral squamous cell carcinoma after curative resection. Int J Cancer 2019.

[58] Boxberg M, Leising L, Steiger K, Jesinghaus M, Alkhamas A, Mielke M, et al. Composition and clinical impact of the immunologic tumor microenvironment in oral squamous cell carcinoma. J Immunol 2019;202:278–91.

[59] Heikkinen I, Bello IO, Wahab A, Hagstrom J, Haglund C, Coletta RD, et al. Assessment of tumor-infiltrating lymphocytes predicts the behavior of early-stage oral tongue cancer. Am J Surg Pathol 2019.

[60] Song JJ, Zhao SJ, Fang J, Ma D, Liu XQ, Chen XB, et al. Foxp3 overexpression in tumor cells predicts poor survival in oral squamous cell carcinoma. BMC Cancer 2016;16:530.

[61] Agarwal R, Chaudhary M, Bohra S, Bajaj S. Evaluation of natural killer cell (CD57) as a prognostic marker in oral squamous cell carcinoma: An immunohistochemistry study. J Oral Maxillofac Pathol 2016;20:173–7.

[62] Jardim JF, Gondak R, Galvis MM, Pinto CAL, Kowalski LP. A decreased peritumoral CD1a+ cell number predicts a worse prognosis in oral squamous cell carcinoma. Histopathology 2018;72:905–13.

[63] Togo M, Yokobori T, Shimizu K, Handa T, Kaira K, Sano T, et al. Diagnostic value of (18)F-FDG-PET to predict the tumour immune status defined by tumoural PD-L1 and CD8(+)tumour-infiltrating lymphocytes in oral squamous cell carcinoma. Br J Cancer 2020.

[64] Fang J, Li X, Ma D, Liu X, Chen Y, Wang Y, et al. Prognostic significance of tumor infiltrating immune cells in oral squamous cell carcinoma. BMC Cancer 2017;17:375.

[65] Huang Z, Xie N, Liu H, Wan Y, Zhu Y, Zhang M, et al. The prognostic role of tumour-infiltrating lymphocytes in oral squamous cell carcinoma: A meta-analysis. J Oral Pathol Med 2019;48:788–98.

[66] Hadler-Olsen E, Wirsing AM. Tissue-infiltrating immune cells as prognostic markers in oral squamous cell carcinoma: a systematic review and meta-analysis. Br J Cancer 2019;120:714–27.

[67] Almangush A, Heikkinen I, Bakhti N, Makinen LK, Kauppila JH, Pukkila M, et al. Prognostic impact of tumour-stroma ratio in early-stage oral tongue cancers. Histopathology 2018;72:1128–35.

[68] Wu J, Liang C, Chen M, Su W. Association between tumor-stroma ratio and prognosis in solid tumor patients: a systematic review and meta-analysis. Oncotarget 2016;7:68954–65.

[69] Richter AN, Khoshgoftaar TM. A review of statistical and machine learning methods for modeling cancer risk using structured clinical data. Artif Intell Med 2018;90:1–14.

[70] Bur AM, Holcomb A, Goodwin S, Woodroof J, Karadaghy O, Shnayder Y, et al. Machine learning to predict occult nodal metastasis in early oral squamous cell carcinoma. Oral Oncol 2019;92:20–5.

[71] Kim DW, Lee S, Kwon S, Nam W, Cha IH, Kim HJ. Deep learning-based survival prediction of oral cancer patients. Sci Rep 2019;9:6994.

[72] Alabi RO, Elmusrati M, Sawazaki-Calone I, Kowalski LP, Haglund C, Coletta RD, et al. Machine learning application for prediction of locoregional recurrences in early oral tongue cancer: a Web-based prognostic tool. Virchows Arch 2019.

[73] Cervino G, Fiorillo L, Herford AS, Romeo U, Bianchi A, Crimi S, et al. Molecular biomarkers related to oral carcinoma: clinical trial outcome evaluation in a literature review. Dis Markers 2019;2019:8040361.