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Review Article

Update on oral and oropharyngeal cancer staging — International perspectives

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Abstract Squamous cell carcinoma of the oral cavity and oropharynx have been used synonymously and interchangeably in the world literature in the context of head and neck cancers. As the 21st century progresses, divergence between the two have become more evident, particularly due to evidence related to human papillomavirus-associated oropharyngeal squamous cell carcinoma. As such, the American Joint Committee on Cancer recently published the 8th edition Cancer Staging Manual, serving as a continued global resource to clinicians and researchers. Through changes in staging related to T and N clinical and pathologic classifications, the new system is expected to influence current management guidelines of these cancers that

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Head and neck cancer management

have distinct anatomic and etiopathogenic characteristics. This article aims to review such impactful changes in a time of critical transition of the staging of head and neck cancer and how these changes may affect clinicians and researchers worldwide.

Introduction

Historically, squamous cell carcinoma of the oral cavity (OCSCC) and oropharynx (OPSCC) would be classified together or as separate entities in the literature of head and neck cancer (HNC). Furthermore, oral tongue and base of tongue cancers were often combined and labeled together as "tongue cancers" though they originate from distinct subsites of the tongue. Most notably, emerging evidence related to human papillomavirus (HPV) associated disease has altered the perspective and approach to OPSCC. OCSCC and OPSCC still stand as potentially life-threatening diagnoses particularly in areas with marginalized cancer care resources.[1] Nearly 300,000 and 142,000 cases emerge annually for OCSCC (including the lip) and OPSCC, respectively, leading to nearly 145,000 and 96,000 deaths.[2] Though research is unraveling novel treatment approaches,[3] it is imperative to discern patient prognoses in the settings of novel molecular diagnostics, counseling, treatment planning, and research.

Cancer staging has provided a framework to determine prognosis and design guideline-based treatment for each stage. The modern system took its initial form in the early 1900's by describing cancer as *local*, *regional*, or *distant* disease. Between 1943 and 1952, Pierre Denoix of France built on this idea by classifying cancers by their anatomic location and extensiveness, pioneering the modern TNM (tumor, node, metastasis) system. This system was swiftly adopted by the Union for International Cancer Control (UICC) of Europe in 1953.[4] Shortly after in 1959, the American Joint Committee on Cancer (AJCC) was founded, adopting the system in a modified form for its use in the United States (US).[5] As both systems gathered wide acceptance, TNM committees of the AJCC and UICC formulated a single system in 1982.[2,4,6]

The resulting series of AJCC/UICC staging systems along with guideline and evidence-based treatment recommendations including the NCCN (National Comprehensive Cancer Network) of the US have offered continual insight on the optimal management course for HNC. Yet, as the landscape of knowledge undergoes change, categorizations naturally grow antiquated, requiring improvement and adaptation. Particularly, during the emergence of HPV-associated OPSCC and improvement in outcomes were realized, studies suggested that a modification of the staging system may be necessary.[7–9] As such, recent research is indicating clearer separations in the prognostic categorizations of OCSCC and OPSCC. Subsequently, the AJCC recently released the 8th ed. staging manual, effective January 1st 2018.[10] The aim of this article is to highlight and comprehensively review the most impactful changes in the new staging system to aid clinicians and researchers across the globe in this time of transition.

Background

Anatomy

Distinguishing the anatomic subsites and borders of the oral cavity and oropharynx are important to the diagnosis and management of OCSCC and OPSCC (Fig. 1). The former begins at the mucocutaneous junction of the lips and extends posteriorly, including the alveolar ridge and gums, the anterior two-thirds of the tongue, floor of the mouth, buccal mucosa, retromolar trigone, and hard palate. The oropharynx begins superiorly at the junction of the soft and hard palate and inferiorly at the circumvallate papilla of the tongue. It is bounded superiorly by the lower surface of the soft palate and inferiorly by the anterior surface of the epiglottis. Subsites of the oropharynx include the soft palate, tonsillar pillar, palatine tonsil, base (posterior 1/3) of tongue (BOT), valleculae, and oropharyngeal walls. These structures collectively represent a significant conduit of the upper aerodigestive tract, including critical lymphoepithelial structures such as the palatine and lingual tonsils, which are common origins of p16-positive OPSCC.

Regional neck lymph nodes are classified into six different levels separated by clinical or image-based anatomic landmarks: level I (submental); level II (upper jugular); level III

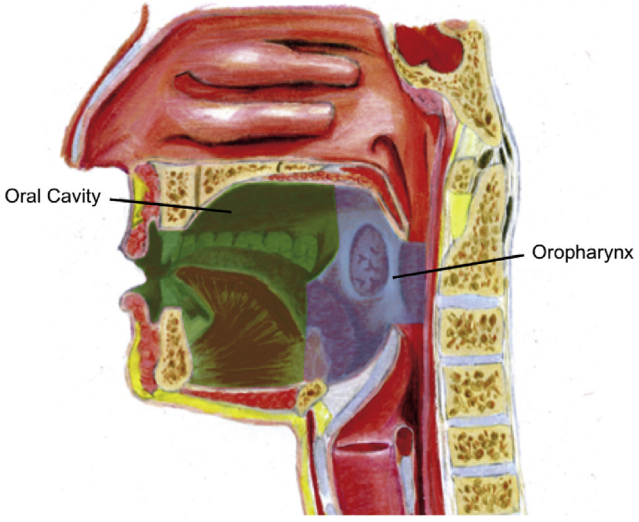

Fig. 1 Anatomic subsitesof the oral cavity (green) and oropharynx (blue) (used and modified with permission from artist, Lauren Visserman).

(mid-jugular); level IV (lower jugular); level V (supraclavicular fossa); level VI (central compartment).

Trends in epidemiology

OCSCC and OPSCC combined represent 3.1% of all cancers worldwide with annual age-adjusted incidences estimated at 4.0 and 2.1 per 100,000, respectively. The highest rates of OCSCC are in Melanesia with age-adjusted incidences per 100,000 of 22.9 for males and 16.0 for females. While the overall rate of OCSCC is observed to decrease, the total global burden is projected to have a 60% increase by 2030 when accounting for the world's growing population.[11,12] On the other hand, OPSCC is most frequent in Western Europe at 7.5 and 1.6 per 100,000 for males and females, respectively. While overall trends of OPSCC vary by region, rates are increasing predominantly among men in more developed countries such as Scotland, Switzerland, Slovakia, and particularly, France.[13,14] These increases are attributed to HPV-positive disease even in the face of diminishing rates of tobacco use. Globally, the prevalence of HPV confirmation in these tumors expanded from 32.3% before 1995 to 52.9% in the recent decade.[15] Similar to OCSCC, OPSCC is predicted to experience a 60% rise in incidence by 2030.[11,12]

In the US, HNC as a group is on the general decline. OCSCC is paralleling this pattern while the incidence of OPSCC is accelerating (Fig. 2) and with HPV-positive disease approaching 80% of all OPSCC.[16] This dramatic rise is projected to overtake the rate of cervical cancer by 2020.[17,18] Concurrently, there is a decline in cancers resulting from tobacco use.[18] Of note, by the Surveillance, Epidemiology, and End Results (SEER) database and American Cancer Society, the incidence of 'tongue' cancer is inferred to account for both oral tongue and BOT and its rise due to increasing rates of the latter, which is a distinct subsite of the oropharynx (Fig. 2).[15,19] Researchers are optimistic that all national databases will eventually categorize the 'oral tongue' as separate from the 'BOT'. Between OCSCC and OPSCC, nearly 50,000 new cases will develop leading to almost 10,000 deaths in the US for 2017 alone.[18]

Patient demographics and clinical characteristics

HPV-positive OPSCC truly indicates a unique subset, as HPV-negative OPSCC and all OCSCC demonstrate similarities in demographics.[20] These distinctions and other characteristics are summarized in Table 1.[16] In addition, studies have indicated HPV-positive OPSCC's predilection for early and large, cystic neck metastasis, resulting in the diagnosis of advanced stage disease (III-IV).[7,21,22] Anatomically, OCSCC is most commonly found on the oral tongue, while OPSCC is typically found to affect the tonsil or BOT. When stratifying OPSCC by HPV status, HPV-positive lesions rarely involve the pharyngeal walls or the soft palate when compared to HPV-negative disease.[23,24]

Diagnosis

Initial workup involves a physical examination, visualizing the primary tumor by either direct or indirect, light-enhanced visualization and/or endoscopy in the outpatient clinic, and sampling the primary tumor with a tissue biopsy or any neck mass with fine needle aspiration biopsy. Although clinical examination alone can establish 'clinical' staging, MRI, CT, and/or CT-PET are often utilized to determine the extent of disease, namely, nodal and distant metastases, improving the accuracy of staging.

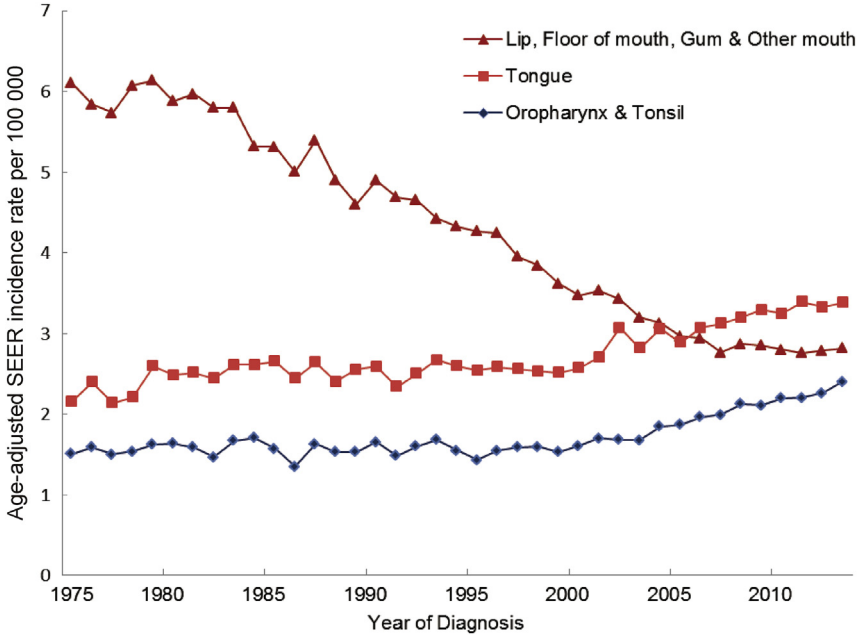

Fig. 2 Age-adjusted SEER incidence rates by subsite in the U.S., all races, both sexes from 1975-2013.[19] OCSCC declining overall. The incidence of tongue cancer is inferred to account for the oral tongue and base of tongue, and its rise due to increasing rates of the latter, a distinct subsite of the oropharynx. Rates of OPSCC rising rapidly.

Table 1 Demographics and clinical characteristics of OCSCC and OPSCCs.

Cancer site	Oral cavity	Oropharynx (p16-negative)	Oropharynx (p16-positive)
Demographics	Tobacco (smoking, chewing, betel nut), alcohol Older More African-Americans Lower SES Lower education	Tobacco (smoking), alcohol Older More African-Americans Lower SES Lower education	Nonsmoker Male Younger Caucasian Increased sexual partners Higher SES Higher education
Common Locations	Oral tongue	Tonsil BOT Pharyngeal wall Soft palate	Tonsil BOT
Common Presentations	Soreness with red or white spots	Sore throat Dysphagia Otalgia Neck mass	Painless neck mass

HPV — human papillomavirus; SES — socioeconomic status; BOT — base of tongue.

HPV testing

Testing for HPV status is now considered routine for OPSCC in North America.[25] However, HPV testing guidelines are yet to be established, and therefore, practices differ by country. Available tests include HPV DNA (E6 oncogene) detection through polymerase chain reaction (PCR), *in situ* hybridization (ISH) for HPV type-specific DNA or RNA, serum and salivary assays, and immunostaining for p16 protein. While p16 immunostaining is the most popular test due to low cost, high sensitivity, and simple execution, it has a markedly decreased specificity compared to the gold standard PCR for HPV DNA.[26] However, standardizing staging by means of p16 may be difficult in developing countries, where access to this prognostic tool and even up-to-date therapies are lacking.[27,28] Among viable algorithms, p16-positive immunostaining followed by PCR for HPV DNA is considered the most useful for oropharyngeal tissues.[31] In addition, given the ubiquitous expression of p16 in human cells, appropriate recognition of pathologic immunostaining patterns is critical. To qualify as p16-positive, strong nuclear and cytoplasmic staining must be observed diffusely in $\geq$70% of tumor cells.[29,30] illustrating the need for further supplementary testing.

Evolving metrics in staging

Until now, the AJCC staging system has experienced very few major changes related to HNC since its inception, and particularly, changes related to molecular testing that could impact the prediction of prognosis and treatment decisions. Since the implementation of the previous AJCC staging system (7th ed., 2010), treatment standards, patient profiles, HPV and HNC knowledge have evolved, resulting in a new staging system with an implementation date of January 1, 2018. Subsequently, clinicians, researchers, and patients will experience changes in diagnostic methodologies, pretreatment discussions, and therapy, standing as sources of future challenges when comparing studies on HNC conducted prior to with those occurring after 2018. To follow is a concise summary of the new AJCC staging systems and a worldwide perspective of its implementation and how this will impact patients and clinicians.

Oral cavity cancer

OCSCC staging experienced crucial changes related to the primary site and also cervical lymph nodes that impact sites beyond the oral cavity:

Primary site
- Depth of Invasion (DOI) now included
- Local tumor invasiveness now redefined

Lymph nodes
- Extranodal extension (ENE) now included
  - Clinical ENE(+) criteria = evidence on physical exam
  - Pathologic ENE(+) criteria = macroscopic $\geq$2 mm only

Depth of invasion

Historically, the OCSCC staging system depended on estimations by the human senses, such as by size of the visible surface and/or palpability of tumor, or by radiographic measurements. This was particularly challenging in the presence of ulcers, redness, or edema to distinguish malignancy versus secondary findings. There did not exist an objective confirmatory clinical test to accurately determine invasion of extrinsic tongue muscles, size, or depth until obtaining pathologic measurements through biopsy or surgery.

Depth of invasion (DOI) has been found to be an independent prognostic measure for both nodal metastasis and survival in OCSCC.[32] Many have studied clinical and pathologic criteria portending its prognostic implication.[37] Multiple studies have mentioned DOI in OCSCC within consistent measurements and techniques with respect to points of which the depth measurement vector is drawn.[33–36] Some describe tumor thickness as depth by utilizing the outer(superficial)

surface of any exophytic, indurated, or 'mushrooming' effects as the reference point; others use the plane corresponding to the outer epithelial layer adjacent to the tumor. According to the new AJCC staging system, DOI is "measured by first finding the 'horizon' of the basement membrane of the adjacent squamous mucosa. A perpendicular 'plumb line' is established from the horizon to the deepest point of tumor invasion".[10] While it is most accurately determined histologically, it could be estimated in clinic by palpation and minimally aided by imaging. This feature is not novel in the field of oncology, as it has been applied to melanoma and squamous cell carcinoma of the cervix, among other malignancies.

Using DOI in a staging system necessitates separation by categories rather than a continuum of 1 mm increments. Although studies in past decades examined 3, 4, and 5 mm increments to determine lymph node metastasis and survival risk stratification, staging experts were tasked with identifying a system that was simple, confirmed by evidence, and achieved prognostic separation via patient tissue biopsies. For the new OCSCC staging, 5 mm increments were decided upon, categorizing survival more effectively compared to the 7th ed. system that only considered tumor size and local invasiveness.[32]

However, accurately quantifying DOI is not possible without histologic examination. Ultimately, the most reliable DOI measurement will be obtained at pathologic examination, which may not be available until after definitive treatment. Implications of this include the need for rapidly returned pathologic examination results to educate the patient and allow radiation to begin in a timely fashion.[37]

Local tumor invasiveness

fdb 9.1.450/W UnicodeHistorically, locally advanced cancers (T3 or T4) considered the extent of tumor rather than size alone. Tumor extent in the distant past utilized terms such as resectable/unresectable, which left significant subjectivity, and also resulted in patients accrued to clinical trials that may have had a wide variety of tumor aggressiveness. More recently, terms were changed to "Moderately advanced local disease", implying T4a classification, versus "Very advanced local disease", implying T4b classification. However, some of these criteria remained subjective even with clinical exam and radiographic imaging. This point is can be illustrated by the prior utilization of "extrinsic muscles of the tongue" by cancer indicating T4a classification. However, research shows that the depth to invade the muscles varies along the axis of the lateral tongue, thereby criticizing its role in staging.[33] The 8th ed. system no longer considers deep/extrinsic muscle infiltration as T4a classification in OCSCC.

Oropharyngeal cancer

OPSCC similarly includes crucial changes related to the primary site and cervical lymph nodes:

Primary site
- T0 Staging
  - Deleted if patient is p16 (HPV) negative
  - Included if a lymph node in the neck is p16-positive with an unknown primary(UKP)
- p16 (HPV) status now included

Lymph nodes
- p16 (HPV) Positive
  - Exranodal extension (ENE) not included
  - Clinical Node Classification
    - cN1 = previous cN1, cN2a and cN2b if $\leq$6 cm
    - cN2 = previous cN2c if $\leq$6 cm
    - cN3 deleted
  - Pathologic Node Classification
    - pN1 = $\leq$4 lymph nodes involved
    - pN2 = $\geq$4 lymph nodes involved
- p16 (HPV)Negative
  - Extranodal extension (ENE) now included
    - Clinical ENE(+) criteria = evidence on physical exam
    - Pathologic ENE(+) criteria = microscopic $\leq$2 mm or macroscopic $>$2 mm
  - Clinical and Pathologic Node Classification
    - N0—N2 = previous N0—N2 if ENE(-)
    - N3 is now N3a and N3b
      - N3a = previous N3 and ENE(-)
      - N3b = now any nodes with ENE(+)

p16 positivity

Stark contrasts in disease behaviors based on p16 status proved parts of the 7th ed. staging ineffective in linking stratified stages to prognostic outcomes, particularly as related to nodal metastasis. This is accounted for by the increase in p16-positive cases, which generate smaller primary tumors with greater cervical node involvement.[38] Thus, though p16-positive patients were frequently diagnosed as advanced stage due to nodal metastasis, outcomes were much more favorable compared to their p16-negative counterpart irrespective of nodal status.[7,21,22]

Other findings further the notion that nodal disease and local invasiveness classifications in p16-positive OPSCC must be revised for prognostic and staging purposes.[7] These include the notably high rate of an occult primary tumor in the setting of an isolated, p16-positive neck mass. Furthermore, research indicated that the number of pathologic lymph nodes obtained through neck dissection is a valuable metric in the staging of p16-positive OPSCC.[41] These observations, in addition to others, led to the proposition for a separate staging system, both clinical and pathological, for HPV-associated OPSCC.[7,8,22,39—42]

Extranodal extension

Extranodal extension (ENE), or historically, extracapsular spread/extension, is the extension of malignancy through an affected lymph node capsule. Depending on its severity, clinicians are able to recognize ENE clinically, radiographically, or histologically. It has always been shown to be a poor prognostic marker for regional recurrence and distant metastasis, and thus, was proposed to be incorporated into the new staging system.[43,44] Interestingly, ENE is not as negatively predictive in appropriately treated p16-positive OPSCC as it is in p16-negative OPSCC and other HNSCC sites.[45,46]

Table 2 Summary comparing 7th and 8th ed. AJCC staging of OCSCC and OPSCC.[10]

Change	7th Ed. (2010)	8th Ed. (2017)		
		Oral Cavity	Oropharynx (p16-negative)	Oropharynx (p16-positive)
T-Classification	**TX:** primary tumor cannot be assessed **T0**: no primary **Tis**: carcinoma *in situ* **T1**: size ≤2 cm **T2**: size 2-≤4 cm **T3**: size >4 cm or extension to lingual surface of epiglottis **T4:** ○ **T4a**: moderately advanced (extrinsic tongue muscle involvement constituted T4a) ○ **T4b**: very advanced	**T1:** size ≤2 cm and **DOI ≤5 mm** **T2:** size ≤2 cm and **DOI 5-≤10 mm** or size 2-≤4 cm and **DOI ≤10 mm** **T3:** size >4 cm or **any tumor > 10 mm DOI**		**T0** if provenp16+ disease without evidence of primary tumor All locally advanced combined to **T4**
N-Classification	**NX:** regional node involvement cannot be assessed **N0**: no LN involved **N1**: single ipsi LN ≤3 cm in size **N2:** **N2a**: single ipsi LN, 3-≤6 cm in size **N2b**: multiple ipsi LNs, all ≤6 cm in size **N2c**: any bi or ctr LNs, all ≤6 cm in size **N3**: any LN >6 cm in size	**Clinical** **N0—N2**: same as previous and **ENE(-)** **N3** now with subcategories: **N3a**: previous N3 (size >6 cm) and **ENE(-)** **N3b**: any **ENE(+)**, either clinical or radiographic **Pathologic** **Criteria for pathologic ENE(+):** Oral cavity: only macroscopic (>2 mm) Oropharynx: micro- (≤2 mm) or macroscopic (>2 mm) **N1—N2**: same as previous and **ENE(-)** with exception: **N2a** includes lymph node **≤3 cm, ENE(+) LN** **N3** now with subcategories: **N3a** is previous N3 (size >6 cm) and **ENE(-)** **N3b: ≥3 cm and ENE(+) LN** or **> 1 ENE(+) LNs**		• Previous N1, N2a, N2b combined to **N1 (≤6 cm with or without ENE)** • Previous N2c isN2 (≤6 cm with or without ENE) • **ENE status not incorporated** •**N1:**≤4 LNs involved •**N2:** >4 LNs involved
TNM Stage Grouping	Clinical or pathological TNM used for same grouping system	Same as previous		**Separate clinical and pathological TNM groupings**

DOI: depth of invasion; LN: lymph node; ENE(+): extranodal extension present; ENE(-): extranodal extension absent; ipsi: ipsilateral; bi: bilateral; ctr: contralateral.

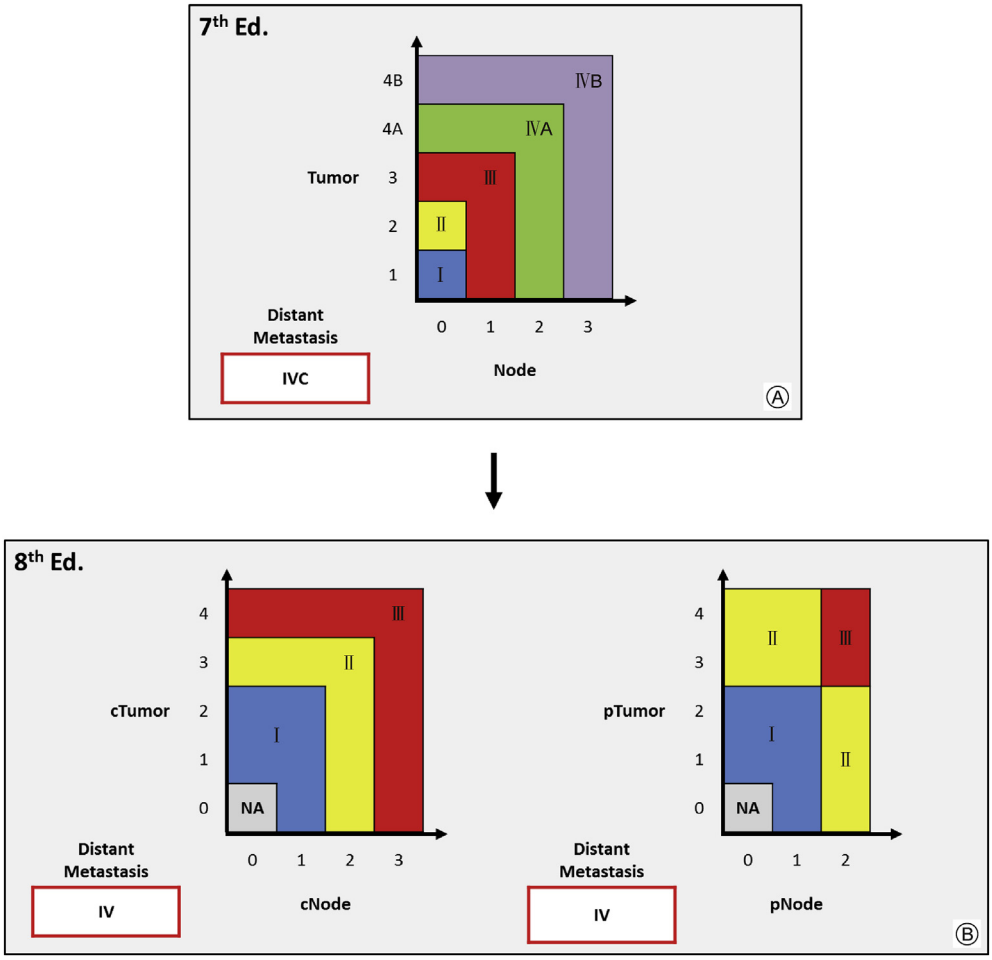

Fig. 3 Overall Stage Based upon TNM Stage Regrouping for p16-positive OPSCC. **A**: 7th ed. stage grouping for OCSCC and OPSCC combined **B**: 8th ed. stage groupings for p16-positive OPSCC are separatefor clinical and pathological staging, showing an expansion of early stage categorization to include traditionally advanced tumor features. NA: not applicable; c: clinical stage; p: pathological stage.

While overt, macroscopic ENE is evident on physical exam, imaging, or surgical dissection, the detection of microscopic ENE is significantly more challenging and controversial among pathologists.[47] Consequently, inter- and intra-observer variability is high.[48] In addition, research describes a more involved histologic technique to detect and distinguish ENE from the rather common neoplastic embolus of the soft tissue.[49] The latter consists of a metastatic lesion to soft tissue outside of regional nodes within fat, muscle, or blood vessels, yet some have considered it the product of metastatic tissue replacing/obliterating what was previously a lymph node.[50,51]

Moreover, without an established standard for ENE classification, the prognostic value of its severity is currently equivocal.[43,50,52] Most have quantified ENE by the distance of malignant extension from the outer boundary of the capsule,[43,50,52] while others report grading ENE by the relative location of malignancy to the lymph node capsule combined with its distance of extension beyond the capsule.[53] One group found that stratifying ENE with a 2 mm extension cutoff did not result in significant differences in survival.[52] Interestingly, however, a separate group reported to determine a prognostic cut-off value of 1.7 mm to dichotomize microscopic ($\leq$1.7 mm) from macroscopic ENE ($>$1.7 mm) in OCSCC.[43] While macroscopic ENE-positive tumors had significantly lower disease-specific survival, there was no difference between ENE-negative and microscopic ENE-positive tumors. The 8th ed. system classifies microscopic ENE as $\leq$2 mm and macroscopic as $>$2 mm, irrespective of associated stromal reaction, and with respect to staging, consider macroscopic (OCSCC) or macroscopic and microscopic (p16-negative OPSCC) to account for pathologic ENE-positive status.

These clinical and pathologic parameters now represent the major changes in OCSCC and OPSCC staging. Additionally, the International Collaboration on Cancer Reporting (ICCR) is in the process of updating the pathologic criteria used in some of these parameters.[54]

The new staging system (8TH ed.)

A rigorous review of the accumulating data has resulted in the 8th edition of the AJCC staging system (2017;

implemented in 2018), major modifications for which are outlined in Table 2.[10]

Moreover, it is imperative to note that p16-positive OPSCC staging has separate clinical and pathological TNM stage grouping systems and does not consider ENE (Fig. 3). To summarize these new groupings, clinical Stage I category is expanded to include T0-T2 with cN0-N1 disease, while T3 or cN2 disease would upstage to clinical Stage II, and T4 or cN3 disease would upstage to clinical Stage III. Similarly, T0-T2 with pN0-N1 disease is considered pathological Stage I, however, pathological Stage II is rearranged to include T3-T4 with pN0-N1 and T0-T2 with pN2 conditions, and pathological Stage III is limited to T3-T4 with pN2 disease. Of note, clinical and pathological Stage IV disease is only determined by the presence of distant metastasis (M1) and pathological N3 no longer exists.[10]

Implications in management

Current therapies for OCSCC and OPSCC include single modality or various combinations of surgery, radiation therapy, chemotherapy, and immunotherapy. Despite changes in the T and N classifications of OCSCC and OPSCC, overall stage-related treatment guidelines have not yet required modification. An example of a well-known evidence based guideline includes the NCCN Guidelines available at www.nccn.org. In general, early-stage OCSCC (I or II) are treated with definitive surgery (or radiation) unless metastatic, unresectable, or surgery is contraindicated. On the other hand, early-stage OPSCC can be treated with surgery via open or transoral (transoral robotic surgery, transoral laser microsurgery) approach, or radiation therapy alone, while for advanced stage (III or IV), combined modality therapy using surgery plus radiation(±chemo) therapy is the standard.[40,55] However, recent evidence suggests the need to individually tailor treatment practices as overtreatment has been a topic of concern particularly for early-stage cancers.[7,56] Subsequently, prospective studies are motivated to minimize morbidities and de-intensify treatment in patients undergoing aggressive multimodal regimens.[40] For advanced, recurrent, unresectable and/or metastatic OCSCC and OPSCC, immunotherapy options are emerging based on recent clinical trials.[57–59]

Summary

OCSCC and OPSCC are clinically and pathologically distinct diseases usually arising in separate demographic populations. The rise in p16-positive OPSCCs has become an important issue in the diagnosis, prevention, treatment, and now staging of these cancers. This evolving landscape has culminated in the 8th ed. of the AJCC staging system, which incorporates novel parameters to improve prognostic categorization. Highlights include DOI in OCSCC, separation of OPSCC by p16 status, modification of the N classification in HPV-positive cases, and inclusion of ENE in non-HPV nodal classification. Clinicians worldwide should understand these changes to provide appropriate treatments respective of geographical, cultural, political, financial, and technologic considerations.

Declaration of Competing Interest

The authors declare no conflicts of interest relevant to this report.

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None.

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