Changes in AJCC Staging of Head and Neck Cancer (8th Edition) effective January 1st, 2018

Rajeev H. Mehta, MD, FACS
ENT Surgical Consultants, Ltd
Assistant Clinical Professor
Department of Otolaryngology
University of Illinois-Chicago
Learning Objectives

• Discuss new American Joint Committee on Cancer (AJCC) staging for human papilloma virus-positive oropharyngeal cancer (HPV+OPC)

• Compare HPV+OPC to HPV negative OPC staging

• Recognize updated staging based on tumor behavior

• Describe how staging affects treatment and prognosis
## AJCC Cancer Staging Manual editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Publication</th>
<th>Effective dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1977</td>
<td>1978-1983</td>
</tr>
<tr>
<td>2nd</td>
<td>1983</td>
<td>1984-1988</td>
</tr>
<tr>
<td>5th</td>
<td>1997</td>
<td>1998-2002</td>
</tr>
<tr>
<td>6th</td>
<td>2002</td>
<td>2003-2009</td>
</tr>
<tr>
<td>7th</td>
<td>2009</td>
<td>2010-2017</td>
</tr>
<tr>
<td>8th</td>
<td>2016</td>
<td>2018</td>
</tr>
</tbody>
</table>
Changes in the AJCC/UICC

7th Edition
- Lip & Oral Cavity
- Pharynx (naso, oro, hypo)
- Larynx (supra, glottic, sub)
- Nasal Cavity & Sinuses
- Salivary Gland
- Mucosal Melanoma (new to the 7th Ed.)

8th Edition
- Cervical Lymph Nodes & Unknown Primary
- Lip & Oral Cavity
- Salivary Gland
- Nasopharynx
- P16+ Oropharynx
- P16- Oropharynx & Hypopharynx
- Nasal Cavity & Sinuses
- Larynx
- Mucosal Melanoma of H & N
- Cutaneous SCCA of H & N
Cancer Staging: Key Principles

• Hazard consistency - staging should result in similar survival for each subgroup

• Hazard discrimination - each subgroup should have a different survival from the one above/below it

• Balance between groups - should be relatively equal numbers in each group for better statistical comparisons

• High predictive ability - Stage should give a good approximation of prognosis/survival
Cancer Staging 7th Edition vs Goal

A  HPV+ OPC by 7th ed TNM stage

Overall survival (%)

- I
- II
- III
- IVA
- IVB

p < 0.0001

Overall Survival - 8th Edition T-Stage

Cumulative Survival

- T1
- T2
- T3
- T4

Time (Months)
Changes in the AJCC/UICC 8th Edition Staging

Effective January 1st 2018

- Pharynx move to:
  - Nasopharynx
  - p16+ Oropharynx
  - p16- Oropharynx
- New criteria for extranodal extension (ENE)
- New staging for neck disease with unknown primary
- Addition of depth of invasion in Oral Cavity T category
- New cutaneous SCCA of head and neck
Time of classification

- **cTNM** = Clinical Classification
  - before treatment but after full workup
- **pTNM** = Pathological Classification
  - after surgery used as the first definitive therapy
- **ycTNM** = Posttherapy Clinical Classification
  - after chemo/RT but before surgery
- **ypTNM** = Posttherapy Pathological Classification
  - first chemo/RT followed by surgery
- **rTNM** = Recurrence or Retreatment Classification
  - after recurrence or progression until treatment
- **aTNM** = Autopsy Classification
  - Cancers not recognized but found incidentally at autopsy
Extranodal Extension (ENE)

- ENE has profound effect on prognosis
- Inclusion of ENE in N Category
  - p16- Oropharynx and Hypopharynx
  - Unknown Primary
  - Oral Cavity
  - Larynx
  - Skin
  - Salivary Gland
  - Nasal Cavity and Sinus
  - Not for p16+ Oropharynx
Clinical Staging
Extranodal Extension (ENE)

- Strict criteria required for ENE positive diagnosis
- Clear evidence of gross ENE
  - skin/muscle invasion
  - dense tethering to adjacent structures
  - nerve invasion with dysfunction
  - supported by imaging
- Imaging alone is not sufficient
- If any doubt, assign ENE negative
Pathological Staging
Extranodal Extension (ENE)

- Clearly defined pathological ENE positive
  - tumor extends through LN capsule
  - tumor extends from LN into surrounding tissue
  - with or without desmoplasia

- ENEmi = microscopic = 2 or less millimeters
- ENEma = major = more than 2 millimeters

- If any doubt, make ENE negative
ENE for p16- OPC

- Clinical
  - Any ENE is N3b

- Pathological
  - ENE (either minor or major) increases N by 1 step
HPV Negative OPC Staging

- **T classification** unchanged
  - except T0 removed; unknown primary

- **N classification** unchanged except Extra Nodal Extension (ENE)
  - N3 divided into N3a and N3b
    - N3a LN > 6cm without ENE
    - N3b any size LN with ENE

- **M classification** unchanged

- Since ENE is now N3b, more patients are stage IVb
HPV negative OPC

T classification

(To moved to unknown primary)

- Tx Primary tumor cannot be assessed
- Tis Carcinoma in situ
- T1 $\leq$ 2cm
- T2 tumor 2-4cm
- T3 tumor > 4cm or extent to lingual epiglottis
- T4a invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
- T4b invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
HPV negative OPC
Clinical N classification

(ENE added = N3b)

• Nx  LN cannot be assessed
• N0  No LN mets
• N1  Single ipsilat LN ≤3cm, ENE -
• N2a Single ipsilat LN 3-6cm, ENE-
• N2b Multiple ipsilat LN ≤ 6cm, ENE-  
• N2c Multiple bilat/contralat LN ≤ 6cm, ENE-
• N3a LN > 6cm, ENE-
• N3b any size LN, ENE positive

Also used for oral cavity, hypopharynx, larynx, unknown primary & cutaneous carcinoma of head & neck
HPV negative OPC
Pathologic N classification

(ENE added = N3b)

- Nx  LN cannot be assessed
- N0  No LN mets
- N1  Single ipsilat LN ≤3cm ENE -
- N2a Single ipsilat LN ≤ 3cm ENE+ or LN 3-6cm ENE-
- N2b Multiple ipsilat LN ≤ 6cm ENE-
- N2c Multiple bilat/contralat LN ≤ 6cm ENE-
- N3a LN > 6cm ENE-
- N3b Single ipsilat LN>3cm ENE+, multiple ipsilat/contralat/bilat LN any size ENE+, single contralat LN any size ENE+

Also used for oral cavity, hypopharynx, larynx, unknown primary & cutaneous carcinoma of head & neck
HPV negative OPC

Suffix

- **T Suffix**
  - (m) synchronous primary tumors found in single organ

- **N Suffix**
  - (sn) LN mets found by surgical biopsy
  - (f) LN mets found by FNA or core needle bx
  - U Mets above lower border of cricoid
  - L Mets below lower border of cricoid

- **M suffix**
  - cM0 No distant mets
  - cM1 Distant mets clinically
  - pM1 Distant mets, confirmed microscopically
## HPV Negative/Not Tested OPC Stage Groups

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>No</td>
<td>Mo</td>
<td>o</td>
</tr>
<tr>
<td>T1</td>
<td>No</td>
<td>Mo</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>No</td>
<td>Mo</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>No</td>
<td>Mo</td>
<td>III</td>
</tr>
<tr>
<td>T1-3</td>
<td>N1</td>
<td>Mo</td>
<td>III</td>
</tr>
<tr>
<td>T4a</td>
<td>No-1</td>
<td>Mo</td>
<td>IVA</td>
</tr>
<tr>
<td>T1-4a</td>
<td>N2</td>
<td>Mo</td>
<td>IVA</td>
</tr>
<tr>
<td>Any T</td>
<td>N3</td>
<td>Mo</td>
<td>IVB</td>
</tr>
<tr>
<td>T4b</td>
<td>Any N</td>
<td>Mo</td>
<td>IVB</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVC</td>
</tr>
</tbody>
</table>
## Overall Stage p16 negative

**OPC**

<table>
<thead>
<tr>
<th>T category</th>
<th>No</th>
<th>N₁</th>
<th>N2a,b,c</th>
<th>N3a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁</td>
<td>I</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T₂</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T₃</td>
<td>III</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T₄a</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T₄b</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
</tr>
</tbody>
</table>

*Stage IVC = M₁ disease*
HPV+ OPSCC

- Younger age
- Little or no tobacco exposure
- Increasing at 5% per year
- Smaller tumors with advanced nodal disease
- Less likely to have extracapsular spread relative to nodal size
- Significantly better local-regional control
- Significantly better survival after treatment
HPV Positive OPC Staging

- **T classification** unchanged
  - except Tis removed (absence of distinct basement membrane in Waldeyer's ring and indolent nature of p16+)
  - T4b removed (survival curves of T4a and T4b are the same)

- **N classification**
  - Difference between clinical & pathologic staging
    - Clinical staging - laterality and size of LN
    - Pathologic staging - number of LNs
    - ENE not included in p16+

- **M classification** unchanged
  - Stage IV reserved for M1 disease

- Overall stage: drastic change
  - Since ENE is now N3b, more patients are stage IVb
HPV Positive OPC

• Cutoff point for p16 is >75% tumor expression with at least moderate (+2/3) staining intensity

• p16 is usually localized to nuclei and cytoplasm so p16 localized only to cytoplasm is considered negative
HPV positive OPC

T classification

(To moved to unknown primary)

- \( T_1 \leq 2\text{cm} \)
- \( T_2 \) tumor 2-4cm
- \( T_3 \) tumor > 4cm or extent to lingual epiglottis
- \( T_4 \) invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible or beyond

- \( (T_4a/T_4b \) distinction only in HPV negative OPC)
HPV positive OPC Clinical N classification (Treated with Radiation) (No ENE included)

- **N₁** = Ipsilateral LNs ≤ 6cm regardless of number had similar impact on survival when treated with radiation (clinical staging)
- **N₂** = Bilat/Contralat LNs < 6cm had a worse outcome
- **N₃** = LNs > 6cm had the worst survival

<table>
<thead>
<tr>
<th>Nx</th>
<th>LN cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>cNo</td>
<td>No LN mets</td>
</tr>
<tr>
<td>cN₁</td>
<td>Ipsilat LN ≤ 6cm</td>
</tr>
<tr>
<td>cN₂</td>
<td>Contralat/Bilat LN ≤ 6cm</td>
</tr>
<tr>
<td>cN₃</td>
<td>LN &gt; 6cm</td>
</tr>
</tbody>
</table>

When treated with radiation (clinical staging), the number of lymph nodes was not significant
HPV positive OPC Pathologic N classification (Treated with Surgery) (No ENE included)

- Neither LN size nor contralateral nodes impacted survival (unlike those treated with radiation)
- Number of LNns caused survival differences

<table>
<thead>
<tr>
<th>Nx</th>
<th>LN cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No LN mets</td>
</tr>
<tr>
<td>pN1</td>
<td>1-4 LNs</td>
</tr>
<tr>
<td>pN2</td>
<td>5 or more LNs</td>
</tr>
</tbody>
</table>

The difference in behavior in N3 neck between Clinical (radiation treatment) vs. Pathologic (surgical treatment) is unexpected
<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>N(_1)</th>
<th>N(_2)</th>
<th>N(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T(_0)</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T(_1)</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T(_2)</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T(_3)</td>
<td>III</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T(_4)</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>
## Pathological TNM Stage
### P16+ OPC 8th Ed

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>N₁</th>
<th>N₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>T₁</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>T₂</td>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>T₃</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>T₄</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
</tbody>
</table>
Unknown Primary

• 1. P16+ LNs --> will be staged as P16+ oropharynx (which includes T0 category)

• 2. EBV+ LNs --> will be staged as nasopharynx (which includes T0 category)

• 3. LNs that are P16 and EBV negative --> will be staged as unknown primary

• 90% of unknown primary H&N SCCA are HPV+ Oropharynx SCCA
Nasopharynx "T" Staging

- **Tx** Primary tumor cannot be assessed
- **T0** No tumor but EBV+ LN
- **Tis** Ca in situ
- **T1** tumor confined to nasopharynx or extension to oropharynx or nasal cavity without parapharyngeal (PPS) involvement
- **T2** extension to PPS and/or involvement of medial or lateral pterygoid or prevertebral muscles
- **T3** involves bone at skull base, cervical vertebra, pterygoids, sinuses
- **T4** intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue involvement beyond lateral surface of lateral pterygoid muscle
Oral Cavity "T" Staging

- **Tx** Primary tumor cannot be assessed
- **Tis** Ca in situ
- **T1** tumor ≤2cm, ≤5mm DOI
- **T2**
  - tumor≤2cm, 5<DOI≤10mm
  - 2<tumor≤4cm, DOI≤10mm
- **T3**
  - tumor>4cm
  - any tumor with 10<DOI≤20mm
- **T4** invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
Oral Cavity SCCA
Depth of Invasion
Cutaneous Carcinoma of the Head & Neck

- Tx Primary tumor cannot be assessed
- Tis Ca in situ
- T1 tumor ≤2cm
- T2 2< tumor ≤4cm
- T3 tumor >4cm or minor bone erosion or perineural invasion or deep invasion
- T4
  - T4a gross bone invasion
  - T4b skull base invasion

Deep invasion:
  - beyond subQ fat
  - tumor >6mm as measured from granular layer of epidermis to base of tumor

Perineural invasion:
  - tumor within nerve sheath deeper than dermis
  - tumor within nerve ≥0.1mm
  - tumor involving named nerves
Summary

1. Pharynx move to:
   - p16- Oropharynx (HPV-)
     - T0 removed --> moved to unknown primary
   - p16+ Oropharynx (HPV+)
     - Tis removed
     - T4b removed
     - Clinical staging - laterality and size of LN
     - Pathologic staging - number of LNs
     - Stage IV reserved for M1 disease
   - Nasopharynx (EBV+)

2. New criteria for extranodal extension (ENE)
   - ENE = N3b
   - Not for p16+ Oropharynx

3. New staging for neck disease with unknown primary
   - P16 negative & EBV negative

4. Oral Cavity
   - Addition of depth of invasion in T category

5. New cutaneous SCCA of head and neck
   - T3 = perineural invasion or deep invasion
References


Shao Hui Huang et al. Primary surgery versus (chemo)radiotherapy in oropharyngeal cancer: the radiation oncologist's and medical oncologist's perspectives. Head and neck oncology, volume 23(2), April 2015, 139-147.