Oral Cavity and Oropharyngeal Cancer: A New Staging System for 2017
Masanari G. Kato, B.S., Terry A. Day, M.D.

Introduction

Historically, squamous cell carcinomas of the oral cavity (OCSCC) and oropharynx (OPSCC) have been grouped together as similar diseases with the terms "oral" and "oropharyngeal" used synonymously. The use of these terms interchangeably has since become obsolete, as translational and clinical research has distinguished one from the other in many respects other than just anatomic site, such as by risk factors, patient demographics, etiopathogenesis, and management.

These, among other emerging findings, have resulted in evidence that the 7th ed. (2010) American Joint Committee on Cancer (AJCC) staging system may not accurately reflect the differences in stage-related prognosis as a resource to guide treatment. Recently, the AJCC released the 8th ed. of the cancer staging manual, effective January 1st 2017. With this new staging system, notable modifications taken from the more recent published research have occurred and are expected to influence current management guidelines.

Background

Anatomy

The anatomic separation of the subsites and borders of the oral cavity and oropharynx are often confused, though important to the diagnosis and management of OCSCCs and OPSCCs. 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 (Figure 1).

The oropharynx begins superiorly at the junction of the soft and hard palate, and inferiorly at the circumvallate papilla of the tongue. Subsites of the oropharynx include the soft palate, tonsillar pillars, tonsils, base (posterior 1/3) of the tongue, vallecula, and the pharyngeal walls, and is bounded superiorly by the lower surface of the soft palate and inferiorly by the epiglottis (Figure 1).
Figure 1. The anatomy of the oral cavity and the oropharynx (used with permission from artist, Lauren Visserman).

**Epidemiology**

Head and neck cancers (HNC) make up 3% of all cancers in the United States, with a favorable, downward trend in its overall occurrence. The rates of OCSCCs has paralleled this pattern while OPSCC incidence has been accelerating (Figures 2A, 2B). This observation is due to the surge in human papilloma virus (HPV) associated OPSCCs, approaching 60-80% of all OPSCCs, a subset now often referred to as an “epidemic” in the head and neck community. Of note, the incidence of “tongue” cancer is inferred to account for both the oral tongue and base of tongue by both the Surveillance, Epidemiology, and End Results (SEER) database and American Cancer Society, and its rise due to increasing rates of the latter, which is a distinct subsite of the oropharynx (Figure 2A). Thus, Figure 2A shows rising “tongue” cancer, which appears to be primarily a result of the increase in base of tongue as can be appreciated in Figure 2B. Researchers are optimistic that future national databases will separate tongue into the “oral” part of the tongue and separate the “base of tongue” into the oropharynx. Between OCSCC and OPSCC, the American Cancer Society estimates nearly 50,000 new cases will develop, leading to almost 10,000 deaths in the US for 2016 alone.
Figure 2. Age-adjusted SEER incidence rates by subsite in the U.S., all races, both sexes from 1975-2013. A. OCSCC declining overall. Of note, 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 B. Rates of OPSCC rising rapidly.

Patient Demographics and Clinical Characteristics

It is interesting that HPV-positivity in the oropharynx patients represent a unique entity, as the HPV-OPSCC and all OCSCC patients appear to be similar in demographics. This distinction along with other clinical characteristics of each is summarized below (Table 1).

Table 1. Common Demographics and Clinical Characteristics of OCSCCs and OPSCCs

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Oral Cavity</th>
<th>Oropharynx</th>
<th>HPV(+)</th>
<th>HPV(−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Smoker/drinker</td>
<td>Smoker/drinker</td>
<td>Nonsmoker</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>Older</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>More African-Americans</td>
<td>More African-Americans</td>
<td>Younger</td>
<td>Caucasian</td>
</tr>
<tr>
<td></td>
<td>Lower SES</td>
<td>Lower SES</td>
<td>Lower SES</td>
<td>Lower SES</td>
</tr>
<tr>
<td></td>
<td>Lower education</td>
<td>Lower education</td>
<td>Lower education</td>
<td>Lower education</td>
</tr>
<tr>
<td>Common Locations</td>
<td>Oral Tongue</td>
<td>Pharyngeal wall</td>
<td>Tonsil</td>
<td>Tonsil</td>
</tr>
<tr>
<td></td>
<td>Soft Palate</td>
<td>Base of tongue</td>
<td>Base of tongue</td>
<td>Base of tongue</td>
</tr>
<tr>
<td>Common Presentations</td>
<td>Soreness with red or white spots</td>
<td>Sore throat</td>
<td>Painless neck mass</td>
<td>Painless neck mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysphagia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otalgia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis

The initial workup of these patients involves a physical exam, visualizing the primary tumor by fiberoptic endoscopy in the outpatient clinic, and sampling the primary tumor with a tissue biopsy or neck mass with fine needle aspiration to confirm the disease. Currently, testing for HPV status is routine for oropharyngeal lesions. Immunostaining for p16 protein is the most popular method. Following diagnosis, imaging modalities such as
MRI, CT, and CT-PET are often utilized to determine the extent of disease, namely, nodal involvement and the presence of distant metastasis.

The authors feel that contrasted CT combined with the CT-PET fusion is a useful and beneficial imaging study that provides information on primary tumor proximity to the lingual neurovascular bundle, the carotid and jugular vascular structures, along with mandible and pterygoid muscles, which aids in accurate staging (Figure 3A). Additionally, contrasted imaging reveals lymph nodes that may be suspicious for harboring regional metastasis even when they are normal by size criteria (Figure 3B).

As noted earlier, HPV+ OPSCC commonly involves the base of tongue (Figure 4A) and advanced nodal disease is more likely present, typically appearing large and cystic (Figure 4B).

**Figure 3.** Imaging of Advanced OCSCC. A. CT-PET showing uptake of primary gingival SCC involving the mandible (green arrow) with nodal metastasis (yellow arrows) B. Contrast CT showing a lymph node less than 1cm in size (red arrow) with metastatic OCSCC.
Figure 4. Imaging of Advanced OPSCC. A. CT-PET showing uptake of primary base of tongue SCC with nodal metastasis (yellow arrows)  B. Contrast CT showing a cystic lymph node (red arrow) with metastatic OCSCC.

Add Green arrow to base of tongue in A

Staging

The clinical assessments outlined above then translate to the clinical stage of the cancer. Like most cancers, OCSCCs and OPSCCs are staged by the TNM (tumor, node, metastasis) staging system, a classification established by the AJCC to categorize cancer patients based on prognostic differences. The resulting alphanumeric code (T0-4, N0-3, M0-1) then corresponds to stage grouping (I to IV).

EMERGING CONCEPTS

Since the implementation of the previous AJCC staging system (7th ed., 2010), treatment standards, patient demographics, and cancer knowledge have evolved. A number of these findings relate to improving the accuracy of the staging system, while others shed light on future strategies to undertake the HPV+ OPSCC epidemic. Changes in staging have resulted from studies revealing predictive prognostic indicators that impact treatment, locoregional control, and survival.

Oral Cavity Cancer

Findings related to OCSCCs vary, though notably, the depth of invasion (DOI) of the primary tumor was found to be an independent prognostic measure for both nodal metastasis and survival in OCSCCs. The DOI is measured histologically by utilizing the basement membrane of normal adjacent tissue as reference. Incorporating the DOI by increments of 5mm helps to categorize patients by survival more effectively compared to the 7th ed. staging system.
Oropharyngeal Cancer

Evidence supporting changes related to OPSCCs has been far more drastic. The stark contrasts in clinical disease behaviors and prognoses between HPV+ and HPV- OPSCCs have caused the 7th ed. staging to prove ineffective. This is based on the account of the increase in HPV+ disease, which tends to have smaller primary tumors and more advanced nodal involvements.

Due to these clinical characteristics, HPV+ patients are frequently given the diagnosis of advanced stage OPSCC, though outcomes are much more favorable compared to their HPV- counterpart. Evidence now reveals that previous classifications of nodal disease as well as local invasiveness in HPV+ OPSCC must be reconsolidated to more accurately reflect prognostic differences between disease stages.

These observations, in addition to numerous others, have led to the proposition for a separate staging system for HPV-related OPSCCs.

Extra nodal Extension

The presence of extranodal extension (ENE) is defined as the extension of malignancy through the capsule of an affected lymph node. Depending on its severity, it could be recognized clinically, radiographically, or histologically. It's known to be a poor prognostic marker indicating an increased likelihood of regional recurrence and distant metastasis, and as a result, propositions for its addition to the staging system have been made. Interestingly, ENE is not as predictive of a negative outcome in HPV+ OPSCC as it is in HPV- OPSCC and other HNSCC sites.

HPV Vaccination

High-risk HPV serotypes (16 and 18) are well known for causing cancers at various sites, namely the cervix, resulting in the development of a number of effective adolescent-administered vaccines. The question as to whether they translate, if at all, to the prevention of HPV-associated OPSCC is logical, but would be substantially difficult to study. However, there are implications of their benefit, and therefore, adolescents of both genders are recommended vaccination.

At the same time, other novel vaccines with the potential to prevent and even treat HPV+ HNC are in the works. Many of these approaches are in their infancy and manipulate HPV’s E6 and E7 proteins, the core of the virus’ tumorigenic virulence. Injections containing genetically modified HPV+ cancer cells and E6 and E7-fused proteins are some future developments that may hold promise.

THE NEW STAGING SYSTEM (8th ed.)

A rigorous review of the accumulating data has resulted in the 8th iteration of the AJCC staging system (2017), major modifications for which are outlined below (Table 2). It is also imperative to note the separate clinical and pathological TNM stage grouping system unique to HPV+ OPSCC, which shows that stage IV disease is determined by the presence of distant metastasis (M1) and T3 does not exist in pathological staging (Table 3).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment [MK1]: Stage Grouping blurb</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### T-stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Oral Cavity</th>
<th>HPV. Oropharynx</th>
<th>HPV+ Oropharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>no primary</td>
<td>T0 deleted</td>
<td>T0 if proven p16+ disease without evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>size ≤2cm</td>
<td>T1: size ≤2cm and DOI ≤5mm</td>
<td>All locally advanced combined to T4</td>
</tr>
<tr>
<td>T2</td>
<td>size 2-4cm</td>
<td>T2: size ≤2cm and DOI 5-10mm or size 2-4cm and DOI ≤10mm</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>size &gt;4cm</td>
<td>T3: size &gt;4cm or &gt;10mm DOI</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td></td>
<td>• T4a: moderately advanced (extrinsic tongue muscle involvement constituted T4a) • T4b: very advanced</td>
<td></td>
</tr>
</tbody>
</table>

### N-stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Oral Cavity</th>
<th>HPV. Oropharynx</th>
<th>HPV+ Oropharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>no LN involved</td>
<td>N1-N2 is same as previous and ENE(-)</td>
<td>Previous N1, N2a combined to N1 (≤6cm with or without ENE)</td>
</tr>
<tr>
<td>N1</td>
<td>single ipsi LN ≤3cm in size</td>
<td>N3 now with subcategories: N3a is previous N3 (size &gt;6cm) and ENE(-) N3b is any ENE(+), either clinical or radiographic</td>
<td>Previous N2b, N2c combined to N2</td>
</tr>
<tr>
<td>N2</td>
<td>o N2a: single ipsi LN, 3-6cm in size o N2b: multiple ipsi LNs, all ≤6cm in size o N2c: any bi or ctr LNs, all ≤6cm in size</td>
<td>• Microscopically evident ENE(+) LNs results in upstaging</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>any LN &gt;6cm in size</td>
<td>• N1: ≤4 LNs involved • N2: &gt;4 LNs involved • N3 deleted</td>
<td></td>
</tr>
</tbody>
</table>

### Stage grouping

<table>
<thead>
<tr>
<th>Clinical or pathological TNM used for same grouping system</th>
<th>Clinical or pathological TNM used for same grouping system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same as previous</td>
<td>Separate clinical and pathological TNM groupings</td>
</tr>
</tbody>
</table>

### DOI – depth of invasion, LN – lymph node, ENE(+) – extranodal extension present, ENE(-) extranodal extension absent, ipsi – ipsilateral, bi – bilateral, ctr - contralateral

#### Table 3. Changes in Stage Grouping for HPV+ OPSCC

<table>
<thead>
<tr>
<th>7th ed. TNM Grouping</th>
<th>8th ed. cTNM Grouping</th>
<th>8th ed. pTNM Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>T0</td>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
<td>I</td>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
<td>II</td>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
<td>III</td>
<td>N3</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>T3</td>
</tr>
<tr>
<td>T4a</td>
<td>IV</td>
<td>T4</td>
</tr>
<tr>
<td>T4b</td>
<td>IV</td>
<td>T4</td>
</tr>
<tr>
<td>M1</td>
<td>IV</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comment [MK2]: Stage grouping table needed?
CHANGES IN MANAGEMENT

Current therapies for OCSCCs and OPSCCs include isolated or various combinations of surgery, radiation therapy, chemotherapy, and immunotherapy. In general, all oral cavity cancer is treated with surgery unless metastatic, unresectable, or there are contraindications to surgery. However, oropharyngeal cancer can be treated with surgery (TOR) or radiation therapy alone for early stage (I or II) while combined therapy using Surgery + Radiation Therapy (SRT) or Chemoradiation (CRT) is the standard for advanced stage (III or IV). (Ref NCCN, etc). The management has historically been stage-dependent, with therapies increasing in intensity with higher stage. However, recent evidence suggests the need to individually tailor treatment practices as overtreatment has been a topic of concern, particularly for early-stage OCSCCs and OPSCCs. Consequently, prospective studies are currently underway to minimize morbidities and de-intensifying treatment in patients undergoing aggressive multimodal regimens.  

SUMMARY

OCSCC and OPSCC are clinically and pathologically distinct diseases. While the overall decrease in incidence of all HNCs is favorable, the rise in HPV+ OPSCCs has become an important issue in the diagnosis, prevention, and treatment of these cancers. This evolving landscape in the modern era has culminated in the release of the 8th ed. of the AJCC staging system, which incorporates critical parameters to improve prognostic categorization. Highlights include the incorporation of depth of invasion in oral tongue cancers, separation of OPSCC staging by HPV status, and inclusion of extranodal extension in nodal staging. By more accurately reflecting the differences in patient prognoses, cancer management is sure to adapt with time. Furthermore, translational research is showing potential in the realm of HPV prevention, diagnostics, and unique therapeutics, adding to the collective efforts to tackle this epidemic.

REFERENCES

11. Kuk SK, Yoon HJ, Hong SD, Hong SP, Lee JI. Staging significance of bone invasion in small-sized (4cm or less) oral squamous cell carcinoma as defined by the American Joint Committee on Cancer. Oral Oncol 2016; 55:31-36.
35. Cracchiolo JR, Baxi SS, Morris LG, et al. Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of

11. Kuk SK, Yoon HJ, Hong SD, Hong SP, Lee JI. Staging significance of bone invasion in small-sized (4cm or less) oral squamous cell carcinoma as defined by the American Joint Committee on Cancer. Oral Oncol 2016; 55:31-36.


