AJCC 8th Edition Major Updates in Cancer Staging: Implications for OPC treatment?

AHNS Transoral Robotic Surgery Course

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- I have no conflicts of interest to disclose related to the content of this presentation.

AJCC TNM Cancer Staging Manual, 8th Edition

- "[We] have been proactive to incorporate new relevant genomic markers, for example, in breast cancer and oropharyngeal cancer, to build and empower the traditional concepts of staging of cancer."
  - Mahul B. Amin, MD, FCAP, Editor

- Dr. Amin added the transition to include new molecular markers is a significant development in this manual, and he believes it "will only grow exponentially in future staging efforts to allow staging to be very contemporary, relevant and applicable in clinical care of individual patients," he said
  - AJCC Press Release, October 2016

AJCC TNM Cancer Staging Manual, 8th Edition

- Originally intended to apply to all new cancers in 2017, implementation was delayed until **January 1, 2018**.
- Allow for infrastructure to be built to accommodate the changes.
  - This is not as nimble an environment for change
    - Big data
    - Electronic medical records
- "Clinicians will continue to use the latest information for patient care, including scientific content of the 8th Edition Manual. **All newly diagnosed cases through December 31st, 2017 should be staged with the 7th edition.**"
- "The time extension will allow all partners to develop and update protocols and guidelines and for software vendors to develop, test, and deploy their products in time for the data collection and implementation of the 8th edition in 2018."

AJCC TNM Cancer Staging Manual, 8th Edition

- While we wait . . .

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Head and Neck Cancers—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

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Key Updates

- Restaging Pharynx cancers based on 3 subgroups
  - Nasopharynx (+/- EBV)
  - HPV (–) Oropharynx AND Hypopharynx
  - HPV (+) Oropharynx
- Entirely new staging paradigm for HPV associated OPC
- New/Updated T staging for:
  - Oral Cavity
  - Nasopharynx
  - Cutaneous SCC and BCC
- Change in nomenclature/classification of “unknown primary” head & neck cancer
- Expanded staging for nodal disease
  - ENE*

Cancer Staging: Key Principles

- First, you need a lot of experts who represent all entities of cancer staging and cancer biology.
  - 28 members of the AJCC Head & Neck Task Force
- Second, you need data.
  - Pathologic data (obtained via surgery)
  - Clinical data (obtained on all patients)
  - Recognize implication of treatment decisions on available data . . .
  - Important to validate new staging systems

Cancer Staging: Key Principles

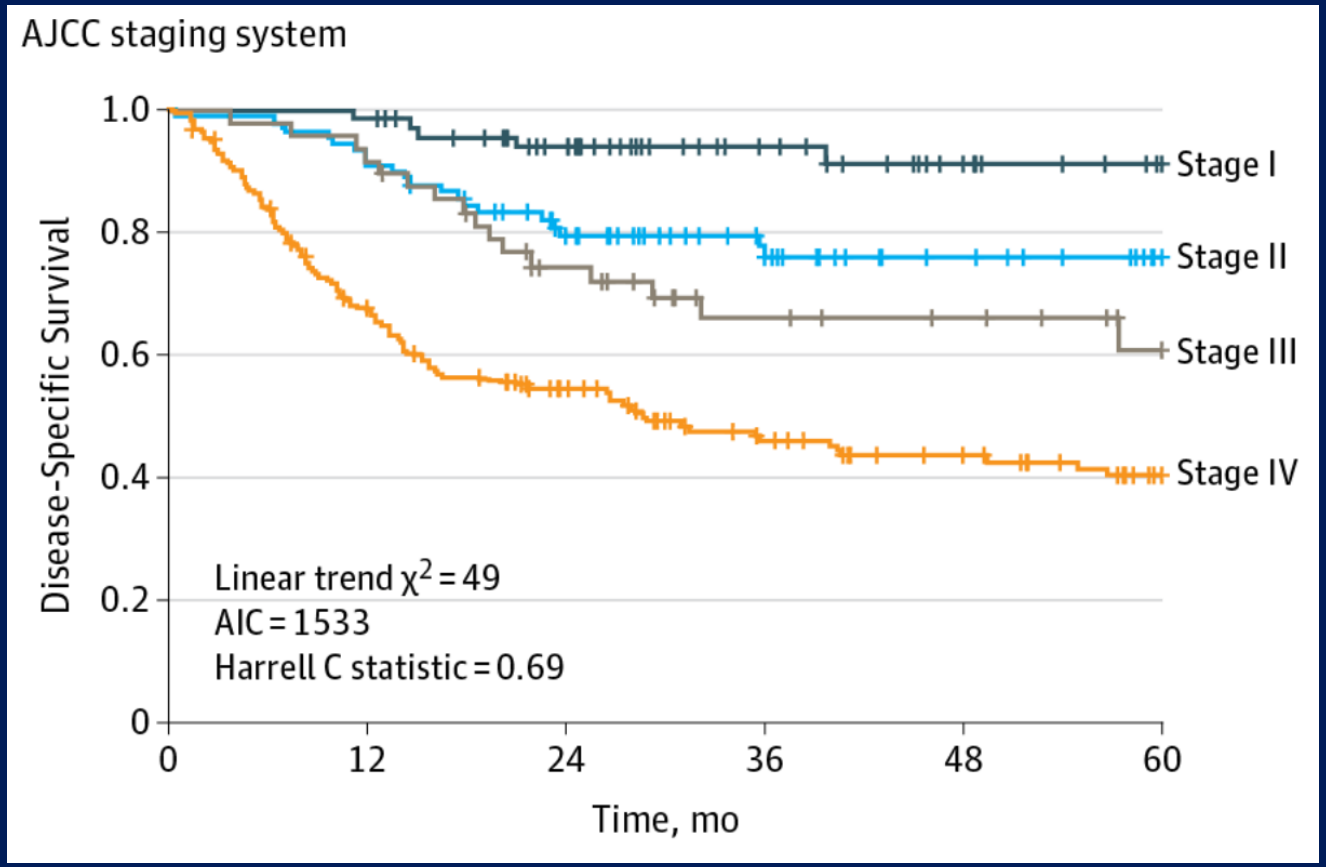
- Staging should result in similar survival for each subgroup, or *hazard consistency*
- Each subgroup should have a different survival from the one above/below it, or *hazard discrimination*
- Should be relatively equal numbers in each group for better statistical comparisons, aka *balance between groups*
- Stage should give a good approximation of prognosis/survival, aka *high predictive ability*
- With each recommendation for stage change, the data is revisited to make sure that these principles are supported . . .thus this is *an iterative process*.

Traditional Staging

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Cancer Staging Principles

- TNM Classification → Overall Stage



Oropharynx Cancer

Update: Separate staging for HPV+ OP cancer

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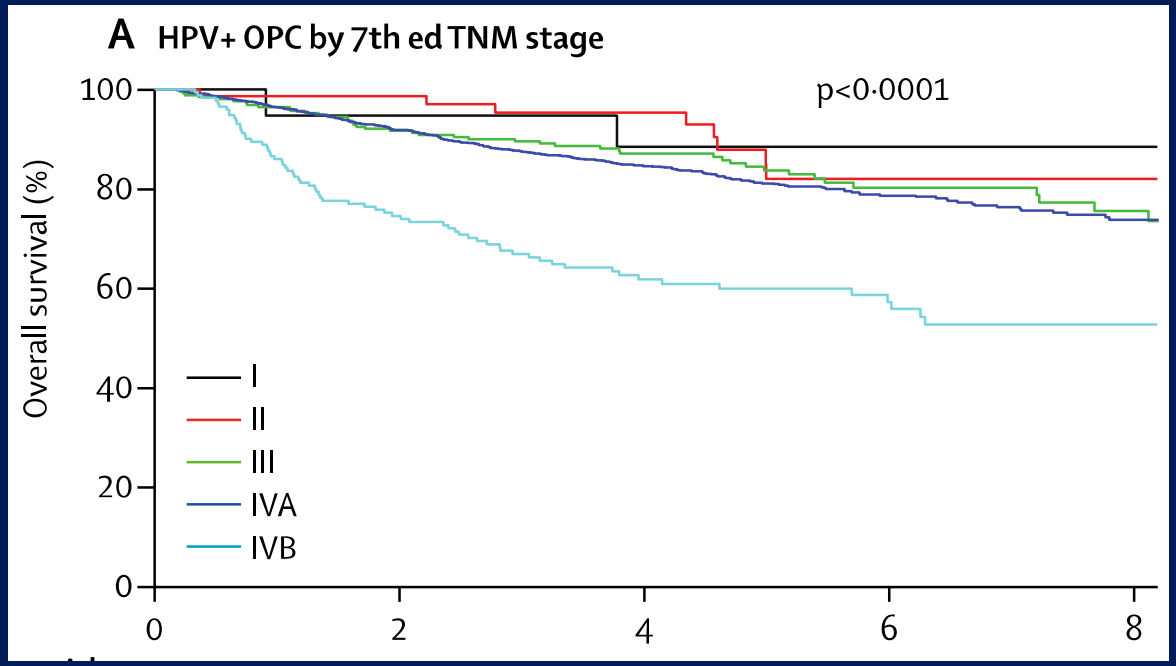
Separation of Oropharynx Staging by HPV Status

- Since 1990, the incidence of HPV associated cancers of the tonsil and tongue base has increased by 5% per year
- HPV–associated tumors occur in younger, healthier individuals with little or no tobacco exposure.
- It is highly responsive to treatment and has an excellent prognosis.

AJCC 7th Edition TNM staging OPC

- Reflects behavior of tobacco-related SCC, *not HPV+ disease*.
- The 7th edition lost the ability to differentiate between stages
  - Hazard discrimination
- The numerical balance shifted toward stage III & IV
  - Loss of predictive ability



Testing for HPV Status . . . p16

- Must be simple, inexpensive, and reproducible
  - Needs to be available worldwide
- Immunohistochemistry for overexpression of the tumor suppressor protein p16
  - Established, reliable surrogate biomarker
  - Independent positive prognosticator for OPC
  - Inexpensive, widely availability, easy to interpret
- OPC will now be staged according to 2 distinct systems, depending on whether or not they overexpress p16
- p16 overexpression = diffuse >/=75% tumor expression, with at least moderate (+2/3) staining intensity

HPV Negative OPC Staging

- T Classification:
- Unchanged except T0 removed
  - Non-viral T0 tumors can be from any site and thus cannot localize to oropharynx

- N Classification:
- Unchanged with the exception of Extra Nodal Extension (ENE)
  - N3 divided into N3a and N3b
    - N3a, lymph node >6cm in dimension, no ENE
    - N3b, any ENE

- M Classification: Unchanged

- Overall Stage: Unchanged
  - ENE now N3b so higher proportion of patients in stage IVb group

T Classification p16 negative OPC

T CATEGORY	T CRITERIA
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[b]
T4b	Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

- Unchanged except T0 removed

Clinical N Staging p16 negative OPC

- Similar to prior staging with addition of ENE
  - Automatically N3b
  - Clinically evident ENE (Fixed, deep muscle or skin invasion)

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

Overall Stage p16 negative OPC

	N CATEGORY			
T CATEGORY	N0	N1	N2a,b,c	N3a,b
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB

- Unchanged
  - IVc = M1 disease

HPV Positive OPC Staging

- T Classification:
- Largely unchanged except:
  - Carcinoma in situ (Tis) removed
  - T4b removed

- N Classification:
- Difference between clinical and pathologic staging
  - Clinical staging based on laterality and size of nodes
  - Pathologic staging based on number of nodes
    - Obviously for surgical patients only
  - ENE not included

- M Classification: Unchanged

- Overall Stage: Drastic Change
  - Stage IV reserved for M1 disease

T Classification in p16 positive OPC

- Carcinoma in situ removed
  - Nonaggressive pattern of invasion of p16 + OPC
  - Absence of a distinct basement membrane in the epithelium of Waldeyer's ring

- T4b distinction removed
  - Survival curves of T4a and T4b are indistinguishable

T Staging HPV+ OPC

T CATEGORY	T CRITERIA
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[b]

- T4a/b distinction has been eliminated, as prognostically there is none
- Tis eliminated due to indolent nature of cancer

Clinical N Classification in HPV+ OPC

- Uses information from physical examination/imaging, thus applicable to all patients regardless of treatment plan
- Ipsilateral lymph nodes less than 6 cm in size, regardless of number, had similar impact on survival
  - N1
- Bilateral or contralateral lymph nodes (less than 6 cm, regardless of number) had a worse outcome
  - N2
- Lymph nodes greater than 6 cm had the worst survival
  - N3

Clinical N Classification in HPV+ OPC

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

- Simplified clinical staging
  - Number of lymph nodes no longer significant
    - When radiation is primary modality . . .
  - ENE not included

Pathologic N Classification in HPV+ OPC

- Obviously applicable only to patients who undergo surgery
  - But the data is different . . .
- Neither lymph node size (lymph nodes >6 cm) nor contralateral nodes impacted survival, unlike those patients treated with radiation
- The number of pathologically positive lymph nodes yielded survival differences:
  - 1 to 4 Nodes: N1
  - 5 or more nodes: N2

Pathologic N Classification in HPV+ OPC

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

- ENE not included
- The difference in behavior in N3 neck between cTNM and pTNM data sets, reflecting radiation treatment versus surgical treatment, is unexpected.
- Prospective data collection will be needed to resolve this issue.

Overall Clinical Staging HPV + OPC

	N CATEGORY			
T CATEGORY	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

- Stage IV reserved for M1 disease

Overall Pathologic Staging HPV + OPC

	N CATEGORY		
T CATEGORY	N0	N1	N2
T0	NA	I	II
T1	I	I	II
T2	I	I	II
T3	II	II	III
T4	II	II	III

- Stage III ONLY for bulky tumors (T3/T4) AND multiple nodes (5+)
- Stage IV reserved for M1 disease

Unknown Primary

Changes in Nomenclature and Classification

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Unknown Primary

- Recent data shows up to 90% of unknown primary H&N SCC represents HPV-associated OP SCC
  - Keller LM et al. p16 status, pathologic and clinical characteristics, biomolecular signature, and long-term outcomes in head and neck squamous cell carcinomas of unknown primary. Head & Neck 2014; 36(12):1677-84. **–75%**
  - Motz K et al. Changes in unknown primary squamous cell carcinoma of the head and neck at initial presentation in the era of human papillomavirus. JAMA Oto 2016; 142(3):223-8. **–90%**
- EBER-ISH found to be reliable detector of EBV in WHO II/III nasopharynx carcinoma
  - Mirazamani N et al. Detection of EBV and HPV in nasopharyngeal carcinoma by in situ hybridization. Exp Molec Path 2006; 81(3):231-234.

Unknown Primary

- Recommending HPV-ISH, p16 immunohistochemistry, and EBER-ISH on pathologic analysis of all unknown primary cervical LNs.

- T0 designation being reserved only for virally mediated metastatic carcinoma (i.e. ability to localize subsite by viral expression)
  - HPV + OPC and NPC

- All HPV negative and EBV negative metastatic carcinoma to be staged according to the system detailed in the cervical node and unknown primary guidelines.
  - The primary could be from ANY mucosal or epithelial site.

Nodal Staging

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Pathologic Nodal Staging
OC, HPV(-) OP, Hypopharynx, Larynx

N CATEGORY	N CRITERIA[b]
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; *or* more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative; *or* metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a	Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; *or* metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; *or* metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; *or* metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

- Similar to prior EXCEPT ENE
  - Automatically N3b unless a single small node (N2a)

Definition of Extranodal Extension

- Incorporated a high “bar” of evidence for ENE to prevent “stage migration”
  - Unnecessary upstaging

- Clinical evidence for ENE:
  - Only ***unambiguous*** ENE, as determined by physical examination:
    - eg, invasion of skin, infiltration of musculature/dense tethering to adjacent structures, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve) *and supported by radiological evidence*
    - Radiologic evidence alone is NOT ENOUGH

- Pathologic evidence for ENE:
  - Minor ENE (ENEmi) = extension 2 mm or less from the capsule.
  - Major ENE (ENEma) =
    - either extension apparent to the pathologist’s naked eye and feel
    - >2 mm from the capsule.
    - Soft tissue deposits without nodal architecture
  - **Either is considered ENE for staging purposes**.

Conclusions

- The Head and Neck Section of the 8th Edition of the AJCC Staging Manual introduces significant modifications from 7th Edition.
  - Designed to better prognosticate outcome, plan treatment, and measure differences between staged groups.

- The most significant update creates a separate staging algorithm for HPV+ SCC of the oropharynx.

Conclusions (continued)

- Other modifications include:
  - Reorganizing of non-melanoma skin cancer to a head and neck-specific chapter
  - Division of cancer of the pharynx into 3 separate groups:
    - Nasopharynx (+/- EBV)
    - HPV (–) Oropharynx AND Hypopharynx
    - HPV (+) Oropharynx
  - Changes to the tumor (T) categories for oral cavity, skin, and nasopharynx
  - Changes in classification/nomenclature for unknown primary H&N carcinoma
  - The addition of extranodal extension (ENE) to N stage in all but the viral-related cancers and mucosal melanoma.

Discussion Points

- Oropharynx:
  - What do people think of difference in staging clinically vs. pathologically and lack of N3 disease in pathologic staging?
    - Implications for understaging surgically treated disease (e.g. TORS) vs. patients treated with chemoRT
- Nodal Disease:
  - What do people think of upstaging ECS to N3b?
    - The assumption is this will increase overall stage to IVB.
    - Implications for stage IVB as “surgically incurable” disease.
- Unknown primary:
  - What do people think of change in nomenclature to T0 for viral-mediated “unknown primary” vs. TX for other subsites?