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New AJCC: How does it impact oral cancers?

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Abstract

Purpose of review: The objective of this article is to critically review the rationale for the changes in the staging of the oral cavity cancers.

Recent findings: After reviewing many recent studies about oral cancer and analyzing multi-institutional data for outcomes, the staging system was updated to include new knowledge of the disease and its biological behavior.

Summary: This article reviews the changes in the staging of oral cavity cancers published in the 8th edition of the AJCC/UICC TNM cancer staging manual and discusses future directions.

Keywords

TNM staging; head and neck cancer; squamous cell carcinoma; epidermoid carcinoma; mouth neoplasms; mouth cancer; oral neoplasms; oral cancer; upper aerodigestive tract neoplasms

Introduction

Since its creation, the TNM classification has been widely used all around the world to plan treatment, to estimate prognosis, and to evaluate treatment results [1, 2]. Although its simplicity has been responsible for its widespread adoption in clinical practice, deficiencies in the staging system may lead to incorrect risk stratification, and consequent under- or overtreatment.

The 8th edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging manual (AJCC8) incorporates changes based on new published information that has led to a better understanding of the clinical and biological behavior of head and neck tumors and their outcomes [3]. A Head and Neck Task Force, composed of experts in head and neck cancer biology and staging, evaluated the chapters from the 7th edition of the AJCC cancer staging manual (AJCC7) and recommended

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Conflict of Interest Statement

None declared

changes, which were further analyzed. The proposed modifications were only incorporated once the group confirmed that evidence was available to support the changes [4].

The main modifications in AJCC8 for oral cavity cancers (OCC) were inclusion of depth of invasion (DOI) of the primary tumor in the T category, and extranodal extension (ENE) in N category. The aim of this article is to review the rationale for the changes in the staging of OCC that were published in 2017 and subsequently updated by the AJCC in June 2018.

Oral Cavity Cancer Staging

OCC is primarily treated with surgery and there is therefore robust clinical and pathological data available for prognostication and staging. For this reason, clinical (cTNM) and pathological (pTNM) staging systems can be accurately described for this disease. The definition of T categories is the same for both clinical and pathological staging. The main difference between clinical and pathological N categories is that presence of unequivocal clinical features of ENE is essential to upstage the patient to cN3b, while presence of histopathologically detected ENE is used for the appropriate pN category.

Changes to the T classification – Depth of Invasion (DOI)

The most important characteristic to stage OCC into different T categories has traditionally been the maximal surface dimension of the tumor. The prognostic impact of both thickness and DOI has been recognized for decades, and AJCC8 now acknowledges the difference in behavior of deeply invasive versus superficial tumors by including their DOI as a modifier to the T category. This change was implemented based on numerous previous studies that showed a correlation between both DOI and thickness with increased risk of nodal metastasis and worse outcomes [5-8]. The International Consortium for Outcomes Research (ICOR) in Head and Neck Cancer performed exploratory analyses using data from 11 institutions worldwide and created 5 different models that were tested for stratification into distinct prognostic categories [9]. This study showed a significant difference in outcomes between T1 tumors with DOI > 5 mm, and T2 through T4 tumors with >10 mm DOI.

The prognostic implications of this DOI based stratification is incorporated into AJCC8 but it should be noted that the cT category was modified based on an analysis of histopathologic DOI, and not on actual pre-surgical clinical DOI data. Clinicians now have the challenge of estimating DOI prior to surgery in order to correctly stage OCC. Clinical estimation of DOI may be difficult even in experienced hands and palpation should be supplemented by appropriate radiologic evaluation. Preoperative assessment of DOI by clinical exam is relatively easier in patients with tongue or floor of mouth tumors compared to other sites such as the hard palate and alveolar ridges that need to be assessed with computerized tomography (CT) and/or magnetic resonance imaging (MRI) scans for assessment of DOI and the deep relationship with adjacent bone (**see Imaging Chapter, editor provide details**). In addition to CT or MRI, ultrasound may provide measurements that can help in the preoperative assessment of DOI [10, 11]. However, these radiographic imaging studies and expertise for interpretation may not be universally available so the prognostic accuracy of the 8th edition cT category relative to the pT category remains to be proven in future studies.

As DOI is now used to upstage tumors, its definition and the method for measuring it are detailed in the staging manual [3]. While tumor thickness is measured perpendicularly from the highest point of the tumor to its deepest point, DOI accounts only for the infiltrative component. DOI does not account for any exophytic component of the tumor, so it should be measured from a “horizon” of the basement membrane of the adjacent squamous mucosa and using a perpendicular line from it to the deepest point of tumor invasion. A recent study looking specifically into differences in prognostic performance when using tumor thickness compared to DOI concluded that it is reasonable to use thickness if DOI is not available in retrospective studies [12].

By adding DOI into the T categories, oral cavity tumors that were previously classified according to AJCC7 as T1 will be upstaged to T2 if the DOI is >5 mm. Tumors that were previously staged as T2 will be upstaged to T3 if DOI is >10 mm. Tumors larger than 4 cm in greatest dimension will be staged T3 if DOI ≤10 mm which is an acknowledgment of the relatively favorable prognosis of large superficial lesions compared to larger tumors with DOI ≥10 mm which are now staged T4a. Table 1 describes the T categories according to the AJCC8 and subsequent staging form supplement.

Changes to the N classification – Extranodal Extension (ENE)

Neck disease is a well-known strong prognostic factor [13]. Number of metastatic lymph nodes, size and location of these nodes affect outcomes and were already part of AJCC7 [14, 15]. Based on previous publications reporting the prognostic impact of ENE this factor has now been added as a modifier to the N category in AJCC8 [16-20].

Clinical features of ENE include invasion of skin of the neck, infiltration of adjoining muscle/s, clinically obvious tethering or fixation to adjacent structures, or invasion of cranial nerve/s, brachial plexus, sympathetic trunk, or phrenic nerve invasion with signs or symptoms of dysfunction of the involved nerve/s. Radiographic imaging features of ENE include infiltration of the perinodal fat, matted nodes, invasion of muscles, encasement of the great vessels in the neck, and denervation atrophy or signs of dysfunction of muscles innervated by cranial nerves IX-XII. (**See imaging Chapter, editor to provide details**).

The general staging rules dictated by the AJCC/UICC state that if uncertainty exists regarding a category, subcategory, or stage group, the lower one should be assigned [3]. Therefore, the staging directions in AJCC8 explicitly state that clinical ENE (ENE_C) should be assigned only if there is *unambiguous clinical* **and** *radiographic evidence of gross ENE*. The prognostic impact of gross ENE is recognized in AJCC8 by assigning the worst cN category to these patients, while at the same time taking care to minimize the risk of over staging based on ambiguous imaging features in the absence of clinical signs of ENE.

Tables 2 and 3 describe the cN and pN categories according to AJCC8 respectively.

Future directions

Staging of cancer has several objectives including estimation of prognosis, creating guidelines for management of cancer, comparing results of treatment between groups,

stratifying patients for entry into clinical trials, and also understanding the global burden of disease. Previous versions of the staging system have relied exclusively on anatomic information for most head and neck disease sites. However, improved understanding of risk factors and the molecular and genetic aspects of cancer has understandably shifted the focus of physicians and patients alike to precision oncology and individualized prognostic prediction. Although the traditional TNM staging paradgim is simple, user-friendly, has high acceptability and high compliance, its rigid structure precludes effective inclusion of developing knowledge about tumor and host factors into a more accurate and personalized prognostic tool. If all factors that are known to significantly affect outcomes were included in the staging system, it would make it so complex and unwieldy to use that most certainly the system would lose its worldwide acceptability.

The AJCC has long recognized the growing need to incorporate non—anatomic key prognostic factors with traditional anatomic features into a computational tool for more precise outcome prediction for individual patients. Nomograms represent one such statistical tool that has been widely tested in different cancers, including head and neck cancers [21-27].

A group of experts in the field of prognostication has been assembled by the AJCC to establish a precision medicine core (PMC) to assess existing knowledge and encourage development of prognostication tools based on high quality data and state-of-the art statistical methodology [28-29]. The goal of a more accurate statistical tool incorporating additional non—anatomic prognostic factors would be to minimize the intra-stage heterogeneity that is a hallmark of current anatomic based staging paradigms as seen in OCC [24]. The utility of nomograms in staging of head and neck cancer in general and OCC in particular remains to be proved. However, it can be safely argued that more accurate prediction of prognosis for individual patients would also allow assignment of each patient to a prognostically more homogeneous stage group and therefore fulfill all the other objectives of staging listed above.

The primary obstacle to global adoption of sophisticated tumor and host factors for nomogram-based prediction is their universal availability especially in low–resource jurisdictions. This could be surmounted by designing a modular nomogram that would allow users to input available information based on their circumstances [30]. The obstacle of user-friendliness can be overcome by leveraging modern technology to develop an electronic interface for data input and statistical calculation of prognosis that would be available as a smart phone application and can be used all over the globe by virtually anyone who has access to this now ubiquitous technology.

Conclusions

The 8th edition of the AJCC staging manual has added DOI and ENE as modifiers to the T and N category of OCC staging, respectively. The inclusion of these additional prognostic factors into the TNM staging system may impact its user-friendliness, however, will also improves its ability to predict prognosis. Increasing knowledge of other tumor and host–related prognostic factors has led to significant progress towards precision medicine for

many cancers. These advances will increase the demand for individualized outcome prediction against which the broader aims and user-friendliness of the current staging paradigm will need to be balanced.

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Abbreviations:

AJCC	American Joint Committee on Cancer
UICC	International Union Against Cancer
DOI	depth of invasion
ENE	extranodal extension

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Research Highlights

- Maximal dimension is an important information to define T stage.
- Number and location of nodal metastasis are important for N categorization.
- The 8th edition of AJCC staging manual incorporated changes for oral cancer.
- Depth of invasion has been incorporated as a modifier for T category.
- Inclusion of extranodal extension into the N category was another important change.

Table 1.

Primary tumor (T) definition for oral cavity cancers.

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor ≤ 2 cm with depth of invasion (DOI) ≤ 5 mm
T2	Tumor ≤2 cm with DOI >5 mm ***or*** Tumor > 2 cm and ≤ 4 cm with DOI ≤ 10 mm
T3	Tumor >2 cm and ≤4 cm with DOI >10 mm ***or*** Tumor >4 cm with DOI ≤10 mm
T4	Moderately advanced or very advanced local disease
T4a	**Moderately advanced local disease** Tumor >4 cm with DOI >10 mm ***or*** Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face) *Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4*
T4b	**Very advanced local disease** Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

* DOI is depth of invasion and **not** tumor thickness

From: AJCC Cancer Staging Form Supplement. Last updated 05 June, 2018. Amin MB, E.S., Greene FL, et al, eds, *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing: American Joint Commission on Cancer; 2017, New York.

Table 2.

Clinical assessment of regional lymph nodes (cN).

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(−)
N2	Metastasis in single ipsilateral lymph node, > 3 cm but not > 6 cm in greatest dimension and ENE(−); **or** metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE(−); **or** in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node > 3 cm but not > 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none > 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(−); **or** Metastasis in any node(s) with clinically overt ENE(+) (ENE_c)
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) with clinically overt ENE(+) (ENE_c)

Note: Midline nodes are considered ipsilateral nodes. ENE_C is defined as invasion of skin, infiltration of musculature, dense tethering or fixation to adjacent structures, or cranial nerve, brachial plexus, sympathetic trunk, or phrenic nerve invasion with dysfunction.

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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Table 3.

Pathological assessment of regional lymph nodes (pN).

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(−)
N2	Metastasis in single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(+); **or** > 3 cm but not > 6 cm in greatest dimension and ENE(−); **or** metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension and ENE(−); **or** in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node ≤ 3 cm in greatest dimension and ENE(+); **or** a single ipsilateral node > 3 cm but not > 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none > 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(−); **or** Metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral or bilateral nodes any size with ENE(+) in any node; **or** a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral or bilateral nodes any size with ENE(+) in any node; **or** Single contralateral node of any size and ENE(+)

Note: Midline nodes are considered ipsilateral nodes. ENE detected on histopathologic examination is designated ENE_{mi} (microscopic ENE ≤ 2m) or ENE_{ma} (macroscopic ENE > 2mm). Both ENE_{mi} and ENE_{ma} qualify as ENE(+) for definition of pN.

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

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