# STAGING IN HNC- TNM AND BEYOND

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Purpose of staging

Principles of staging in HNC

Moving ahead within the TNM and beyond the TNM

# Purpose of staging

Predicting prognosis

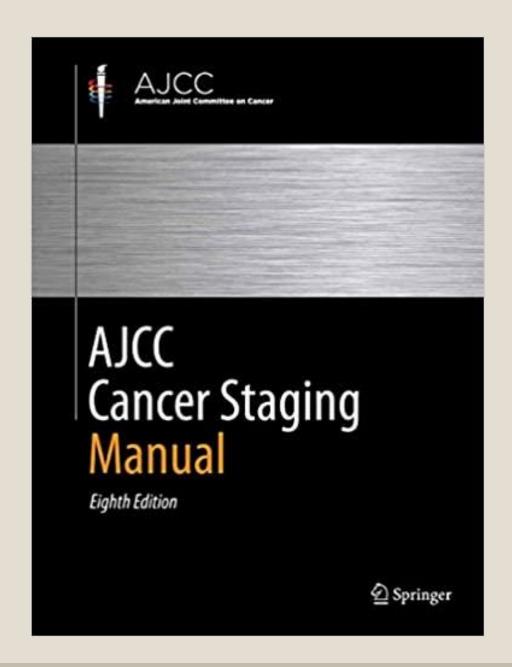
- Guiding treatment decisions (outcomes of previous patients with similar stage)
- key component of inclusion, exclusion, and stratification criteria for clinical trials

 Basis of clinical and translational cancer research (exchange and comparison of info among diff centres and registries)

# TNM staging

AJCC-UICC

I N M



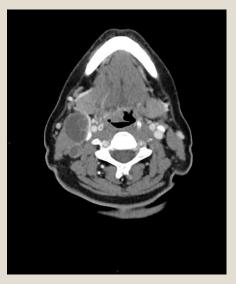
# Principles of staging

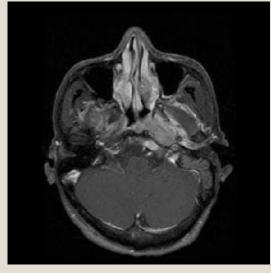
Clinical staging

Pathological staging

# Principles of staging

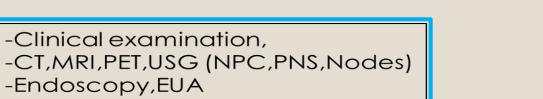
- Clinical staging-
- using best possible estimate of the extent of disease (cTNM)
- before initiation of first treatment.

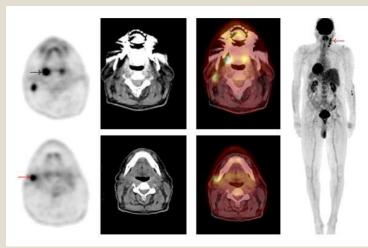












# Principles of staging

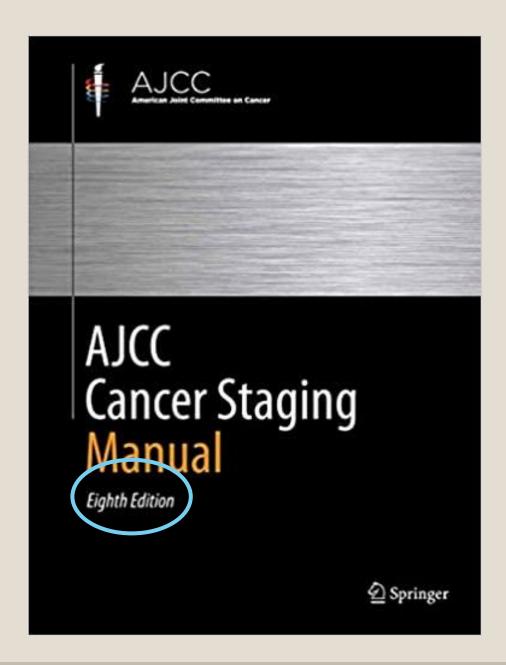
- Additional and important staging, but cannot replace clinical staging.
- Based on clinical stage information supplemented/modified by operative findings and pathological evaluation of the resected specimens (primary and/or nodes)

- Pathological staging
- pT- actual measurement of unfixed tumor in surgical specimen
- pN- If SND- > 10 LN, If RND, MRND > 15 nodes
   But examination of fewer negative nodes will be
   assigned N0 category.
- When biopsy proven mets- pM1

# TNM staging

AJCC-UICC

T N M



# Why revise and move ahead and beyond TNM??

Advancement in what we know-clinical and pathological data, diagnostic/imaging modalities, treatment modalities

Prognostic significance of staging systems change



Evaluate for suitability of staging systems

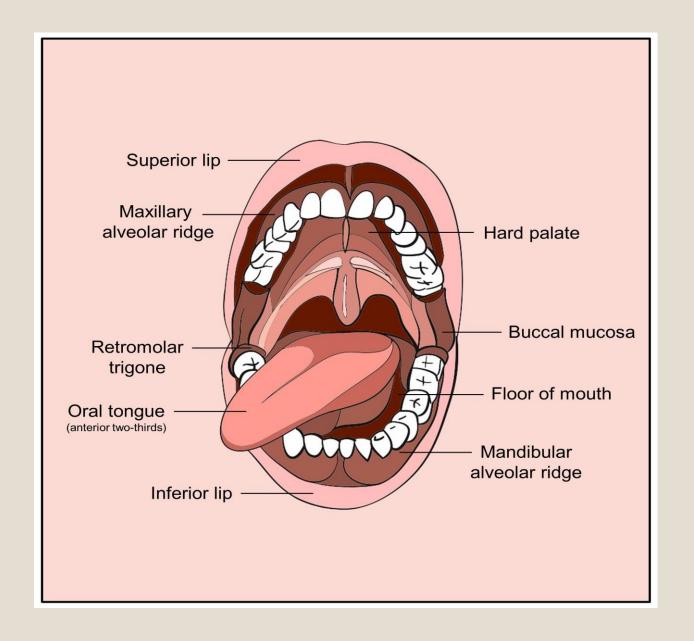


Further exploration

#### Part II Head and Neck

5.	Staging Head and Neck Cancers
6.	Cervical Lymph Nodes and Unknown Primary Tumors of the Head and Neck
7.	Lip and Oral Cavity.
8.	Major Salivary Glands
9.	Nasopharynx
10.	HPV-Mediated (p16+) Oropharyngeal Cancer
11.	Oropharynx (p16–) and Hypopharynx
12.	Nasal Cavity and Paranasal Sinuses
13.	Larynx
14.	Mucosal Melanoma of the Head and Neck
15.	Cutaneous Squamous Cell Carcinoma of the Head and Neck





Mucosal Lip

Depth of Invasion

Extranodal extension



**Mucosal Lip-** vermilion surface or that portion of the lip that comes into contact with the opposed lip

Hay, A., Shah, J. (2020). Staging of Oral Cancer. In: Warnakulasuriya, S., Greenspan, J. (eds) Textbook of Oral Cancer. Textbooks in Contemporary Dentistry. Springer, Cham. https://doi.org/10.1007/978-3-030-32316-5\_6

## Depth of invasion

SCIENTIFIC PAPERS

Predictive Value of Tumor Thickness in Squamous Carcinoma Confined to the Tongue and Floor of the Mouth

Ronald (. Spiro, MD, Andrew G. Huvos, MD, George Y. Wong, PhD, Jeffrey D. Spiro, MD, Clare A. Gnecco, MS, and Elliot W. Strong, MD. New York, New York

From the Head and Neck Service, Departments of Surgery and Pathology, and the Division of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York.

Requests for reprints should be addressed to Ronald H. Spiro, MD, 425 East 67th Street, New York, New York 10021.

Presented at the 32nd Annual Meeting of the Society of Head and Neck Surgeons, Colorado Springs, Colorado, May 7-10, 1986.

Volume 152, October

JAMA Otolaryngology-Head & Neck Surgery | December 2014 | Volume 140, Number 12

Original Investigation

Primary Tumor Staging for Oral Cancer and a Proposed Modification Incorporating Depth of Invasion An International Multicenter Retrospective Study

The International Consortium for Outcome Research (ICOR) in Head and Neck Cancer

### International Consortium for Outcomes Research in Head and **Neck Cancer**

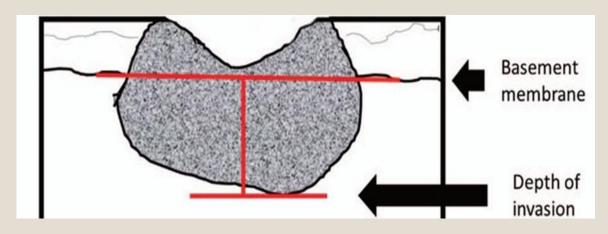
- Retrospective analysis
- 3149, 11 centres, oral SCC
- Median followup 40 months

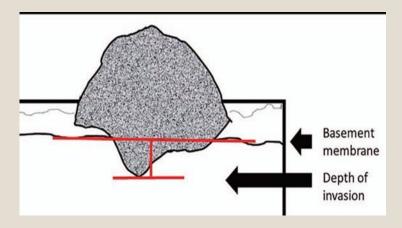
DOI was a significantly associated with diseasespecific survival (P < .001)

Proposed an improved oral cancer T staging system based on incorporation of DOI

# Depth of invasion

- Deepest level of Invasion beneath the plane defined by surrounding normal mucosa
- Not the same as tumor thickness (exophytic portion)





https://www.researchgate.net/profile/Lester-Thompson-3

16

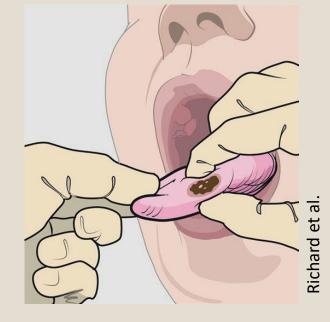
## Can we predict DOI before pathological examination??

History - dysphagia (sufficient invasion of oral structures)

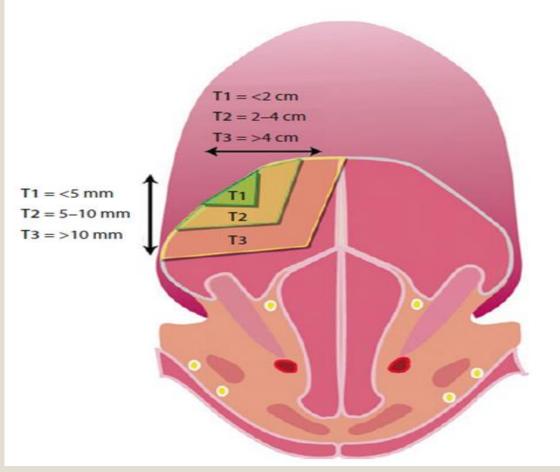
- drooling, swallowing with difficulty
- trismus (not caused by pain)

Clinically – (by bidigital\*, bimanual\* palpation)

- crude measure







Richard et al. Jatin Shah's head and neck surgery and oncology. 5thed. Elsevier;2020

DOI increases T category by 1 for each 5 mm of tumor depth (until ≥ 10 mm)

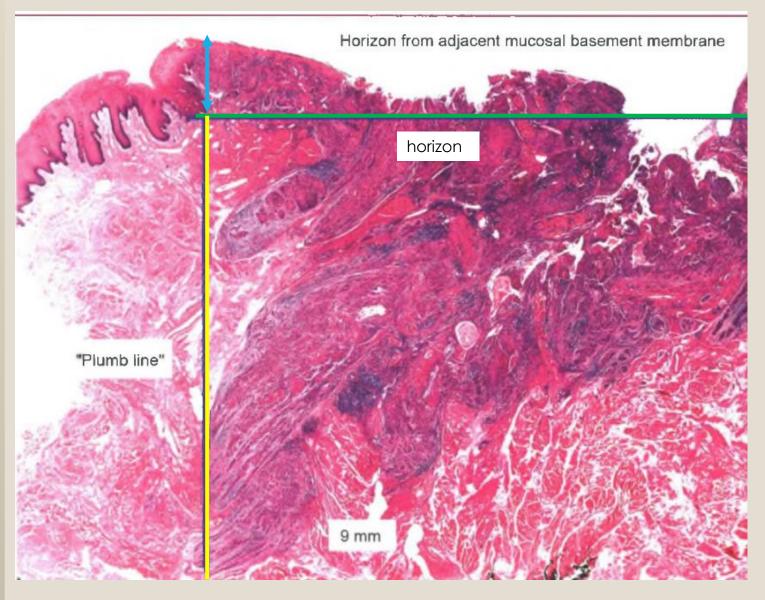
Even experienced clinicians may have difficulty in differentiating

Superficial and less invasive lesion(< 5mm)

Moderate depth (>5, < 10mm)

Deeply invasive lesion (>10mm)

-if there are doubts----- select the lesser depth to avoid stage migration



- The **horizon** is established at the level of the basement membrane relative to the closest intact squamous mucosa.
- -dropping a "**plumb line**" perpendicular from the horizon to determine the greatest DOI.
- -recorded in mm.
- Increases T category by 1 for each 5 mm of tumor depth (until ≥ 10 mm)

## Extranodal extension

Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma

Volkert B. Wreesmann MD, PhD,¹ Nora Katabi, MD,² Frank L. Palmer, BA,¹ Pablo H. Montero, MD,¹ Jocelyn C. Migliacci, MA,¹ Mithat Gönen, PhD,³ Diane Carlson, MD,⁴ Ian Ganly, MD, PhD,¹ Jatin P. Shah, MD,¹ Ronald Ghossein, MD,² Snehal G. Patel, MD¹\*

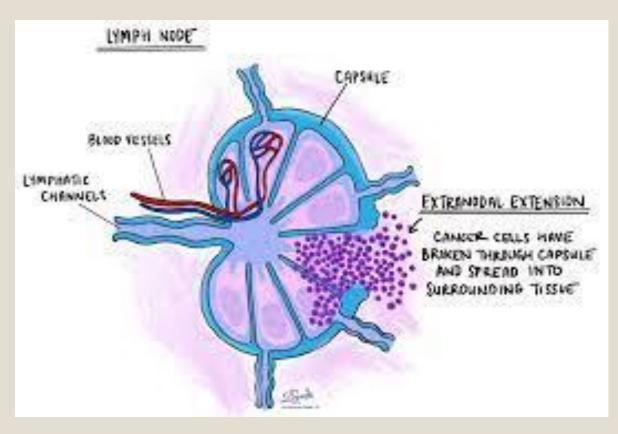
<sup>1</sup>Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, <sup>2</sup>Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York,

Accepted 3 July 2015

Published online 30 October 2015 in Miley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24190

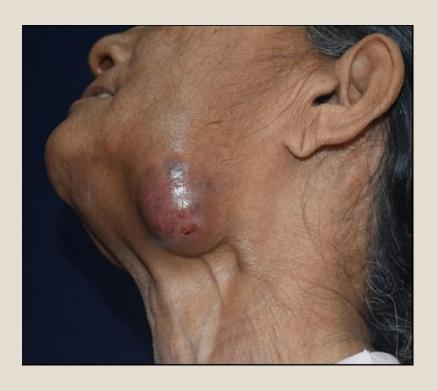
- Pathological review of 245 pathologically +ve neck dissection specimens of oral SCC
- 73 months follow-up
- DSS was significantly
- better for patients without ECS than patients with ECS (p<0.01)</li>

## Extranodal extension



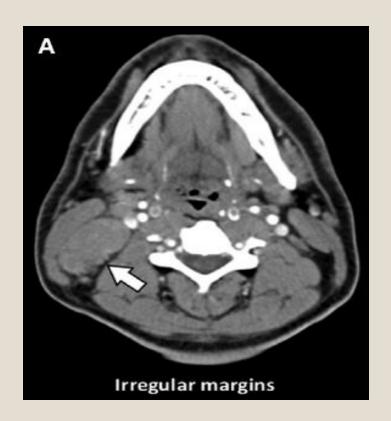
## ENE for cN

- Assignment of ENE should be based almost entirely on physical examination, rather than imaging.
- Unambiguous Gross ENE on clinical exam supported by strong radiological evidence.



- multiple matted nodes
- fixed nodes
- skin invasion
- muscle invasion
- infiltration of cranial nerve, brachial plexus, sympathetic trunk, phrenic nerve

- Irregular enhancement of the nodal capsule (amorphous spiculated margins
- Infiltration into adjacent fat/muscle (involvement of internodal fat resulting in loss of normal oval to round nodal shape)

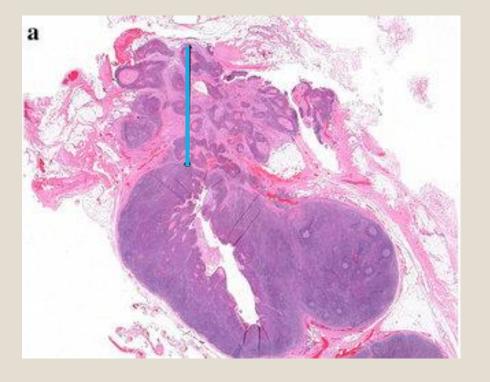






Faraji F, Aygun N, Coquia SF, et al. Computed tomography performance in Laryngoscope. 2020;130(6):1479-1486. doi:10.1002/lary.28237

# ENE for pN



Bullock MJ. Current Challenges in the Staging of Oral Cancer. Head Neck Pathol. 2019;13(3):440-448. doi:10.1007/s12105-

- ENEmi microscopic ENE ≤ 2mm
- ENEma- Macroscopic ENE-
  - ENE apparent to naked eye at the time of dissection
  - OR microscopic ENE >2mm beyond the LN capsule

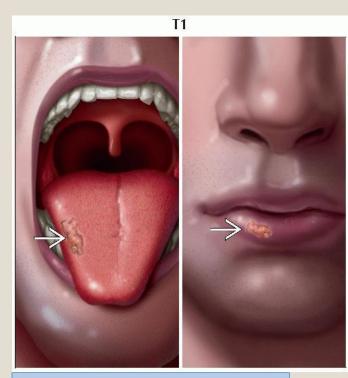
ENE HAS BEEN INCORPORATED IN ALL HEAD AND NECK CANCER SITES EXCEPT NASOPHARYNGEAL CANCER AND HPV ASSOCIATED P16+ OPC

Tx

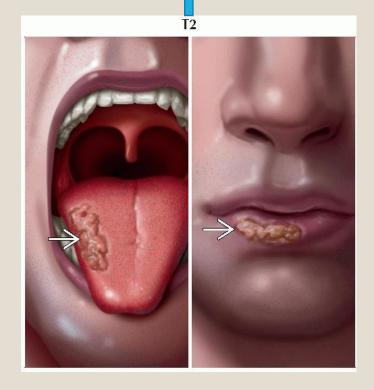
Tis

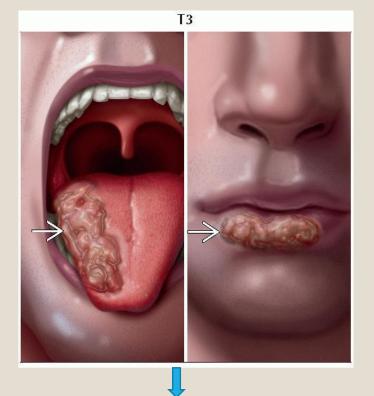
Tumor  $\leq$  2 cm, DOI > 5 mm and  $\leq$  10 mm or

tumor > 2 cm but  $\le 4$  cm, and  $\le 10$  mm DOI



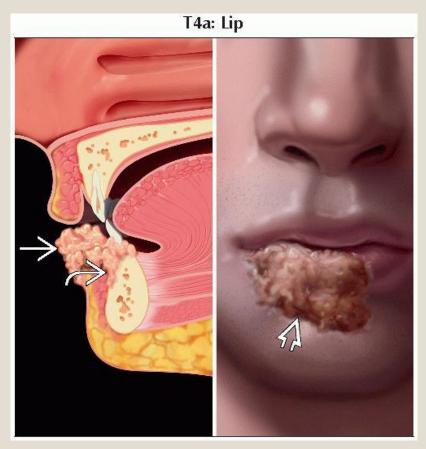
Tumor  $\leq 2 \text{ cm}$ ,  $\leq 5 \text{ mm depth of invasion}$ (DOI)





Tumor>4 cm or any tumor> 10 mm DOI

#### T4a- moderately advanced local disease



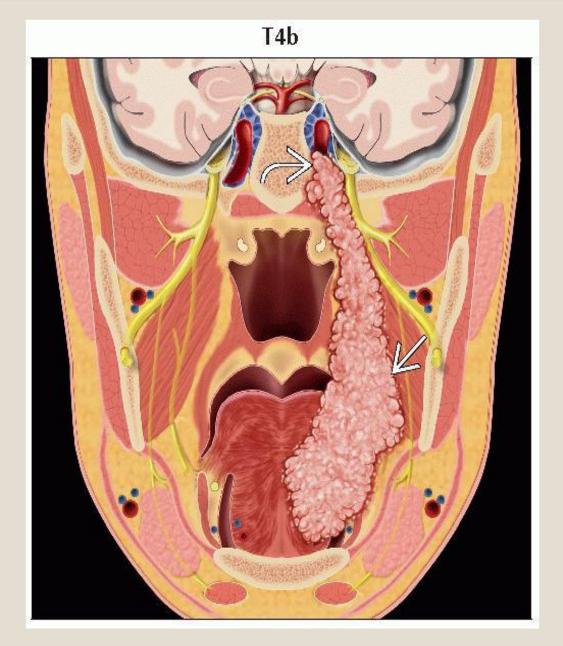
lip-cortical bone, skin of the face, inferior alveolar nerve, floor of mouth

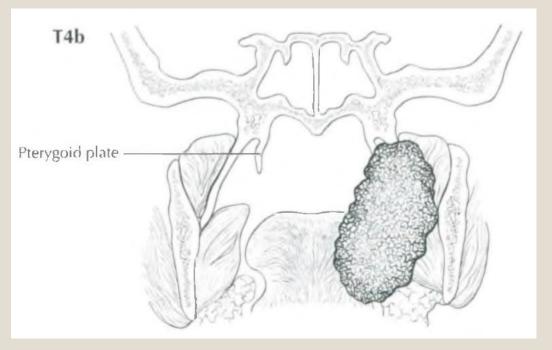
#### T4a-oral cavity





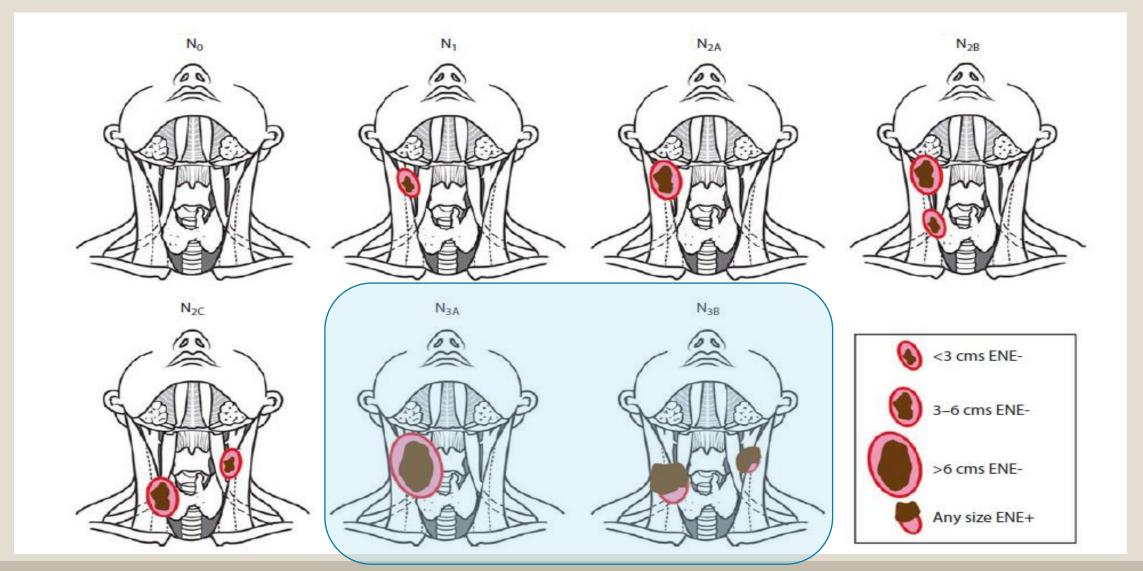
Adjacent structures only- eg- through cortical bones of mandible, maxilla into the maxillary sinus or skin of the face. A superficial erosion of bone/tooth socket (alone) by a primary in the gingiva is not T4a





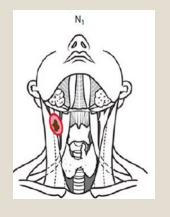
T4b- very advance local disease- pterygoid plates, masticator space, skull base, encases ICA

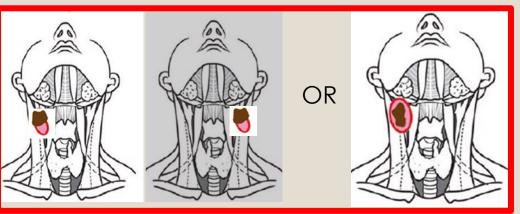
# cN categories

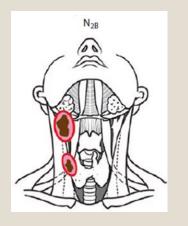


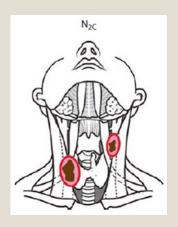
# pN categories



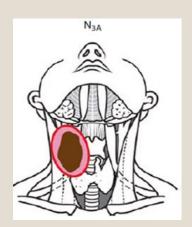


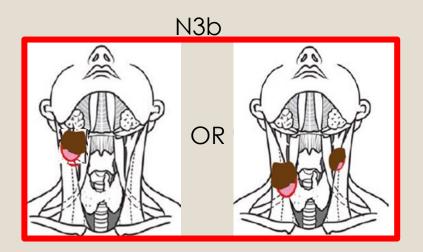






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## Survival data

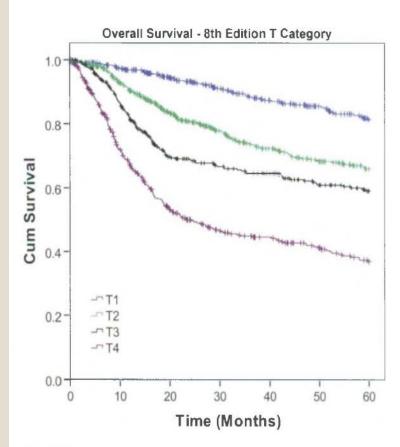


Fig. 5.2 Overall Survival based on 8th edition T category criteria. Kaplan Meier methods were used to perform cancer-specific analyses predicting overall survival as the endpoint on a population of oral cavity cancer patients from MSKCC and PMH

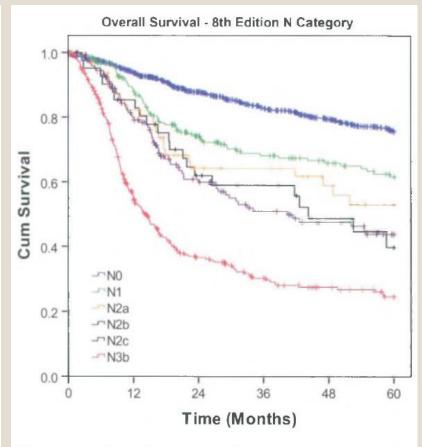


Fig. 5.4 Overall Survival based on 8th edition N category criteria that incorporate ENE as a prognostic factor. Kaplan Meier methods were used to perform cancer-specific analyses predicting overall survival as the endpoint on a population of oral cavity cancer patients from MSKCC and PMH

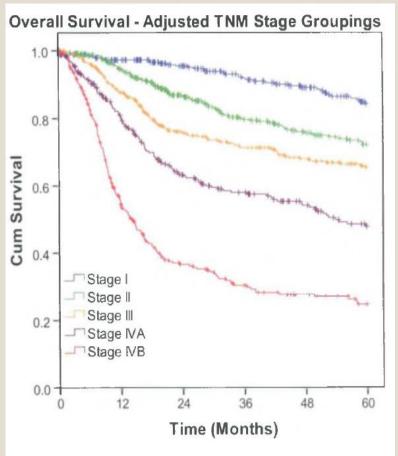
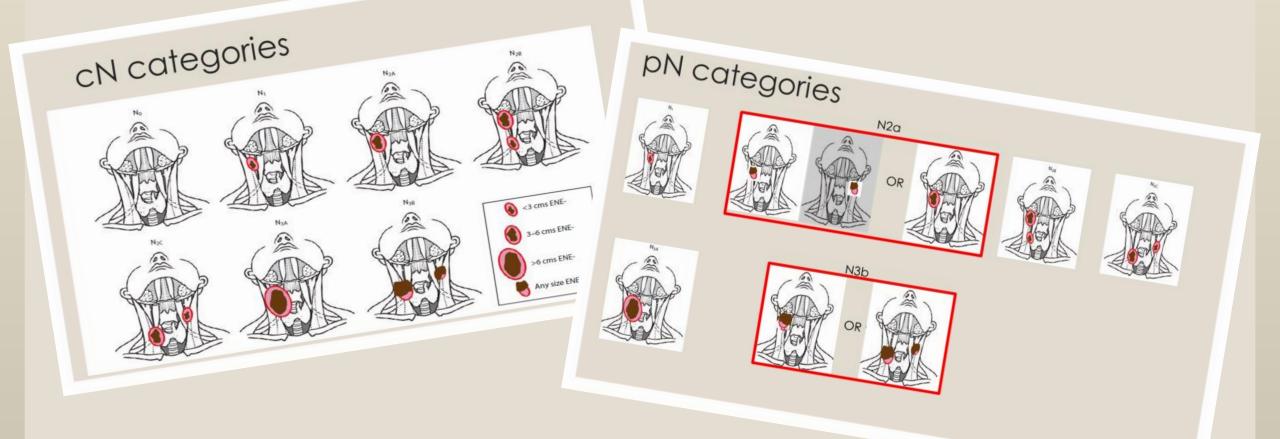


Fig. 5.6 Overall Survival based on Kaplan Meier methods were used to perform cancer-specific analyses predicting overall survival as the endpoint on a population of oral cavity cancer patients from MSKCC and PMH15

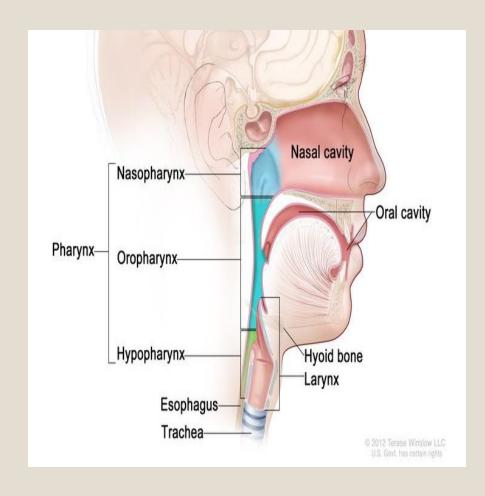


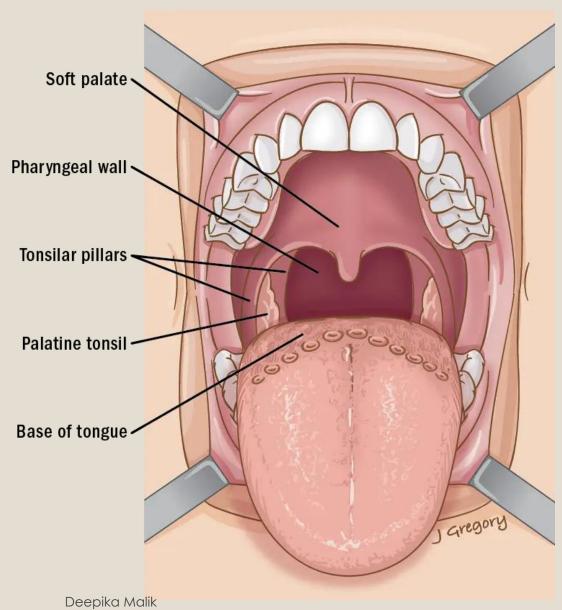
ALL HEAD AND NECK CANCER SITES EXCEPT

NASOPHARYNGEAL CANCER AND HPV ASSOCIATED

P16+ OPC

# HPV MEDIATED (P16+) OROPHARYNGEAL CANCER\*





# Why a separate staging system?

- Epidemic of HPV mediated OPC over the last 2 decades (of 5%/year)
- Significantly different behaviour and natural history of disease
  - > YOUNGER
  - > HEALTHIER
  - > LITTLE OR NO TOBACCO EXPOSURE





#### IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

#### VOLUME 90 Human Papillomaviruses



2007

 Particularly over the last 15 years, since the official recognition of viral cause of OPC by WHO in 2007, evidence emerged that the previous staging system was unsuited to this particular group

### p16

IHC for p 16 overexpression has emerged as a robust surrogate biomarker for HPV-mediated carcinogenesis

{Overexpression of tumor suppressor protein p16 (cyclin-dependent kinase 2 A)}

- Lower cost
- Widespread availability
- Ease of interpretation
- Independent positive prognosticator



# Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study

Brian O'Sullivan, Shao Hui Huang, Jie Su, Adam S Garden, Erich M Sturgis, Kristina Dahlstrom, Nancy Lee, Nadeem Riaz, Xin Pei, Shlomo A Koyfman, David Adelstein, Brian B Burkey, Jeppe Friborg, Claus A Kristensen, Anita B Gothelf, Frank Hoebers, Bernd Kremer, Ernst-Jan Speel, Daniel W Bowles, David Raben, Sana D Karam, Eugene Yu, Wei Xu

www.thelancet.com/oncology Published online February 26, 2016

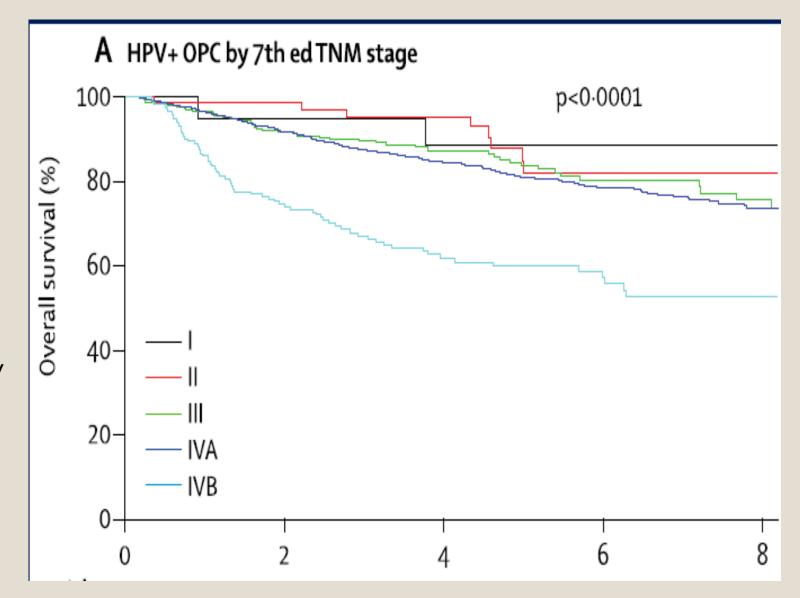
o 2600 patients, 190	O7 HPV +	
∘ 5 year OS		HPV +ve
Stage I	76%	88%
Stage II	68%	82%
Stage III	53%	84%
Stage IVA	45%	81%
Stage IVB	34%	60%

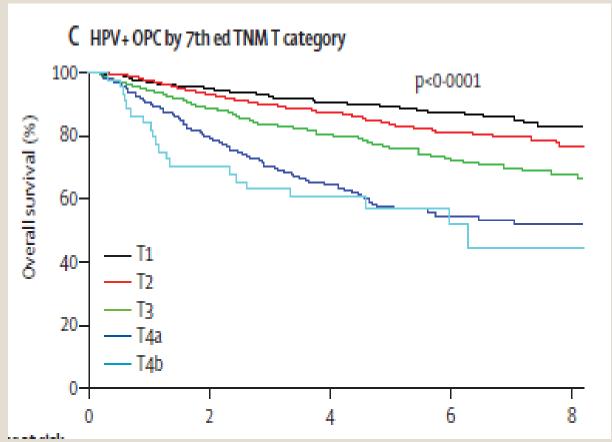
### The 7th edition

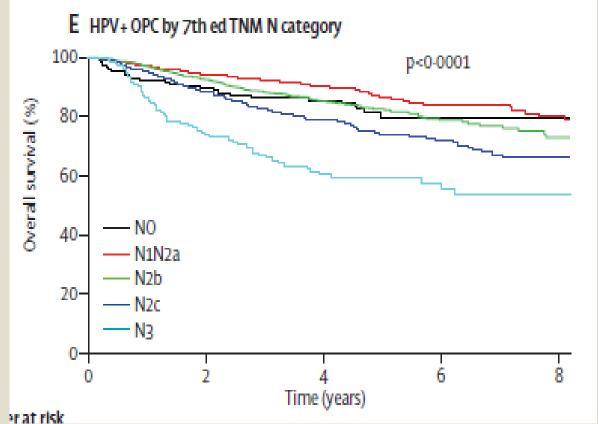
-lost the ability to differentiate between stages -Hazard discrimination

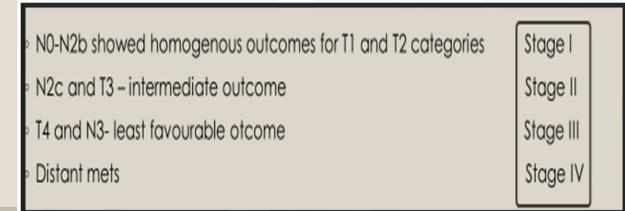
-lost hazard consistency

-Loss of predictive ability

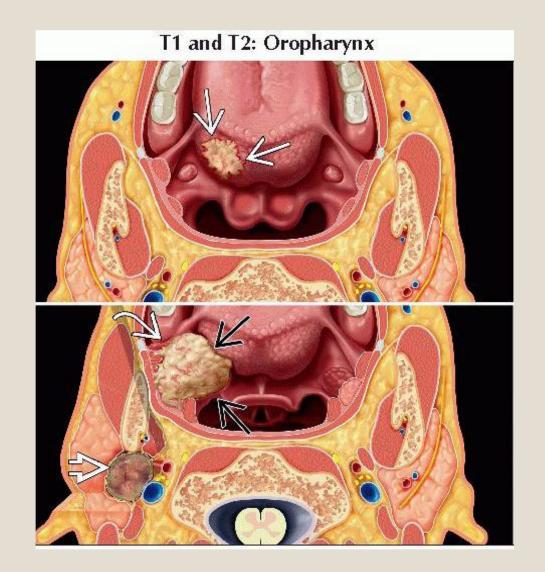


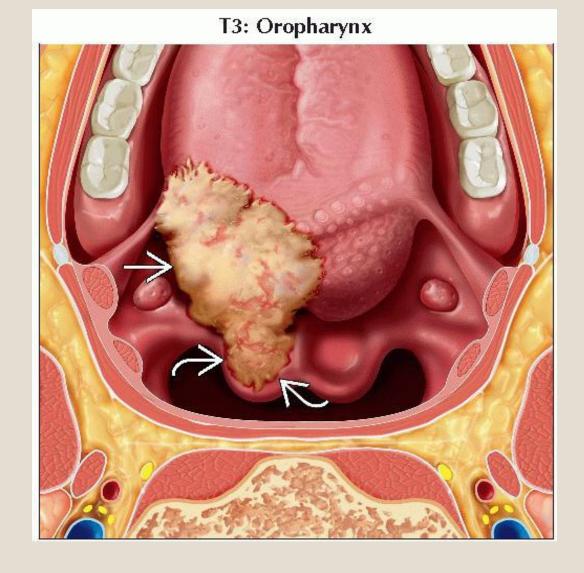


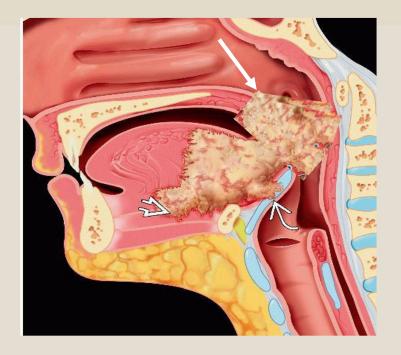


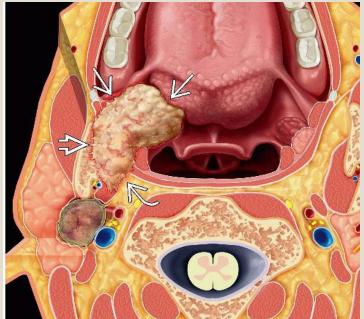


48% of seventh edition TNM stage III-IV would migrate to eight edition TNM stage I







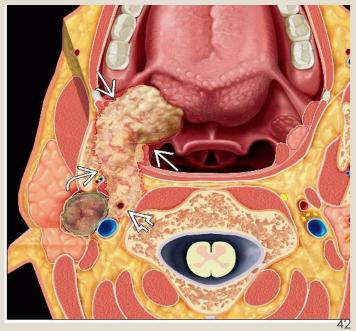


### **T4**

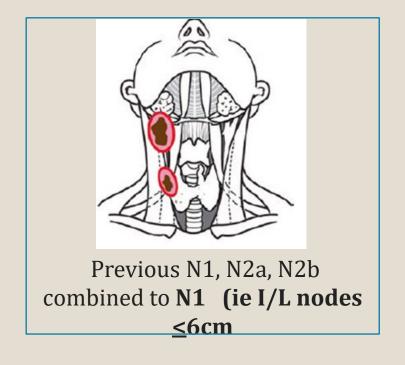
#### Tumor invades the

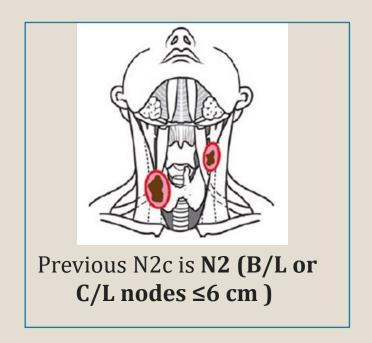
- larynx,
- extrinsic muscle o f tongue,
- medial pterygoid,
- hard palate
- mandible or beyond

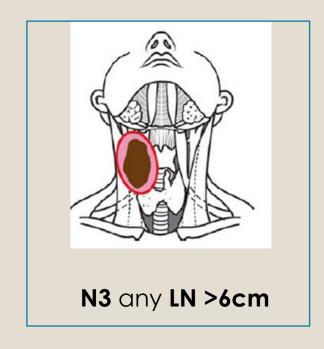




### Nodal







Role of ENE is less obvious in p16+ OPC, therefore not a factor in staging

# Pathological p16+ OPC

Oral Oncology 51(2015)514-520



Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology



High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer



Parul Sinha <sup>a</sup>, Dorina Kallogjeri <sup>a,b</sup>, Hiram Gay <sup>c</sup>, Wade L. Thorstad <sup>c</sup>, James S. Lewis Jr. <sup>a,d</sup>, Rebecca Chernock <sup>a,d</sup>, Brian Nussenbaum <sup>a</sup>, Bruce H. Haughey <sup>a,\*</sup>

Nx- regional LN cannot be assessed

pN0- no regional LN mets

pN1- mets in  $\leq$  4 LNs

pN2- mets in > 4 LNs

<sup>&</sup>lt;sup>a</sup> Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO, United States

<sup>&</sup>lt;sup>b</sup> Clinical Outcomes Research, Washington University School of Medicine, St. Louis, MO, United States

<sup>&</sup>lt;sup>c</sup> Radiation Oncology, Washington University School of Medicine, St. Louis, MO, United States

d Pathology, Washington University School of Medicine, St. Louis, MO, United States

#### AJCC PROGNOSTIC STAGE GROUPS

#### Clinical

When T is	And N is	And M is	Then the stage group is	
T0, T1 or T2	N0 or N1	M0	1	
T0, T1 or T2	N2	MO	II	
T3	N0, N1 or N2	M0	II	
T0, T1, T2, T3 or T4	N3	M0	III	
T4	N0, N1, N2 or N3	M0	III	
Any T	Any N	MI	IV	

### **Pathological**

When T is	And N is	And M is	Then the stage group is		
T0, T1 or T2	NO, N1	M0	1		
T0, T1 or T2	N2	M0	II		
T3 or T4	N0, N1	MO	II		
T3 or T4	N2	M0	III		
Any T	Any N	MI	IV		

# Important considerations\*

✓Only radiological imaging may not help in distinguishing whether the BOT tumor is extending along mucosa of lingual surface of epiglottis (T3) or it is only abutting against it.

**NEED Direct Clinical observation** 

- ✓ When skull base involved , important to carefully evaluate for PNI
  and intracranial spread of disease. Important for radiation planning
- ✓RPN to be carefully evaluated for OPC especially for PPW tumor Unless cystic or necrotic, RPN appear isodense to adj prevertebral muscles on CT, easily overlooked

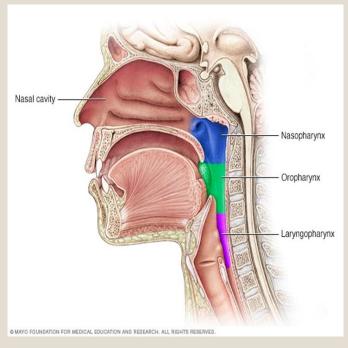


# NPC- a unique HNC

- Natural behaviours
- Therapeutic considerations
- Staging

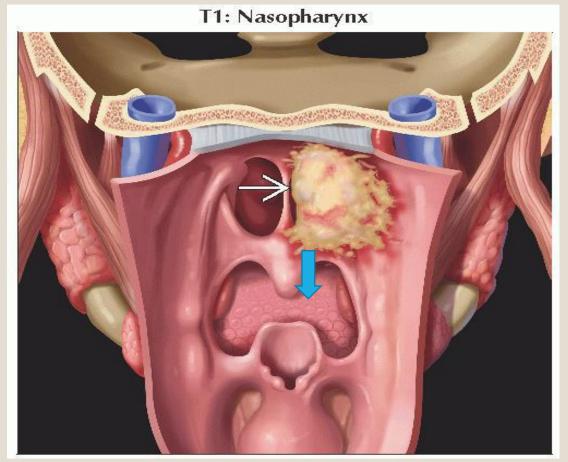
AJCC/UICC
Chinese systems

Ho's staging from Hongkong

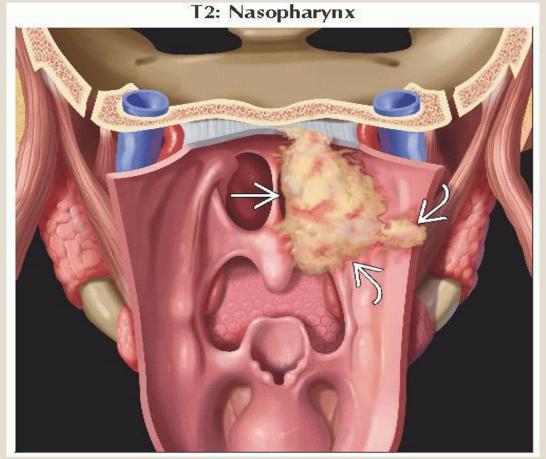


8th AJCC NPC staging

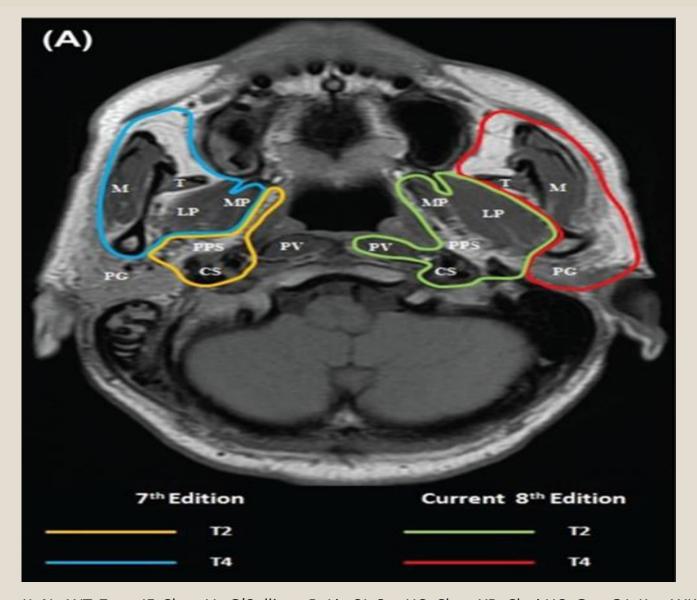
### T0- no tumor identified, but EBV +ve cervical nodal involvement



Tm confined to the nasopharynx. Tumor that extends to the oropharynx &/or nasal cavity without parapharyngeal extension

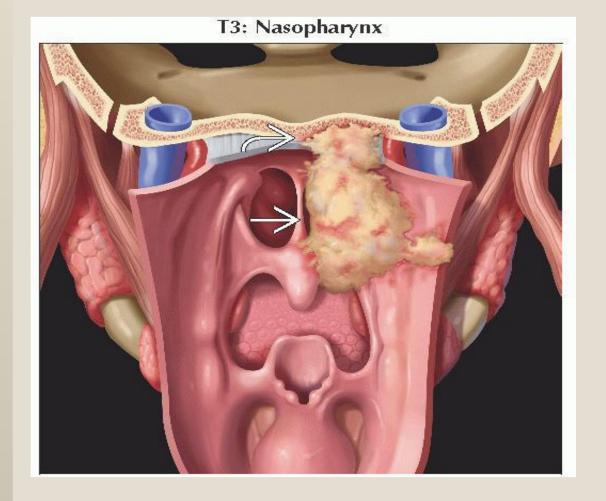


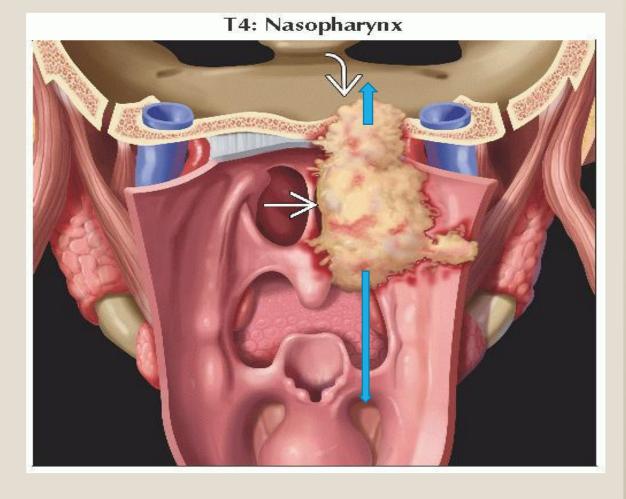
Tm with parapharyngeal space extn and/or adjacent soft tissue involvement (medial pterygoid, LP, Prevertebral muscles)



Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, Sze HC, Chen YB, Choi HC, Guo QJ, Kan WK, Xiao YP, Wei X, Le QT, Glastonbury CM, Colevas AD, Weber RS, Shah JP, Lee AW. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy.

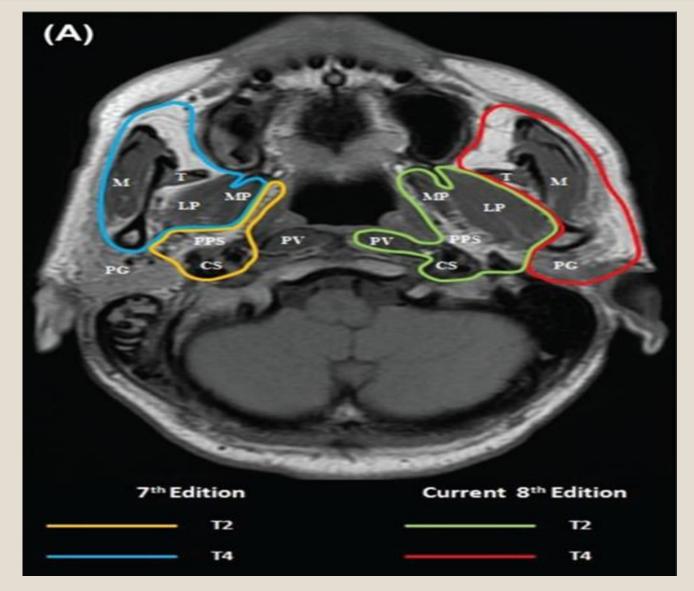
Cancer. 2016 Feb 15;122(4):546-58. doi: 10.1002/cncr.29795. Epub 2015 Nov 20. PMID: 26588425; PMCID: PMC4968037.





Infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses

Intracranial, hypophx, cranial nerves, orbit, parotid gland and/or soft tissue inv beyond the lateral surface of LP muscle

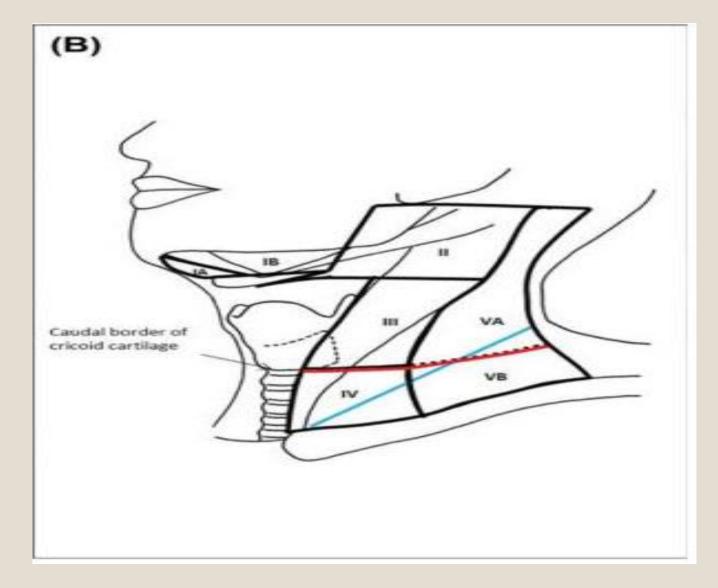


In T4, the original "infratemporal fossa/masticator space" is replaced by specific description of soft tissue involvement BEYOND THE LATERAL SURFACE OF LP MUSCLE to avoid potential ambiguity

Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, Sze HC, Chen YB, Choi HC, Guo QJ, Kan WK, Xiao YP, Wei X, Le QT, Glastonbury CM, Colevas AD, Weber RS, Shah JP, Lee AW. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy.

Cancer. 2016 Feb 15;122(4):546-58. doi: 10.1002/cncr.29795. Epub 2015 Nov 20. PMID: 26588425; PMCID: PMC4968037.

Deepika Malik



- The previous N3b criterion of "supraclavicular fossa" is now changed to "below caudal border of cricoid cartilage"
- N3a and N3b are merged into a single N3

Pan JJ, Ng WT, Zong JF, Chan LL, O'Sullivan B, Lin SJ, Sze HC, Chen YB, Choi HC, Guo QJ, Kan WK, Xiao YP, Wei X, Le QT, Glastonbury CM, Colevas AD, Weber RS, Shah JP, Lee AW. Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 2016 Feb 15;122(4):546-58. doi: 10.1002/cncr.29795. Epub 2015 Nov 20. PMID: 26588425; PMCID: PMC4968037.

Seventh edition		Eighth edition	
IVC	Any T, any N M1		
Summary of changes			
	T category		
To is added for EBV-positive cervical node(s) involvement despite unidentified primary tumor			
Involvement of medial pterygoid, lateral pterygoid, and pre-	evertebral muscles is now staged as T2		
• In T4, the original "infratemporal fossa/masticator space" is replaced by specific description of soft tissue involvement to avoid potential ambiguity			
N category			
The previous N3b criterion of "supraclavicular fossa" is now changed to "below caudal border of cricoid cartilage"			
N3a and N3b are merged into a single N3	Stage group		
The previous Stages IVA and IVB are merged into IVA     The previous IVC is now upstaged to IVB			

# Changes to T0 category

- Elimination of the T0 category for all oral cavity, skin, larynx, salivary gland, HPV oropharynx, hypopharynx, and sinus.
- For patients with a malignant cervical node, with no known primary-needs to be staged according to the staging for unknown primary with neck node
- >T0 category is retained for 2 scenarios-

Node is positive for p16 >>> p16+ OPC staging

Node is positive for EBV → NPC staging

### Cutaneous SCCof the Head and Neck

- A new staging classification in the 8<sup>th</sup> edition
- Cutaneous squamous cell carcinoma (CSCC) and other nonmelanoma skin carcinomas of the head and neck (except Merkel cell carcinoma [MCC]) (including the dry vermilion part of lip)\*

TX I	Primary	tumor	cannot	be	ident	ified
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Tis Carcinoma in situ

TI Tumor smaller than 2 cm in greatestdimension

T2 Tumor 2 cm or larger, but smaller than 4 cmin greatest dimension

Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion\*

Tumor with gross cortical bone/marrow. skull base invasion and/or skull base foramen invasion

T4a Tumor with gross cortical bone/marrow invasion

T4b Tumor with skull base invasion and/or skull base foramen involvement

### Why look further BEYOND traditional TNM??

#### Cancer cachexia update in head and neck cancer: Pathophysiology and treatment

Marion E. Couch, MD, PhD, MBA,<sup>1\*</sup> Kim Dittus, MD, PhD,<sup>2</sup> Michael J. Toth, PhD,<sup>3</sup> Monte S. Willis, MD, PhD,<sup>4</sup> Denis C. Guttridge, PhD,<sup>5</sup> Jonathan R. George, MD,<sup>6</sup> Eric Y. Chang,<sup>7</sup> Christine G. Gourin, MD,<sup>8</sup> Hirak Der-Torossian, MD, MPH<sup>1</sup>

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Accepted 11 March 2014

Published online 7 April 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23696

Research

#### Original Investigation

Prognostic Importance of Comorbidity and the Association Between Comorbidity and p16 in Oropharyngeal Squamous Cell Carcinoma

S. Andrew Skillington, BA; Dorina Kallogjeri, MD, MPH; James S. Lewis Jr, MD; Jay F. Piccirillo, MD

## ASSOCIATION BETWEEN DEPRESSION AND SURVIVAL OR DISEASE RECURRENCE IN PATIENTS WITH HEAD AND NECK CANCER ENROLLED IN A DEPRESSION PREVENTION TRIAL

Kathryn E. Lazure, MPAS,<sup>1</sup> William M. Lydiatt, MD,<sup>2,3</sup> David Denman, MD,<sup>3</sup> William J. Burke, MD<sup>4</sup>

Accepted 3 October 2008

Published online 23 March 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.21046

WPOI PNI Smoking status Grade

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# Future of HN cancer staging- moving further beyond TNM

#### **Limitations** of Current system

- Unable to easily adapt to advances in understanding of cancer biology and incorporate new prognostic variables as they become available
- Static system- unable to use subsequent events in the course of disease
- Still a population based approached, not personalised
- Main end point is OS

### Precisión Medicine Core (PMC) of the AJCC

- Risk Models for Individualized Prognosis in the Practice of Precisión Oncology
- Work on prognostication models rather than prognostic classifiers with the belief than individualized predictions are more accurate and more useful for clinical decision making.
- Prognostication tools were identified in the form of equations, equations and risk scores, equations and calculators, nomograms, risk scores, and other presentations.

AJCC cancer staging 8th edition

### TAKE HOME MESSAGE

Oral cavity cancers have inclusion of DOI

OPC's are distinguished by **p16** IHC

Inclusion of ENE for all sites (except NPC and p16+ OPC)

### Further reading-

- -Risk Models for Individualized Prognosis in the Practice of Precision Oncology, chapter 4, AJCC 8<sup>th</sup> edition
- -Kattan MW. Hess KR. Amin MB. et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA: acancer jo um a l fo r clinicians*. Jan 19 2016.

