2018 Update on Radiation Treatment for Head/Neck Cancer

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Conflict of Interest

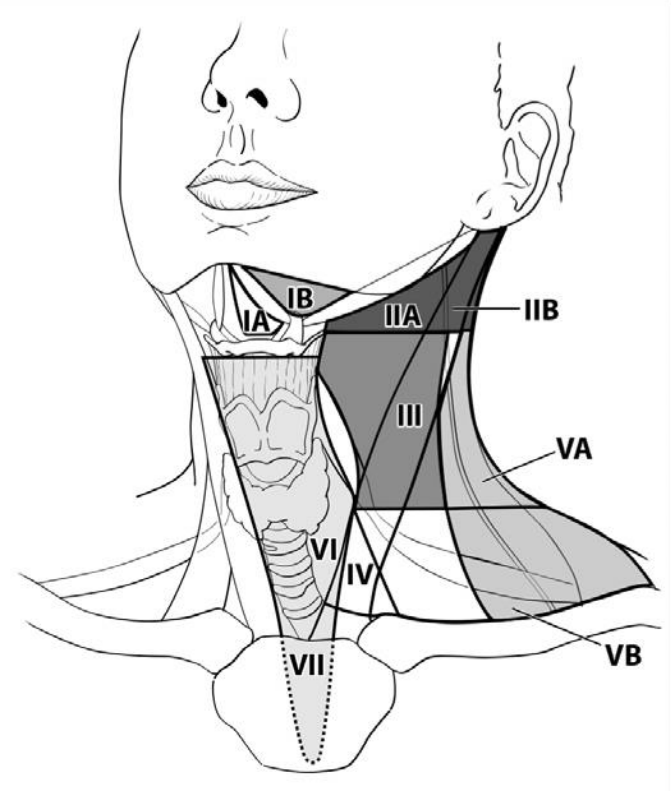
- EMD Serono—Consultant

Learning Objectives

1. Understand the basic treatment pathways that guide management of head/neck cancer cases (oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, major salivary glands) including the roles of surgery, radiation therapy and use of systemic agents
2. Become familiar with the new AJCC staging system for HPV-associated oropharynx cancers
3. Improve technical competence in planning head/neck IMRT cases
4. Improve understanding of the use of leading edge head/neck cancer technologies (proton RT, immunotherapy)

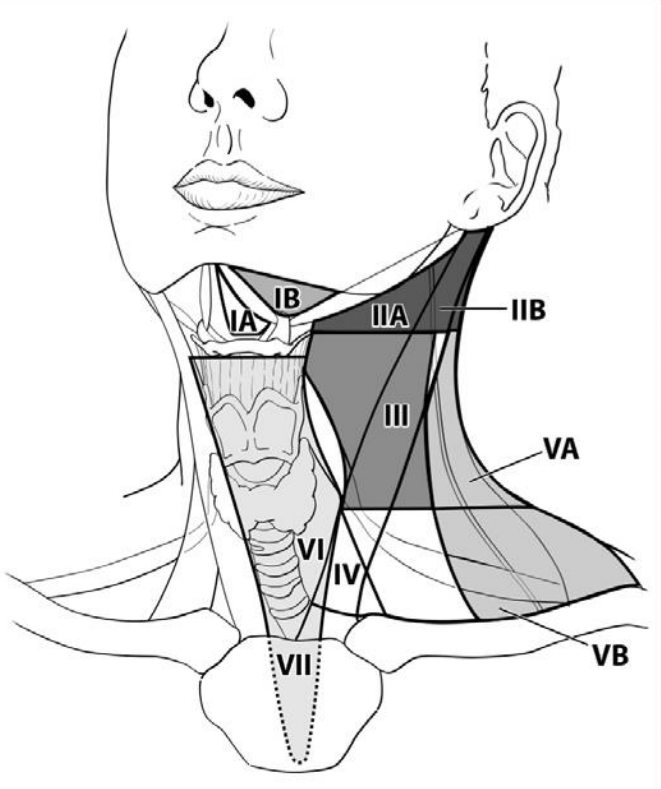
Neck Nodal Levels

Neck Nodal Levels



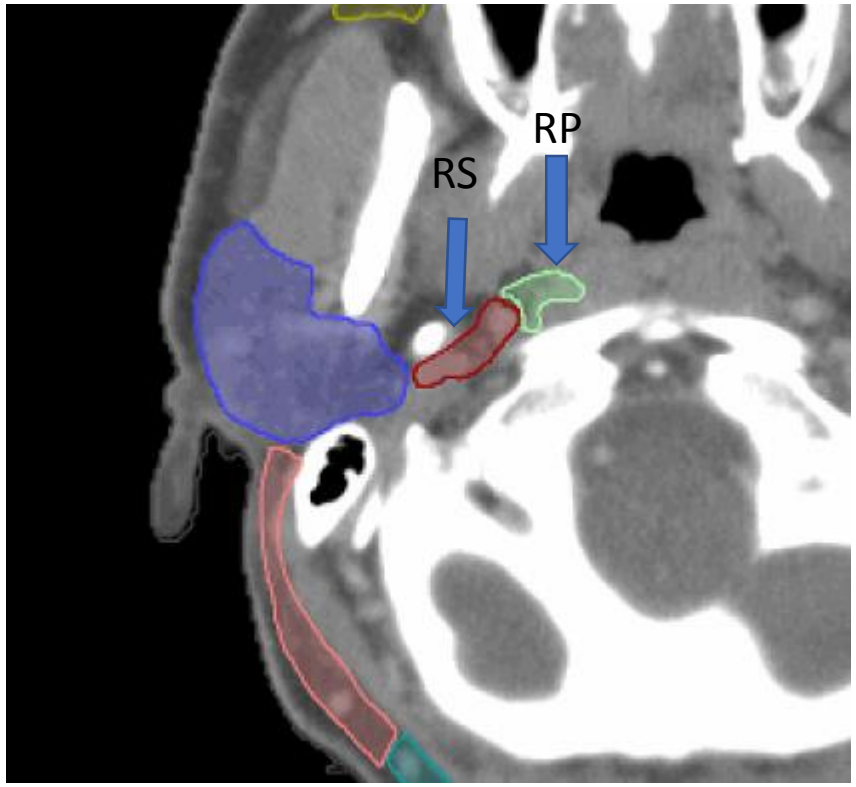
- Ia: Submental
  - Between anterior bodies of digastric muscles
  - Drains lower lip, chin and (secondary drainage for) anterior tongue
- Ib: Submandibular
  - From upper to lower margin of submandibular gland, medial to mandible and lateral to digastric muscle
  - Drains oral cavity and lower nasal cavity

Neck Nodal Levels



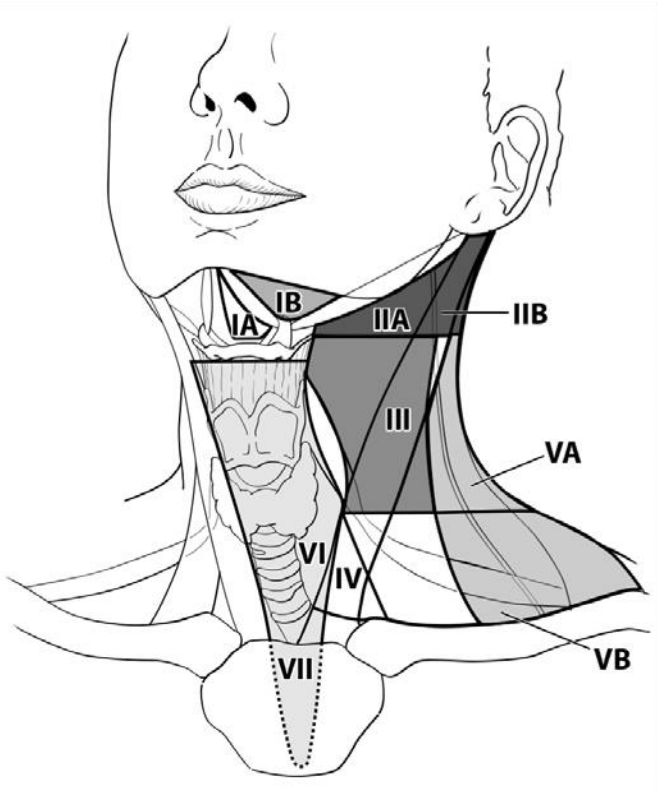
- II: Upper Jugular
  - From underside of lateral process of C1 to hyoid, medial to SCM, lateral to scalene muscles. Divided into IIA and IIB by the posterior border of the IJV.
  - Drains most HN sites
    - Nasal cavity
    - Nasopharynx
    - Oropharynx
    - Oral cavity (secondary)
    - Larynx
    - Hypopharynx
    - Major salivary glands

Neck Nodal Levels



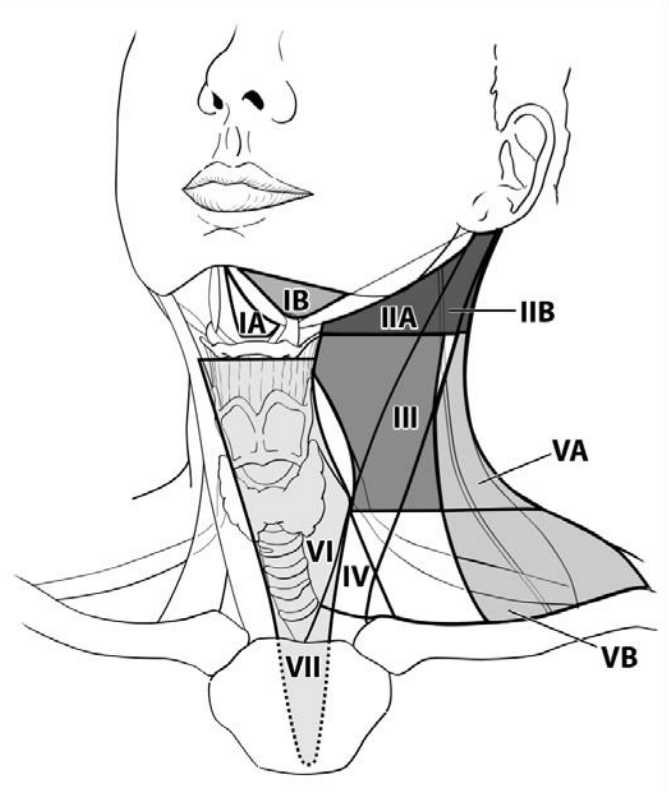
- VIIa: Retrostyloid ("high level II")
  - Tissue surrounding carotid/jugular vascular bundle, from jugular foramen to upper border of level II
  - Drains nasopharynx
  - Retrograde drainage pathway for bulky involvement of level II
- VIIb: Retropharyngeal
  - From top of C1 to body of hyoid, between constrictors and longus colli/longus capitis muscles
  - Drains nasopharynx, soft palate, tonsillar fossa, posterior pharyngeal wall

Neck Nodal Levels



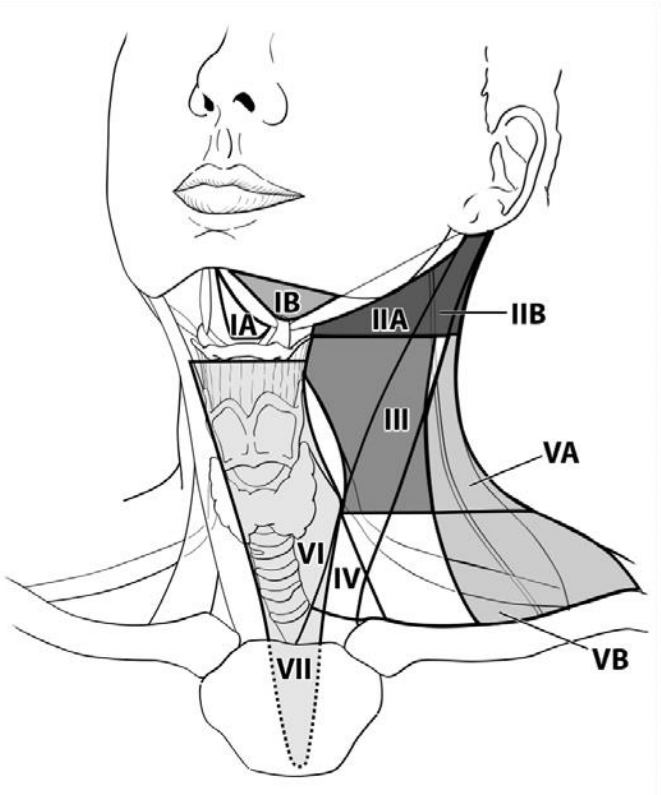
- III: Mid-Jugular
  - From bottom of hyoid to bottom of cricoid, medial to SCM and lateral to the scalene muscles
  - Drains most HN sites
    - Nasopharynx
    - Oral cavity
    - Oropharynx
    - Larynx
    - Hypopharynx

Neck Nodal Levels



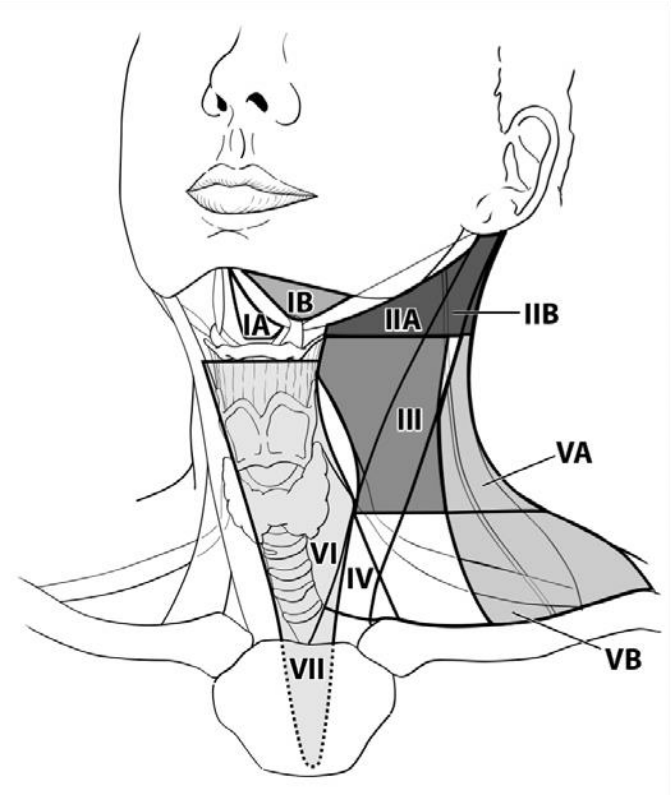
- IVa: Lower Jugular
  - From bottom of cricoid to 2 cm above sternoclavicular joint, postero-medial to SCM, anterior to scalene muscle
- IVb: Medial supraclavicular
  - From 2 cm above upper edge of manubrium to upper edge of manubrium, postero-medial to SCM, anterior to scalene muscle
- Hypopharynx, larynx, thyroid, cervical esophagus, distal drainage from higher cervical levels

Neck Nodal Levels



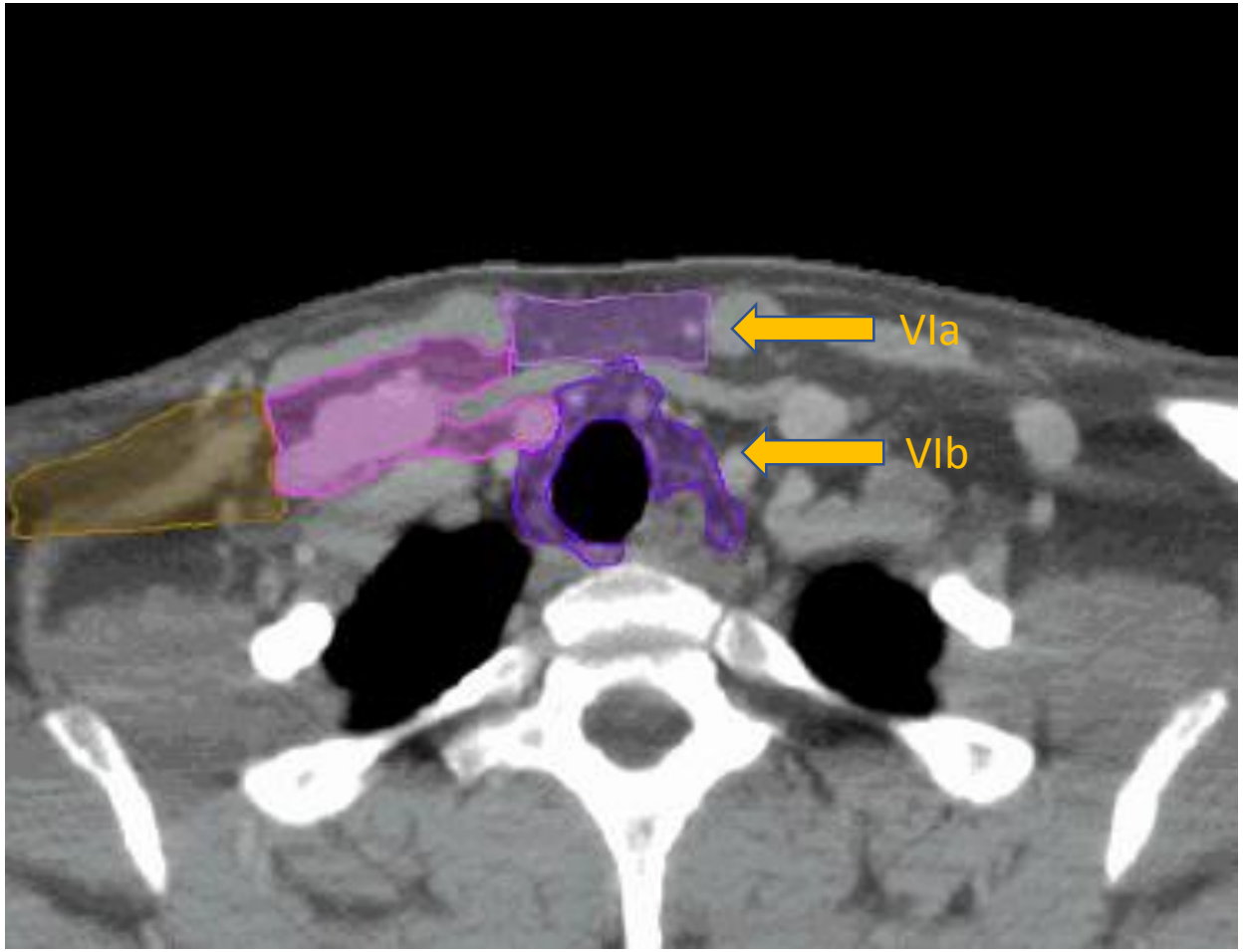
- V: Posterior Triangle
  - From hyoid to transverse cervical vessels, posterior to tail of SCM and anterior to trapezius, from platysma to scalene muscles
  - Drains nasopharynx, oropharynx, thyroid, posterior scalp

Neck Nodal Levels



- VI: Anterior compartment
  - VIa—From lower edge of hyoid to upper edge of sternal manubrium, anterior to infrahyoid muscles and between SCMs
  - VIb—From lower edge of hyoid bone to upper edge of sternal manubrium, posterior to infrahyoid muscles, anterior to larynx, thyroid gland, esophagus and surrounding trachea
  - Level VI drains lower face, tip of tongue, FOM, anterior neck, hypopharynx, thyroid, larynx, cervical esophagus

Level VIa and VIb



Simulation/Planning/IGRT

Simulation Techniques

- Supine, arms at sides, neck extended
- Thermoplastic head/shoulders (long) mask
  - Custom neck cushion for some patients
  - Arm straps to pull shoulders down
- Oral devices
  - Dental trays (ideally 3-5 mm thick) vs. tubular or “popsicle” bite block
  - Custom device is optimal
- CT
  - IV contrast
  - 2 mm slice thickness

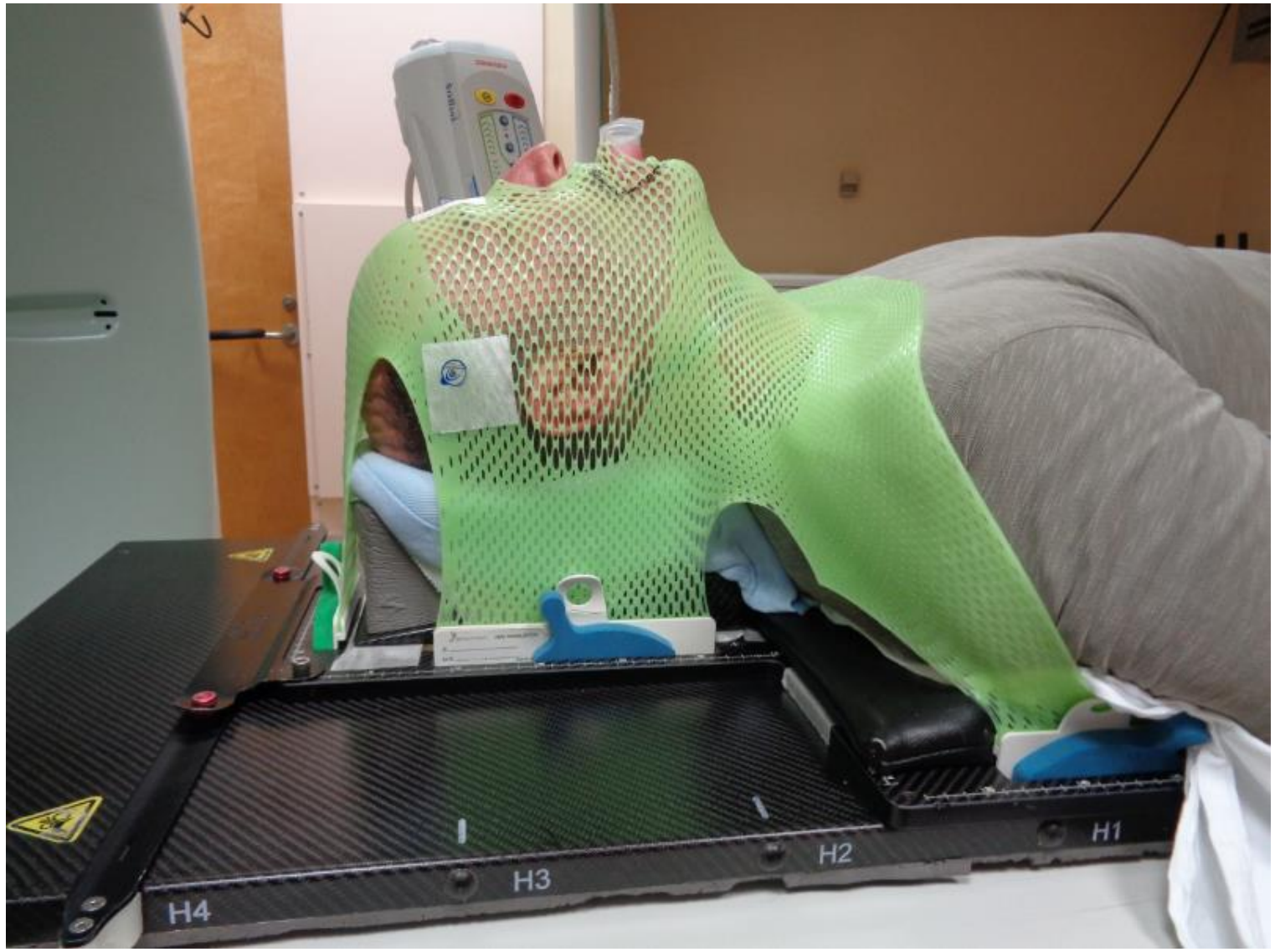
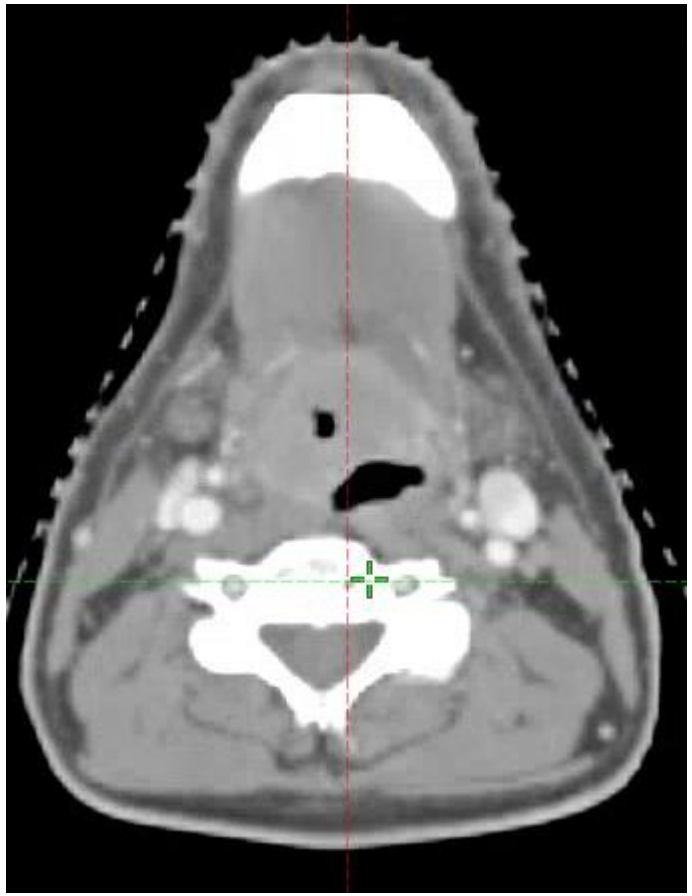
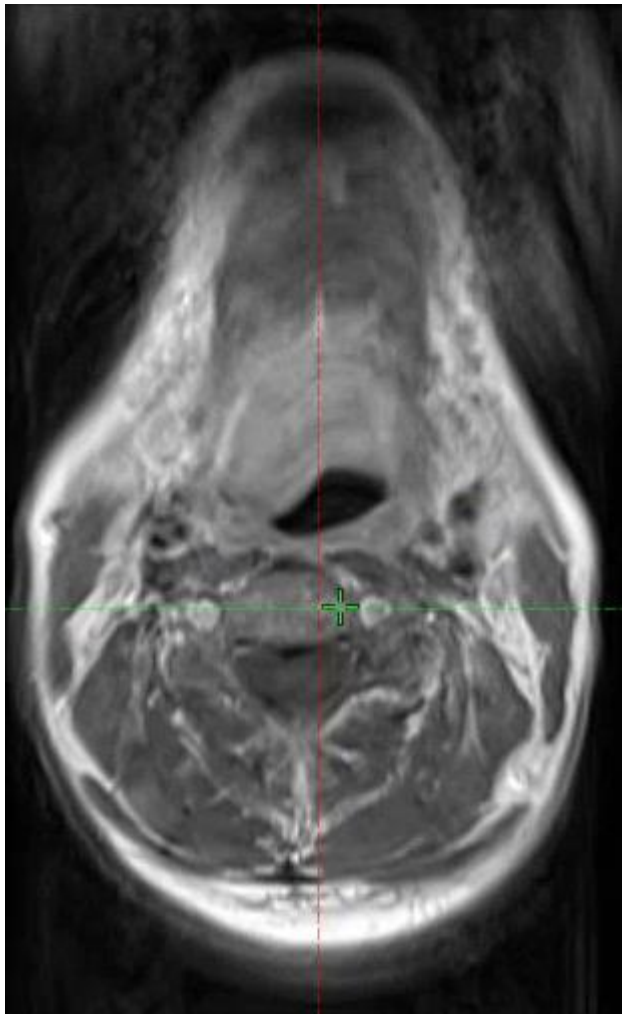
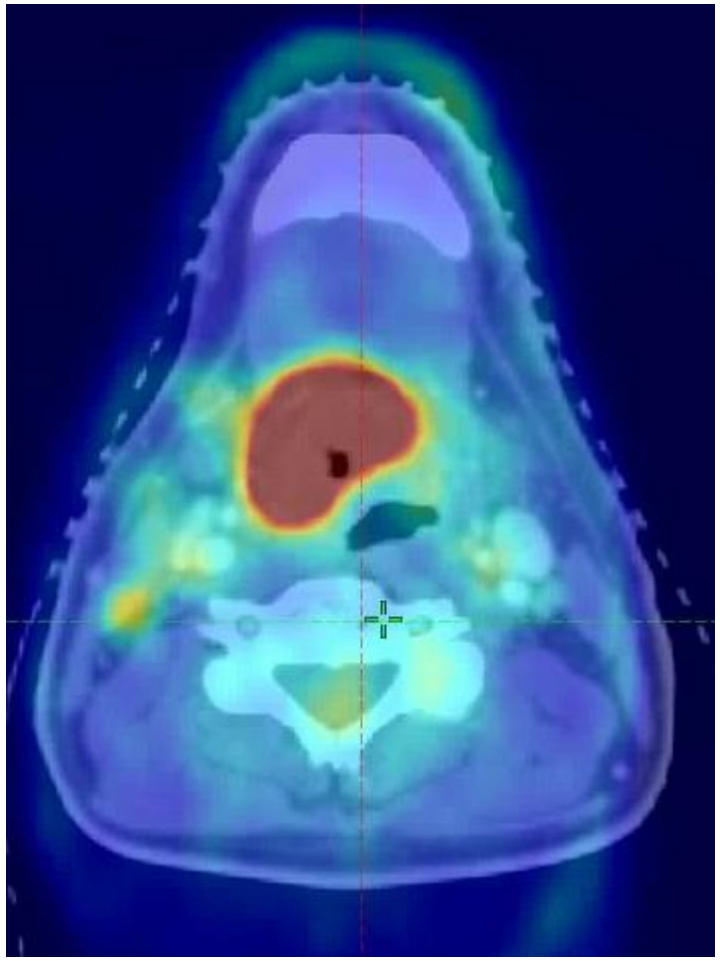

H4
H3
H2
H1

Image Fusion

- For DEFINITIVE cases
  - Role of PET fusion
    - Delineate tumors with questionable borders on CT
    - Detect and locate involved sub-cm nodes
  - Role of MRI fusion
    - Best anatomic delineation of tumors with questionable borders on CT
      - Don’t forget T2 sequence—often very helpful
- For POST-OPERATIVE cases
  - Fuse pre-op CT, PET and/or MRI
  - Fusions aid in delineation of tumor bed

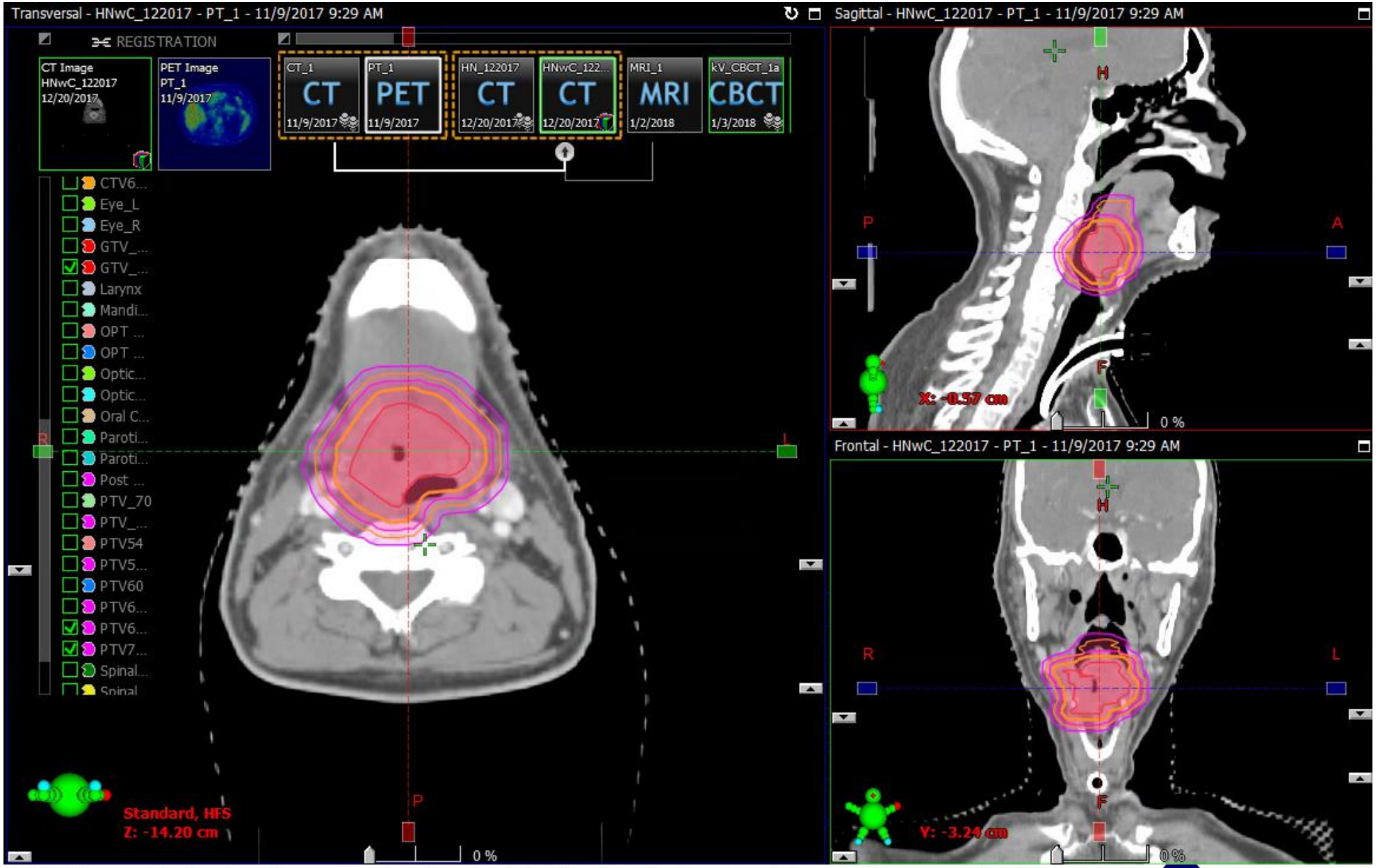






Planning Concepts

- High risk/intermediate risk/low risk volumes
  - **70/63/56 in 35 fractions (5 or 6 fractions/week)**
  - 70/60/54 in 33 fractions (5 fractions/week)
- GTV → CTV → PTV (no skipped steps)
  - GTV
  - 0.5-0.7 cm margin to CTV 70
  - 0.3 cm to PTV 70 (other centers skip this step)
  - 0.5 cm to CTV63, but include lymphatic compartment
  - 0.3 cm to PTV63
  - CTV56 to elective nodal areas, then 0.3 cm to PTV56
  - 3 mm PTV margin assumes daily IGRT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MRI
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kV_CBCT_1a
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CTV6...
Eye_L
Eye_R
GTV_...
GTV_...
Larynx
Mandi...
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Optic...
Oral C...
Paroti...
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PTV5...
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Standard, HFS
Z: -14.20 cm
0 %
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P
A
F
X: -0.57 cm
0 %
Frontal - HNwC_122017 - PT_1 - 11/9/2017 9:29 AM
H
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L
F
Y: -3.24 cm
0 %

Postop Treatment of Musculocutaneous Flaps

- Delineate flap on RT-planning CT
- CTV includes entire flap plus margin (about 1 cm) plus clips to encompass fully the surgical bed
- The flap itself is not at risk for recurrence, but the highest risk tissues are adjacent to the flap-normal tissue interface

Image Guided Radiation Therapy (IGRT)

- Daily kV
- Daily CBCT
  - Better than kV at detecting rotation, changes in external contour, fit of mask
  - Particularly powerful technique when combined with 6-degree treatment couch

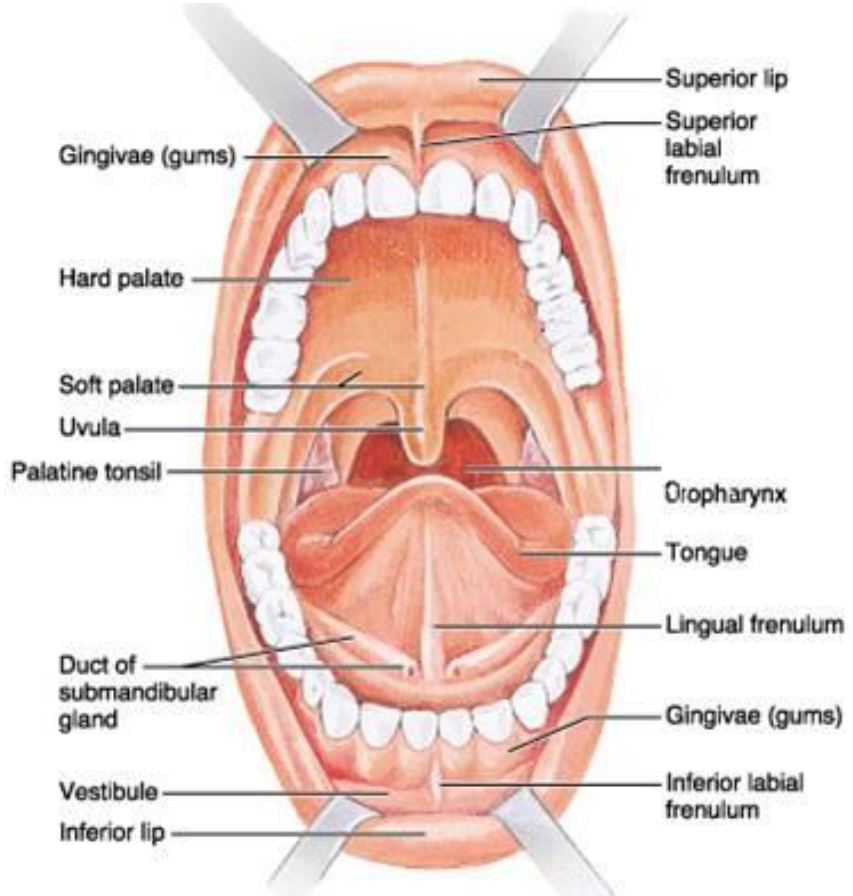
Treatment Approach by Site

Oral Cavity

Oral Cavity

Structures:

- Oral (mobile, anterior) tongue
- Floor of mouth
- Hard palate
- Gingiva
- Retromolar trigones
- Buccal surfaces
- Lips
- *Dividing line between oral cavity and oropharynx is circumvallate papillae*



Oral Cavity Staging: AJCC 7th vs. 8th Editions

- Primary purpose of changes is to incorporate the prognostic impact of extranodal extension (ENE or ECE) into the staging system for the first time.
  - *Clinical* evidence of ENE moves the cN stage directly to a new nodal substage, cN3b.
  - *Pathologic* evidence of ENE can upstage in 2 ways:
    - A pN1 node with ENE becomes pN2a
    - Any other nodal situation (pN2-N3) with ENE becomes pN3b.
  - There is no change to the stage groupings.

Oral Cavity: Treatment Approach

- Primarily a “surgical disease.”
  - All stages are approached with definitive surgery if tumor and nodes are resectable.
  - Do not get confused into suggesting non-surgical approaches unless
    - Tumor is unresectable
    - There is a medical contraindication
    - There is consideration of definitive brachytherapy (very rarely used in 2018)
    - Be careful not to discuss “tongue cancer.” Clarify between oral tongue (oral cavity) and tongue base (oropharynx), as algorithms are very different.
  - Surgery is complete resection, generally with ipsilateral neck dissection.

Oral Cavity, cont.

- Indications for postoperative RT alone:
  - T3 or T4 stage
  - Close surgical margin, not adequately cleared with additional margins
  - Perineural invasion
  - Lymphovascular invasion
  - 2 or more positive nodes
- Indications for postoperative RT with concurrent cisplatin:
  - Positive surgical margin
  - Extranodal tumor extension (ENE, ECE)
  - Chemo is generally bolus cisplatin 100 mg/m^2 q 3 weeks

Pooled RTOG/EORTC Post-op

DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

Jacques Bernier, MD, PhD,[1] Jay S. Cooper, MD,[2] T. F. Pajak, PhD,[3] M. van Glabbeke, Ir,[4] J. Bourhis, MD, PhD,[5] Arlene Forastiere, MD,[6] Esat Mahmut Ozsahin, MD, PhD,[7] John R. Jacobs, MD,[8] J. Jassem, MD,[9] Kie-Kian Ang, MD,[10] J. L. Lefèbvre, MD[11]

Pooled RTOG/EORTC Post-op

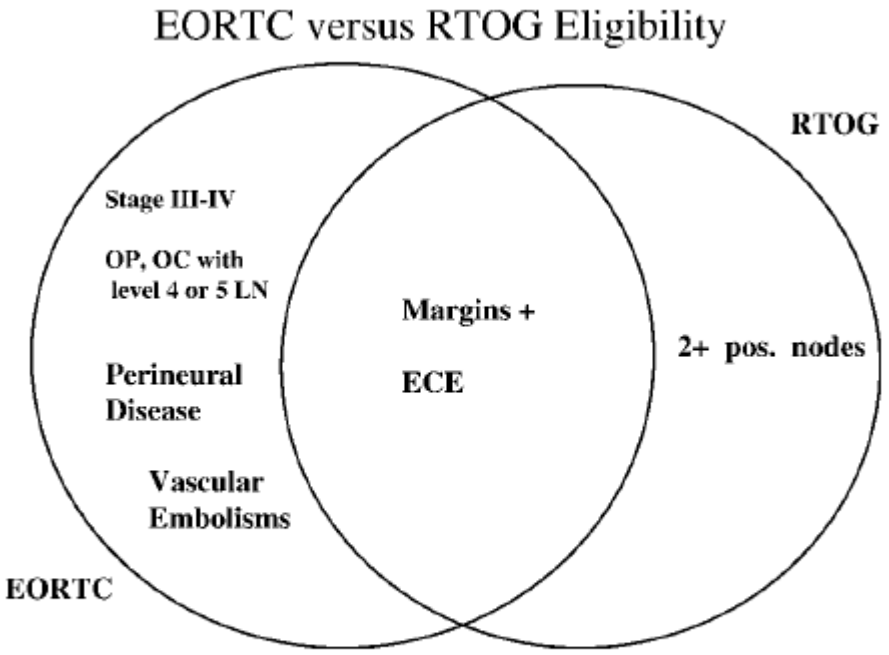
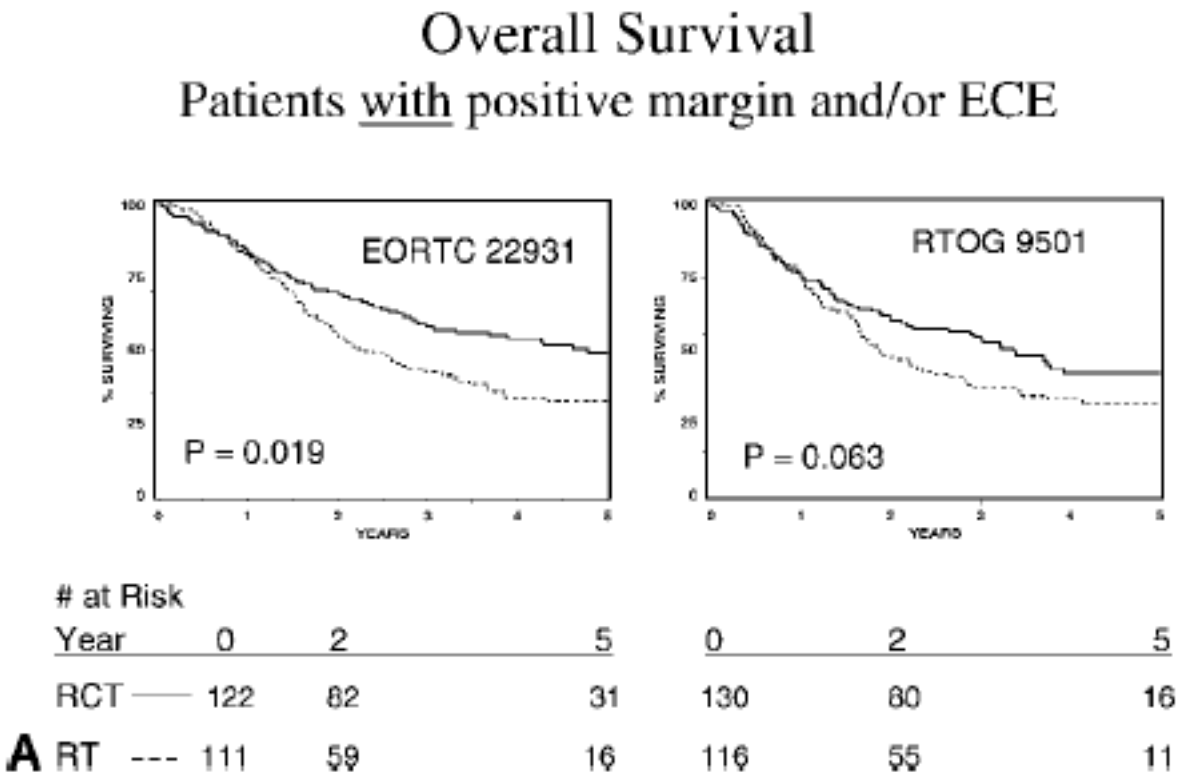
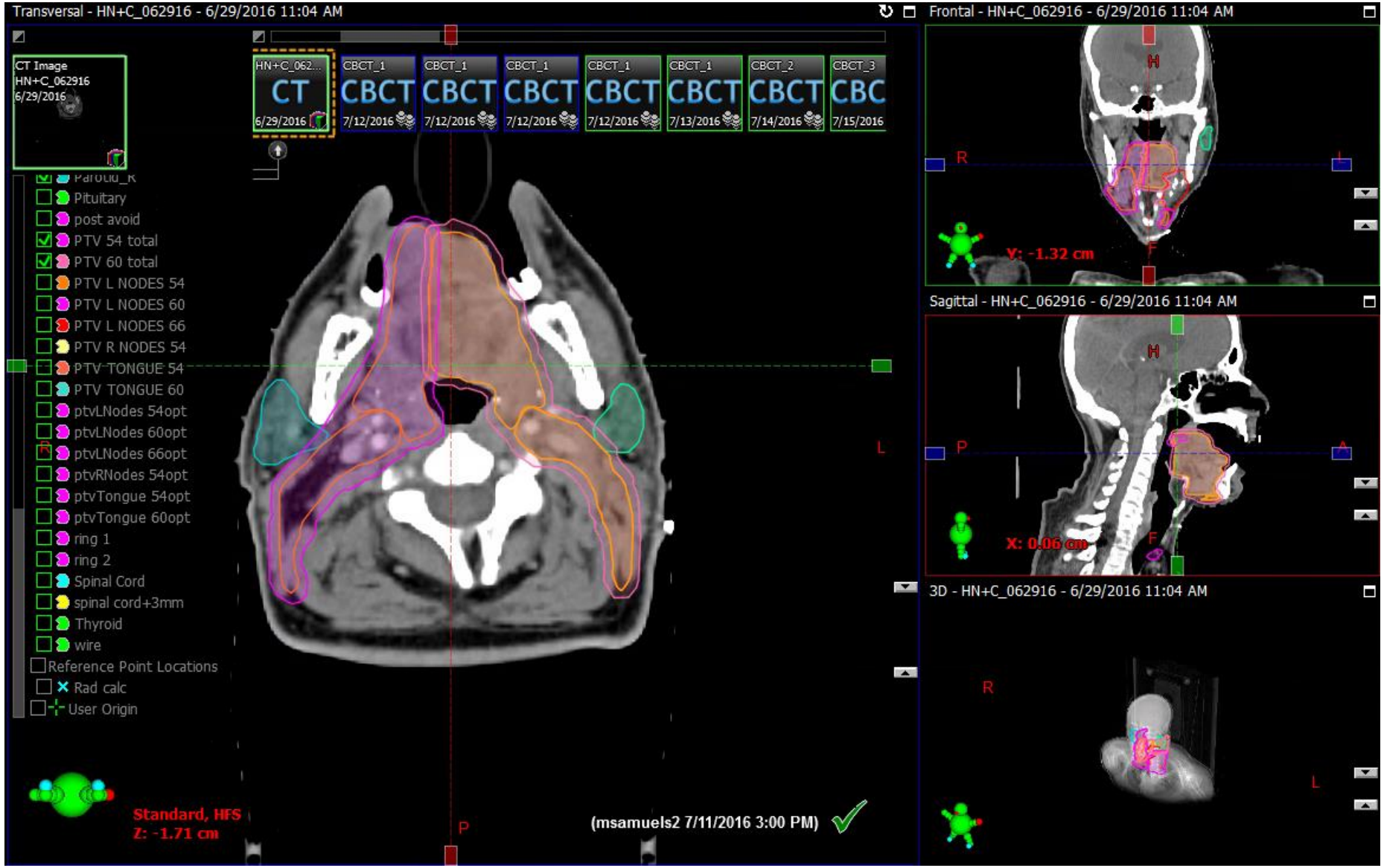


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.



Oral Cavity: Volumes and Doses

- Postoperative RT should acknowledge that most oral cavity structures are midline and that postop RT will need to include generous coverage of the oral cavity and necks bilaterally.
- For oral tongue and floor of mouth, CTV60 (30 fxs) usually includes the entire oral tongue and FOM complex, with involved nodal regions and adjacent regions at 60 Gy and elective nodal regions at 54 Gy. Levels IB-IV should be covered in almost all cases. Level IA for lower lip and anterior tongue primaries. Regions with ENE nodes get 66 Gy.
- RMT, lateralized gingival and buccal cases may be treated ispilaterally.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PTV L NODES 60
PTV L NODES 66
PTV R NODES 54
PTV TONGUE 54
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ptvLNodes 66opt
ptvRNodes 54opt
ptvTongue 54opt
ptvTongue 60opt
ring 1
ring 2
Spinal Cord
spinal cord+3mm
Thyroid
wire
Reference Point Locations
Rad calc
User Origin
Standard, HFS
Z: -1.71 cm
(msamuels2 7/11/2016 3:00 PM)
Frontal - HN+C_062916 - 6/29/2016 11:04 AM
Y: -1.32 cm
Sagittal - HN+C_062916 - 6/29/2016 11:04 AM
X: 0.06 cm
3D - HN+C_062916 - 6/29/2016 11:04 AM

Oral Cavity: Enrolling Trials

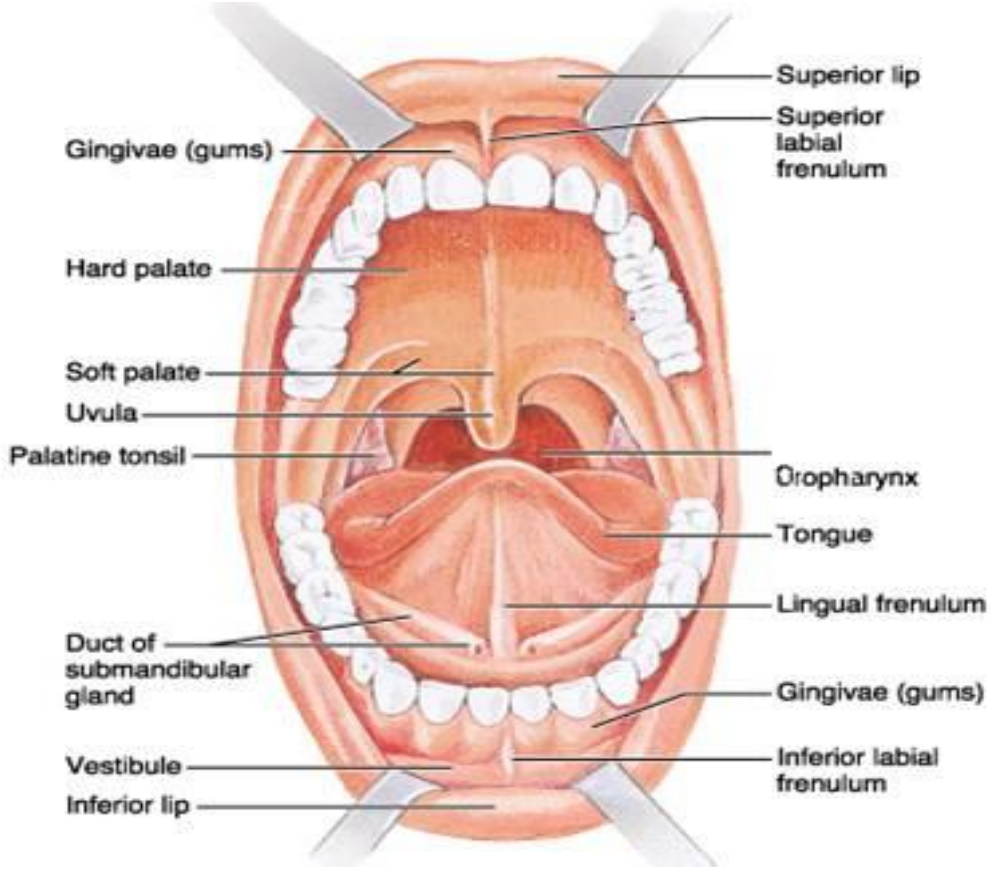
- RTOG 0920 (just closing)
  - For intermediate risk cases requiring postoperative RT without chemotherapy
  - Randomization between postoperative RT alone vs. RT + weekly cetuximab
- ECOG 3132
  - For intermediate risk cases requiring postoperative RT without chemotherapy
  - Tissue sent for mutational analysis
  - p53 mutated cases are randomized to postoperative RT alone with or without weekly cisplatin

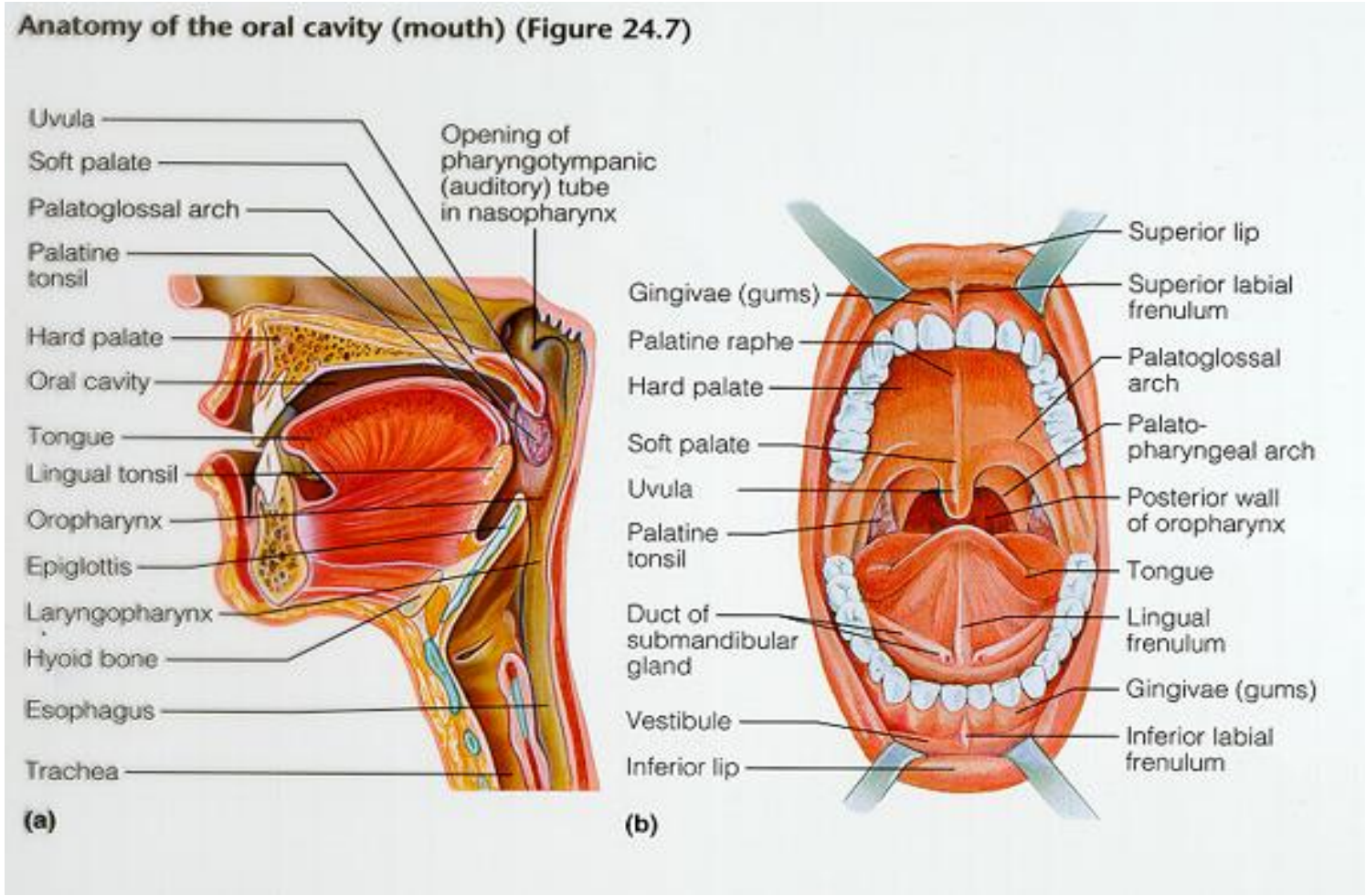
Oropharynx

Oropharynx

Structures:

- Tongue base
- Soft palate
- Anterior and posterior tonsillar pillars
- Tonsillar fossae
- Lateral and posterior oropharyngeal walls
- Vallecula (potential space between tongue base and epiglottis)
- *Superior border is soft palate/hard palate junction, inferior border is hyoid bone*

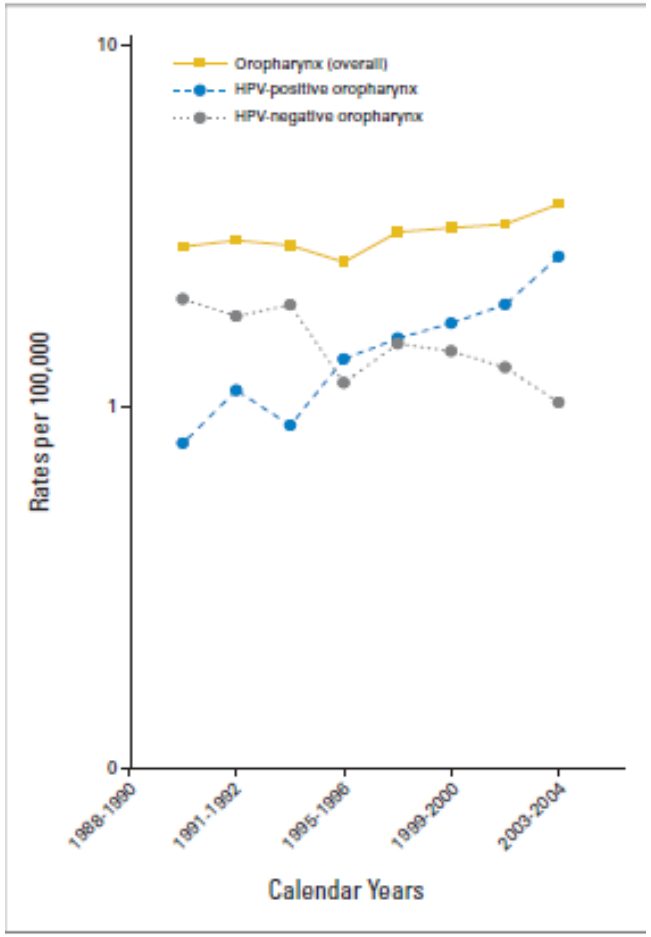



Anatomy of the oral cavity (mouth) (Figure 24.7)
Uvula
Soft palate
Palatoglossal arch
Palatine tonsil
Hard palate
Oral cavity
Tongue
Lingual tonsil
Oropharynx
Epiglottis
Laryngopharynx
Hyoid bone
Esophagus
Trachea
Opening of pharyngotympanic (auditory) tube in nasopharynx
(a)
Gingivae (gums)
Palatine raphe
Hard palate
Soft palate
Uvula
Palatine tonsil
Duct of submandibular gland
Vestibule
Inferior lip
Superior lip
Superior labial frenulum
Palatoglossal arch
Palato-pharyngeal arch
Posterior wall of oropharynx
Tongue
Lingual frenulum
Gingivae (gums)
Inferior labial frenulum
(b)

Oropharynx Staging: AJCC 7th vs. 8th Editions

- Main purpose of revised 8th Edition staging was primarily to align HPV-associated (HPV+) case staging with good prognosis of disease compared to HPV-negative (HPV-) cases. Secondary purpose was to incorporate the impact of ENE on prognosis in HPV- cases.
- Why was this necessary?
  - Epidemic of HPV+ oropharynx cases (70-80%) in US
  - Rapid rise of incidence over past 20 years
  - Prognosis of HPV+ cases exceeds tobacco-associated cases by about 15-20%
  - Using the 7th Edition staging system for HPV+ cases, outcomes for stages I-IVA were similar.
  - The 8th Edition delineates clinical and pathologic factors that actually correlate with changes in prognosis in HPV+ cases, and eliminates consideration of factors that do not correlate with prognosis.

HPV-Associated Oropharynx Cancer



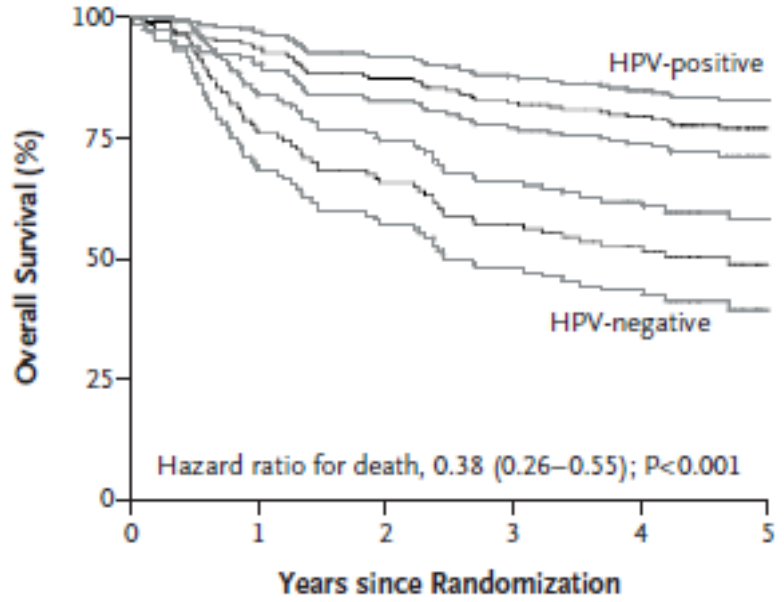
Chaturvedi (2011): Incidence of OPX Ca Over Time by HPV Status

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

N Engl J Med 2010;363:24-35.

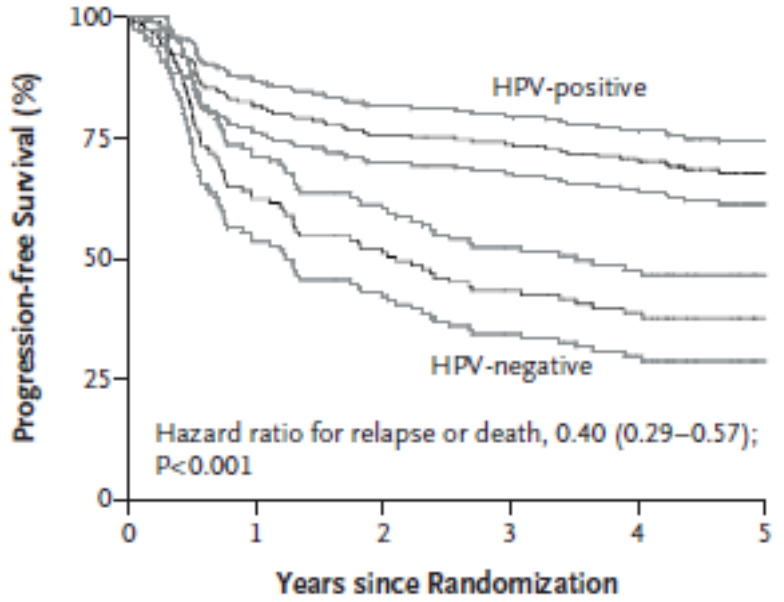
A Overall Survival According to Tumor HPV Status



No. at Risk

HPV-positive	206	193	179	165	151	73
HPV-negative	117	89	76	65	51	22

B Progression-free Survival According to Tumor HPV Status



No. at Risk

HPV-positive	206	168	155	148	136	65
HPV-negative	117	73	59	49	37	15

HPV-Associated Oropharynx: Summary of Changes

- T-staging (clinical and pathologic)
  - T4a becomes T4; T4b eliminated

✓	*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*
* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.		

HPV-Associated Oropharynx: Summary of Changes

- cN-Staging: Changes to cN1, cN2

4.2.1 Clinical N (cN)

✓	*cN Category*	*cN 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

✓	*N Suffix*	*Definition*
	(sn)	Select if regional lymph node metastasis identified by SLN biopsy only.
	(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only.

HPV-Associated Oropharynx: Summary of Changes

- pN-Staging: Changes to pN1-2, elimination of pN3

4.2.2 Pathological N (pN)

✓	*pN Category*	*pN 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

✓	*N Suffix*	*Definition*
	(sn)	Select if regional lymph node metastasis identified by SLN biopsy only.
	(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only.

HPV-Associated Oropharynx: Summary of Changes

- M-staging is unchanged

✓	*M Category*	*M Criteria*
	cM0	No distant metastasis
	cM1	Distant metastasis
	pM1	Distant metastasis, microscopically confirmed

- Grading

8 Histologic Grade (G)

No grading system exists for HPV-mediated oropharyngeal tumors.

HPV-Associated Oropharynx: Summary of Changes

- Definition of p16 status
  - If it is not tested, it is p16 (HPV) negative, regardless of clinical factors

5.1 Definition of p16/HPV Status

✓	*P16/HPV Status*
	Positive (+)
	Negative (-) If negative, use staging form for p16- Oropharynx, Chapter 11.
➡	Not tested. If not tested, use staging form for p16- Oropharynx, Chapter 11.

HPV-Associated Oropharynx: Summary of Changes

- Changes to **clinical** stage groupings:
  - You need T3 or N2 to get to St. II
  - You need T4 or N3 to get to St. III
  - You need M1 to get to St. IV

6.1 Clinical (cTNM)

✓	*When p16/HPV Status is…*	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Positive	T0, T1 or T2	N0 or N1	M0	I
	Positive	T0, T1 or T2	N2	M0	II
	Positive	T3	N0, N1 or N2	M0	II
	Positive	T0, T1, T2, T3 or T4	N3	M0	III
	Positive	T4	N0, N1, N2 or N3	M0	III
	Positive	Any T	Any N	M1	IV

HPV-Associated Oropharynx: Summary of Changes

- Changes to **pathologic** stage groupings:
  Same as clinical, but:
  - pT3 moves up to St. III **if N2,** stays in St. II if N0-N1
  - pT4 drops back to St. II **if N0-N1**, pT4 remains St. III if N2

6.2 Pathological (pTNM)

✓	*When p16/HPV Status is…*	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Positive	T0, T1 or T2	N0, N1	M0	I
	Positive	T0, T1 or T2	N2	M0	II
➡	Positive	T3 or T4	N0, N1	M0	II
➡	Positive	T3 or T4	N2	M0	III
	Positive	Any T	Any N	M1	IV

HPV-Negative Oropharynx: Summary of Changes

- T-Staging is unchanged

✓	*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*
	T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.		

HPV-Negative Oropharynx: Summary of Changes

- HPV- **clinical** N-staging: clinical (imaging/palpation) ENE=N3b

4.2.1 Clinical N (cN)

✓	*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(−)
	N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) and clinically overt ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
➡	N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

HPV-Negative Oropharynx: Summary of Changes

- HPV- **pathologic** N-staging
  - ENE=N3b exc. single ENE node <3 cm=N2a

✓	*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(−)
	N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
→	N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
	N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
	N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
	N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
→	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).		

HPV-Negative Oropharynx: Summary of Changes

- HPV- stage groupings and grades: unchanged

Always refer to the specific chapter for rules on clinical and pathological classification of this disease.

✓	*When p16/HPV Status is…*	*And T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Negative, not tested	Tis	N0	M0	0
	Negative, not tested	T1	N0	M0	I
	Negative, not tested	T2	N0	M0	II
	Negative, not tested	T3	N0	M0	III
	Negative, not tested	T1,T2,T3	N1	M0	III
	Negative, not tested	T4a	N0,N1	M0	IVA
	Negative, not tested	T1,T2,T3,T4a	N2	M0	IVA
	Negative, not tested	Any T	N3	M0	IVB
	Negative, not tested	T4b	Any N	M0	IVB
	Negative, not tested	Any T	Any N	M1	IVC

✓	*G*	*G Definition*
	GX	Grade cannot be assessed
	G1	Well differentiated
	G2	Moderately differentiated
	G3	Poorly differentiated
	G4	Undifferentiated

Oropharynx: Treatment Approach

- Unlike oral cavity, oropharynx is a disease where we think of definitive RT or chemoRT first, BUT
  - TORS (*Trans-Oral Robotic Surgery*) or TLM (*Trans-Oral Laser Microsurgery)* are options for selected cases (we will return to this topic shortly)

Influence of HPV status on treatment: None yet

- RTOG 1016
  - Definitive chemoRT study for HPV+
  - RT/cis vs. RT/cetuximab
  - Closed 2014—no results yet
- NRG HN002
  - Definitive RT to 60 Gy vs. Definitive chemoRT to 60 Gy
  - Closed 2017—no results yet
- ECOG 3311
  - TORS study for HPV+
  - Intermediate risk group postop RT at 60 vs. 50 Gy
  - Closed 2017—no results yet
- As of today, no influence of HPV status on treatment strategy

Oropharynx, cont.

- RT vs. chemoRT
  - Using the AJCC 7th edition staging system (ignoring changes in N-staging in the new system for HPV+ cases), cases up to T2N1 can be treated with RT alone
  - Chemoradiation for
    - Multiple clinically involved nodes
    - Single involved node >3 cm
    - clinical evidence of ENE
    - cT3-T4

Oropharyx: Volumes and Doses

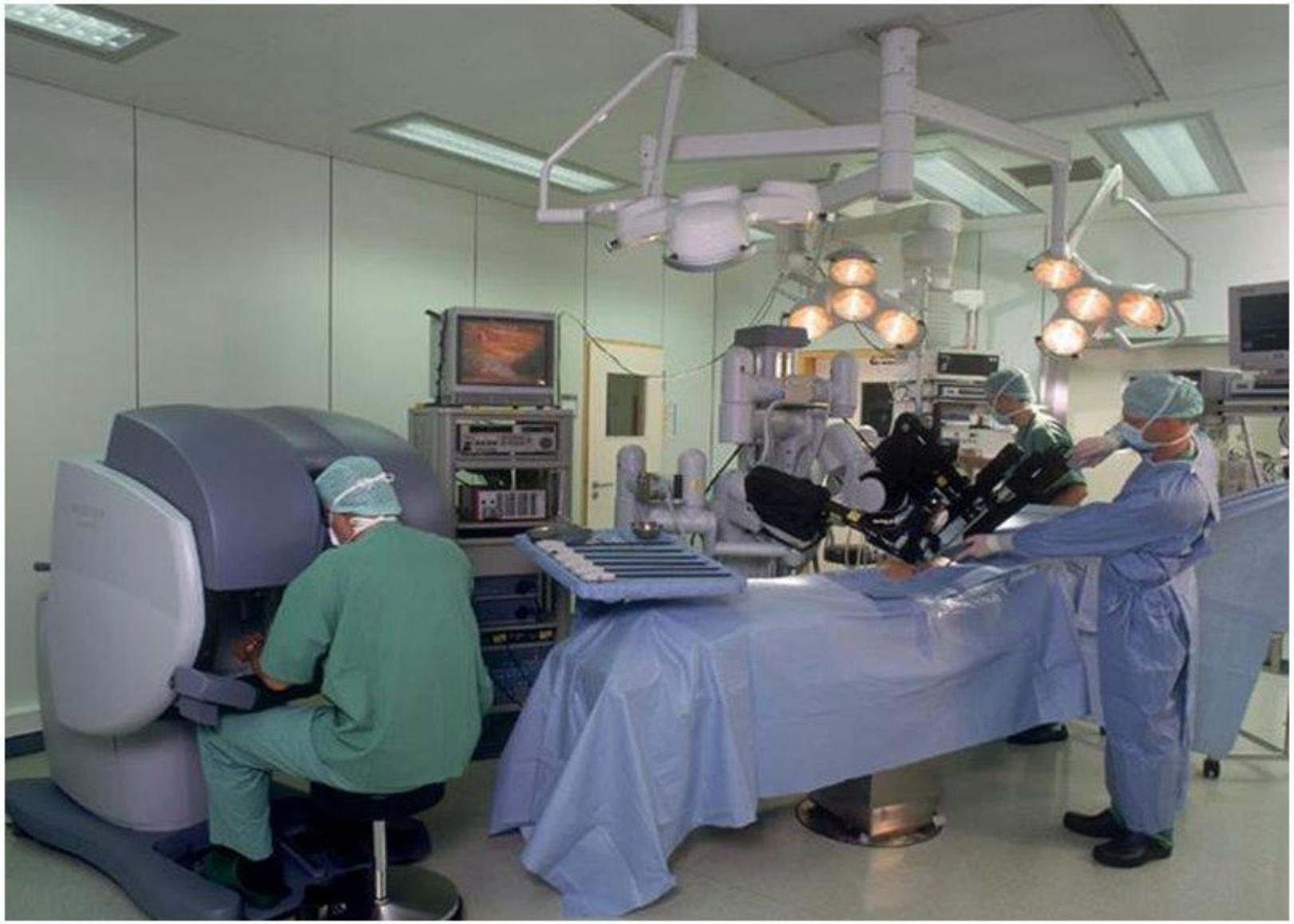
- GTV70 is determined by multi-modality imaging (CT/PET/MRI)
- CTV70 is 5-7 mm expansion depending on clarity of GTV delineation
- PTV70 is 3 mm expansion, assuming daily IGRT
- CTV63 is 5 mm expansion, plus inclusion of lymphatic region related to primary location
- PTV63 is 3 mm expansion
- Clinically involved nodes treated to 70 Gy
- Typically cover levels II-IV, IB only if bulky level II involvement or tumor extends to oral cavity. Retropharyngeal and retrostyloid coverage to be discussed later.
- Nodal region doses as discussed in the last section

Definitive Oropharynx: Ipsilateral vs. bilateral

- Tongue base and soft palate are MIDLINE structures and require bilateral RT/chemoRT
- Tonsillar cases are eligible for consideration for ipsilateral RT. How to select?
  - No T3-T4
  - No more than 1 cm extension to soft palate
  - No more than minimal, superficial extension to lateral tongue base
  - Nodal burden is not excessive enough to cause retrograde lymphatic flow
    - No bulky adenopathy—this is a judgement call (some allow single node <3 cm only)
    - No clinical ENE

Trans-Oral Robotic Surgery (TORS)/ Trans-Oral Laser Microsurgery (TLM)

- Substantial advance on previous mandible-splitting techniques
  - Provides en-bloc resection of primary tumor with oncologic margins and primary closure
  - Usually accompanied by a conventional neck dissection
  - Lower morbidity and faster recovery than previous surgical approaches
- Intent of TORS is to provide equal tumor control to definitive RT/chemoRT with less toxicity
  - This requires careful patient selection relying on the ability to predict the post-TORS pathology report in advance
  - The fundamental comparison is between TORS and the non-surgical alternative



TORS, cont.

- Which patients are NOT eligible for TORS?
  - Surgery will cause major functional deficits
    - T3-T4 primaries
    - More than minimal soft palate extension
    - Central tongue base tumors
  - Medical contra-indications
  - Trismus or other difficulties with exposure

TORS, cont.

- For the rest, the post-TORS pathology report will result in 3 possible risk groups:
  - Low-risk—This means no further treatment indicated ("home run")
    - pT0-2N0-1 using AJCC 7th edition
    - Lowest possible toxicity for any curative approach
  - Intermediate risk—This means postoperative RT alone to 60 Gy indicated ("base hit")
    - pT3-4, PNI, LVSI, close margin, 2 or more involved nodes
    - Combined toxicity of TORS and 60 Gy is roughly similar to definitive RT or chemoRT to 70 Gy
  - High risk—This means postoperative chemoRT to 66 Gy ("strike out")
    - Positive margins or ENE
    - Combined toxicity of TORS and 66 Gy chemoRT exceeds chemoRT to 70 Gy w/o TORS

TORS: Implications of Future Trial Results

- ECOG 3311
  - If the intermediate risk group results show postop RT at 50 Gy is equal to 60 Gy, this would tilt the balance in the comparison towards TORS for this group (TORS + 50 Gy vs. RT or chemoRT to 70 Gy)
- NRG HN002 or following phase III study
  - If definitive RT alone or chemoRT to 60 Gy is equivalent to 70 Gy, then this would tilt the balance in the comparison towards definitive RT/chemoRT

Oropharynx Guideline Document

VOLUME 35 · NUMBER 36 · DECEMBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

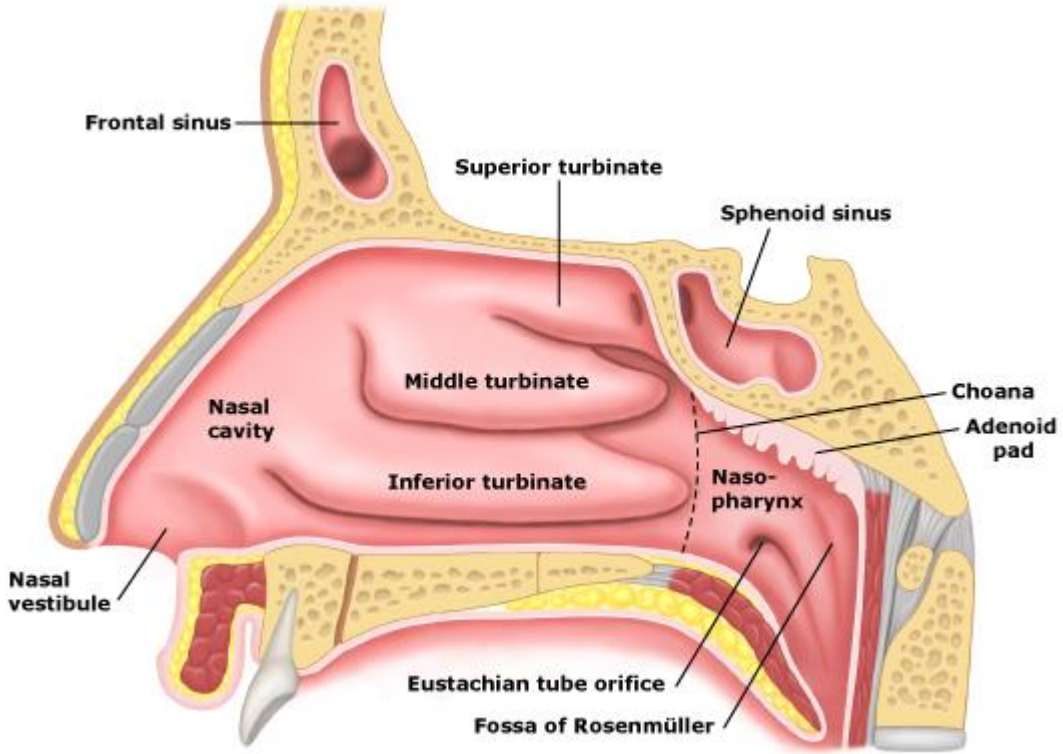
Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

Harry Quon, Neha Vapiwala, Arlene Forastiere, Erin B. Kennedy, David J. Adelstein, Holly Boykin, Joseph A. Califano, F. Chris Holsinger, Brian Nussenbaum, David I. Rosenthal, Lillian L. Siu, and John N. Waldron

Nasopharynx

Nasopharynx

- Anterior border is posterior nasal choanae
- Superior border is clivus
- Posterior border is pre-vertebral tissues
- Inferior border is inferior edge of soft palate



Epidemiology

- WHO types I, II, III
  - Type III is EBV-related and endemic to East Asia and SE Asia
  - Some type II cases are EBV related
  - Type I is more common in non-Asian populations and is closer to a typical SCCa
- Preliminary data indicates that following serum EBV DNA levels before and after treatment may be an effective indicator of treatment response

Nasopharynx: Treatment Approach

- Primarily a “radiation therapy disease”
- No significant changes in staging for AJCC 8th edition
- T1N0 is RT alone, all other stages treated with chemoRT

Chemotherapy in Nasopharynx Cancer

Chemoradiotherapy Versus Radiotherapy in Patients With Advanced Nasopharyngeal Cancer: Phase III Randomized Intergroup Study 0099

By Muhyi Al-Sarraf, Michael LeBlanc, P.G. Shanker Giri, Karen K. Fu, Jay Cooper, Te Vuong, Arlene A. Forastiere, George Adams, Wael A. Sakr, David E. Schuller, and John F. Ensley

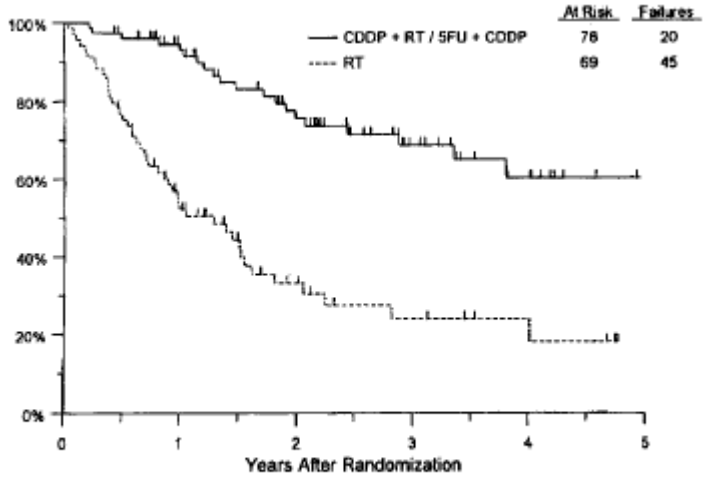


Fig 1. PFS for completely eligible patients on radiation (RT) only and combined chemotherapy (CT)/RT. CDDP, cisplatin; F5U, fluorouracil.

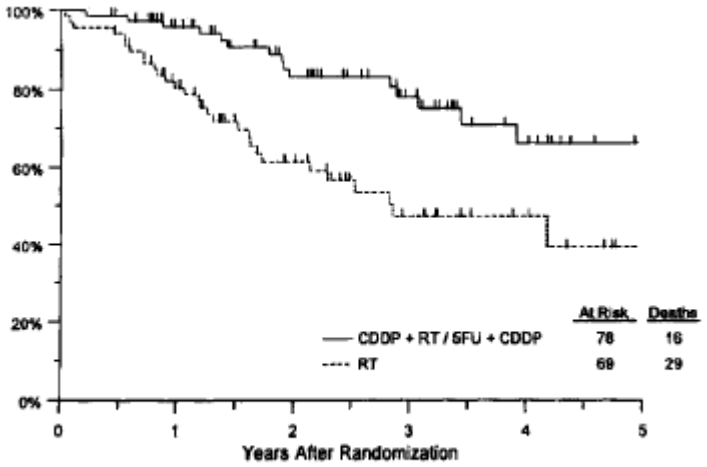


Fig 2. Overall survival for completely eligible patients on RT only and combined CT/RT (----).

Chemotherapy in Nasopharynx Cancer

Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

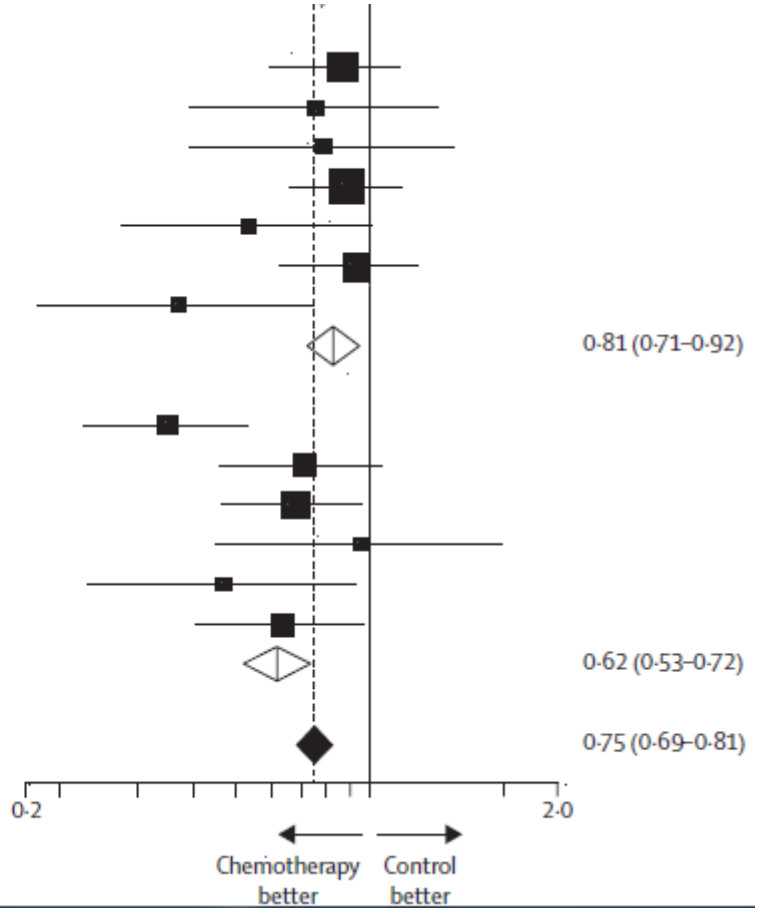
*Pierre Blanchard, Anne Lee, Sophie Marguet, Julie Leclercq, Wai Tong Ng, Jun Ma, Anthony T C Chan, Pei-Yu Huang, Ellen Benhamou, Guopei Zhu, Daniel T T Chua, Yong Chen, Hai-Qiang Mai, Dora L W Kwong, Shie Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Li Zhang, Edwin Pun Hui, Tai-Xiang Lu, Jean Bourhis, Jean Pierre Pignon, on behalf of the MAC-NPC Collaborative Group**

Lancet Oncol 2015; 16: 645–55

Published Online
May 7, 2015
http://dx.doi.org/10.1016/
S1470-2045(15)70126-9

Chemotherapy, cont.

Concomitant					
PWHQEH-94[17]	101/174	108/176	−8·6	52·1	
QMH-95Conc[18]	28/56	31/55	−4·2	14·6	
QMH-95Conc+[18]	25/57	27/54	−3·3	12·8	
VUMCA-95 (unpublished)	138/256	146/253	−10·7	70·7	
Guangzhou 2001[25]	26/59	33/56	−7·3	14·4	
Guangzhou 2002–02[26]	90/204	100/204	−4·0	47·5	
Guangzhou 2003[27]	15/116	32/114	−9·9	11·7	
Subtotal	423/922	477/912	−48·0	223·9	0·81 (0·71–0·92)
Concomitant + adjuvant					
INT-0099[2]	61/97	81/96	−27·7	32·8	
SQNP01[20]	64/111	75/110	−11·5	34·3	
NPC-9901[21]	77/172	104/176	−17·9	45·1	
NPC-9902CF[22]	23/51	21/42	−0·9	10·9	
NPC-9902AF[22]	19/44	31/52	−7·6	12·4	
Guangzhou 2002–01[28]	56/158	73/158	−13·8	32·0	
Subtotal	300/633	385/634	−79·4	167·4	0·62 (0·53–0·72)
Total	**1150/2518**	**1344/2510**	**−175·9**	**617·2**	0·75 (0·69–0·81)
Test for heterogeneity:	p=0·30	I^2=12%			
Test for interaction:	p=0·041				
Residual heterogeneity:	p=0·36				



NRG ONCOLOGY

NRG-HN001

Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)

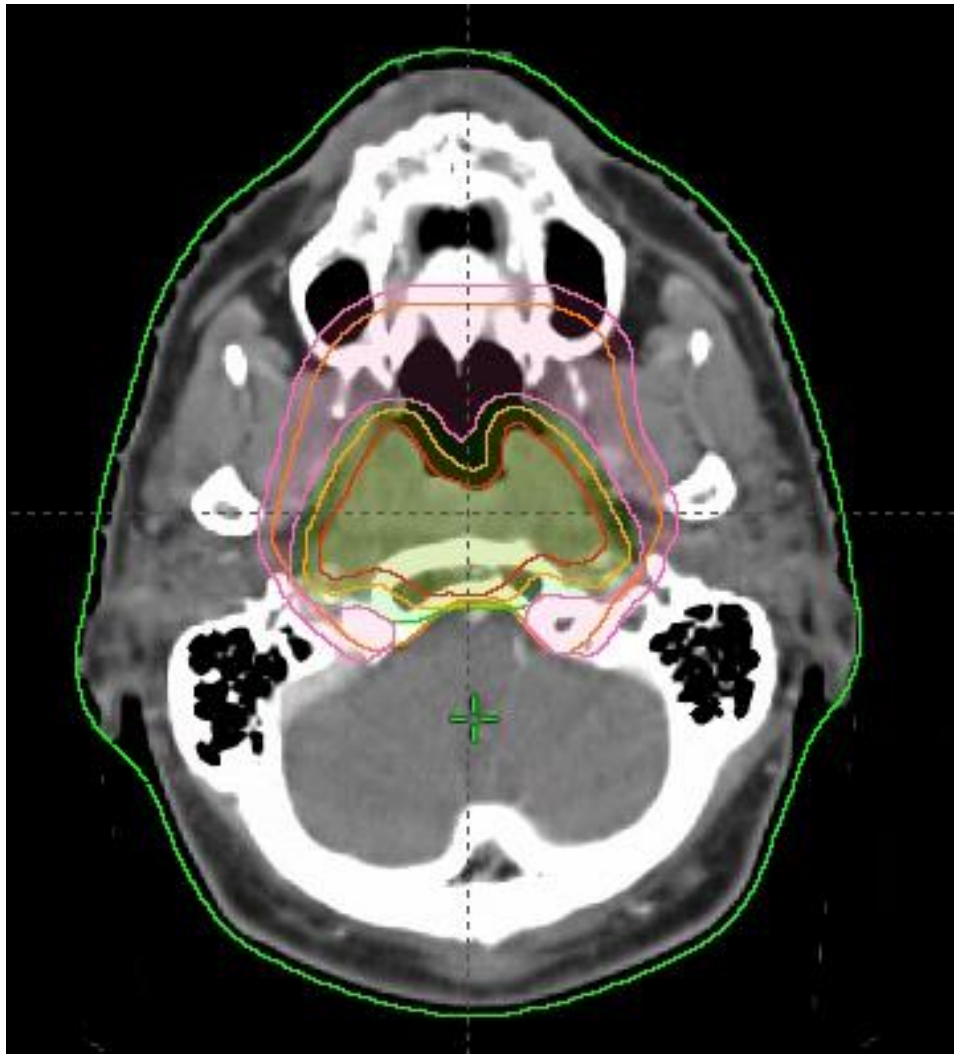
SCHEMA (Continued)

STRATIFY	RANDOMIZE	Randomized Phase II: Detectable Plasma EBV DNA Cohort
N Stage 1. N0-1 2. N2-3 **T Stage** 1. T1-2 2. T3-4 **Zubrod Performance Status** 1. 0 2. 1		**Arm 1** (Control Arm, "PF"): Cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation **Arm 2** (Experimental Arm, "GT"): Gemcitabine (1000 mg/m^2) days 1 and 8 and Paclitaxel (80 mg/m^2) days 1 and 8 every 21 days for 4 cycles beginning 4 weeks after completion of radiation

STRATIFY	RANDOMIZE	Phase III: Undetectable Plasma EBV DNA Cohort
N Stage 1. N0-1 2. N2-3 **T Stage** 1. T1-2 2. T3-4 **Zubrod Performance Status** 1. 0 2. 1		**Arm 3** (Control Arm, "PF"): Cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation **Arm 4** (Experimental Arm): Observation

Nasopharynx: IMRT planning

- These cases are not very common in US outside of NY, CA
- MRI imaging is mandatory to plan NPX cases
  - Determine tumor extension, esp. involving nerves and foramina of skull base
  - Consultation with neuroradiologist may be helpful
- 70 Gy in 33-35 fxs to primary tumor with margin
- CTV60 is key planning consideration
  - Large number of structures must be covered in tricky area
  - Consider use of “checklist” in textbook to avoid missing any
- Coverage of RP nodes and level V is mandatory, but Ib is optional



Larynx

Larynx

Structures:

Supraglottic larynx

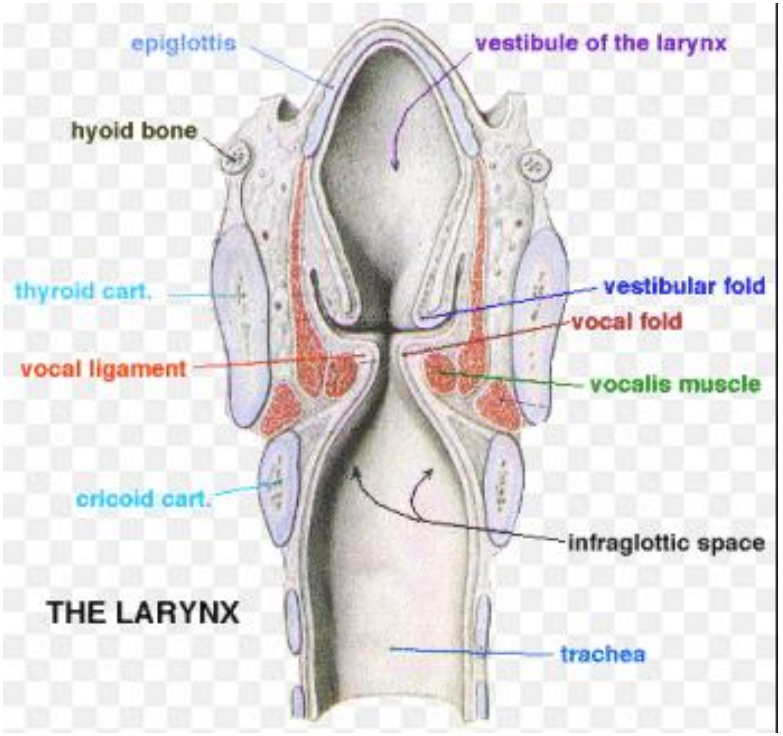
- Epiglottis
- Ary-epiglottic folds
- Arytenoids
- False Cords

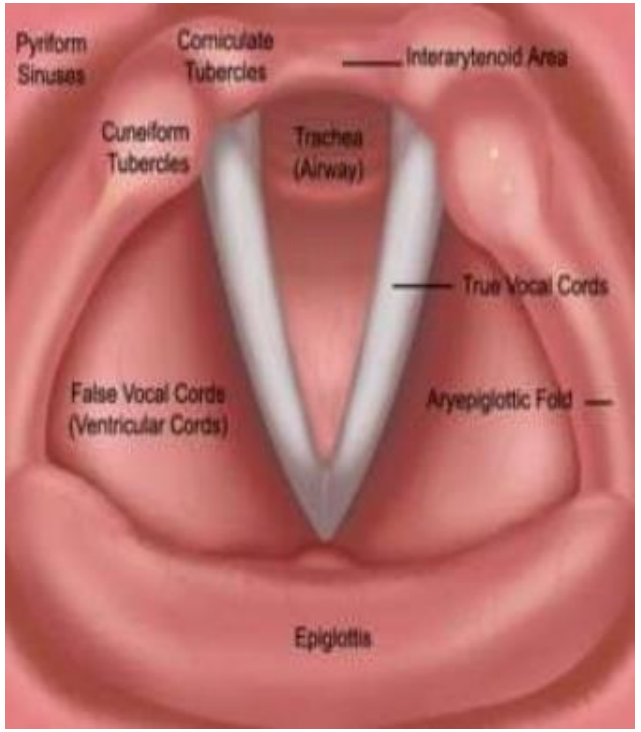
Glottic larynx

- From apex of laryngeal ventricle to just below cords
- True vocal cords

Subglottic larynx

- From just below cords to bottom of cricoid





Larynx Staging Changes

- Same changes to clinical and pathologic nodal staging as we reviewed for oral cavity (impact of clinical and pathologic ENE)

Fiberoptic Laryngoscopy

- Fundamental skill for any head/neck radiation oncologist
- Especially important for evaluation of larynx cases, but also for other sites (tongue base, nasopharynx, hypopharynx)
- Should not be delegated to ENT if at all possible
- *Laryngoscopy video*

Glottic Larynx: Treatment Approach

- T1-2, T3 and T4 all have different algorithms
- T1-2
  - Radiation vs. cord-stripping
  - Radiation preferred unless disease is very superficial
  - T1: 63 Gy/28 fxs
  - T2: 65.25/29 vs. 68-70/34-35
  - Selected T2b cases (impaired vocal cord mobility) may benefit from cisplatin/RT

Hypofractionation

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 77–82, 2006
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0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.06.014

CLINICAL INVESTIGATION **Head and Neck**

RADIOTHERAPY FOR EARLY GLOTTIC CARCINOMA (T1N0M0): RESULTS OF PROSPECTIVE RANDOMIZED STUDY OF RADIATION FRACTION SIZE AND OVERALL TREATMENT TIME

HIDEYA YAMAZAKI, M.D.,* KINJI NISHIYAMA, M.D.,* EIICHI TANAKA, M.D.,*
MASAHIKO KOIZUMI, M.D.,† AND MASASHI CHATANI, M.D.‡

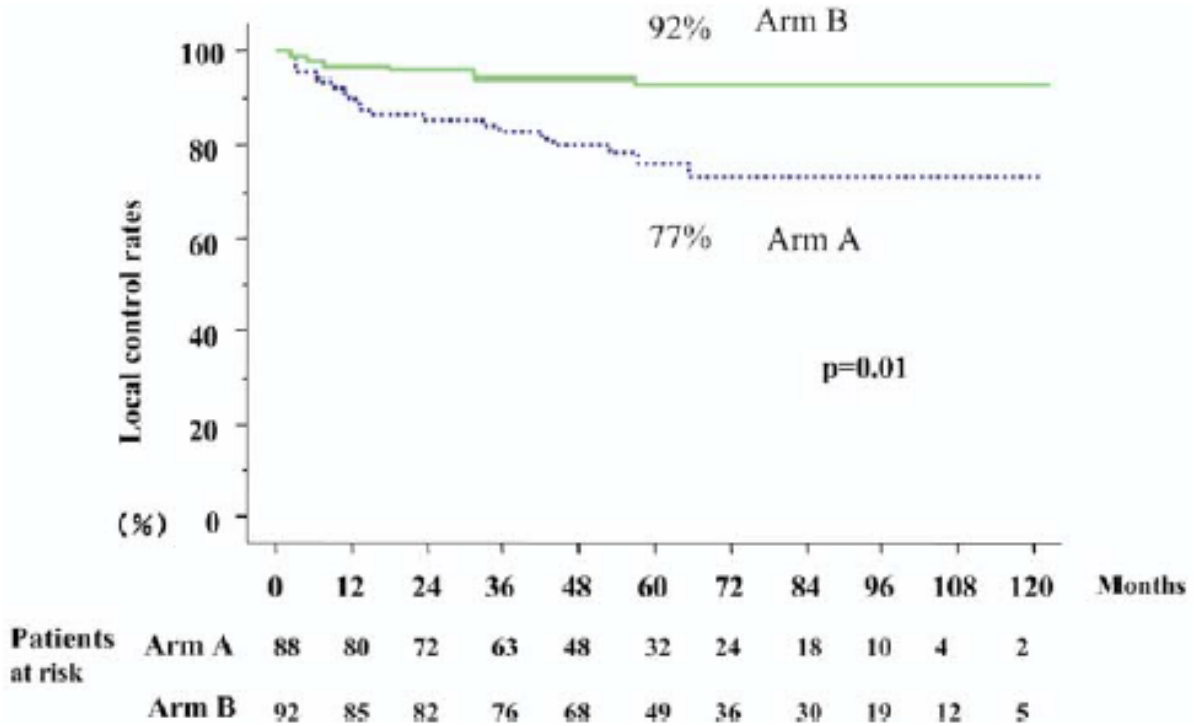

Fig. 1. Local control rates between Arms A and B.

Field Design: 3D vs. IMRT (carotid sparing)

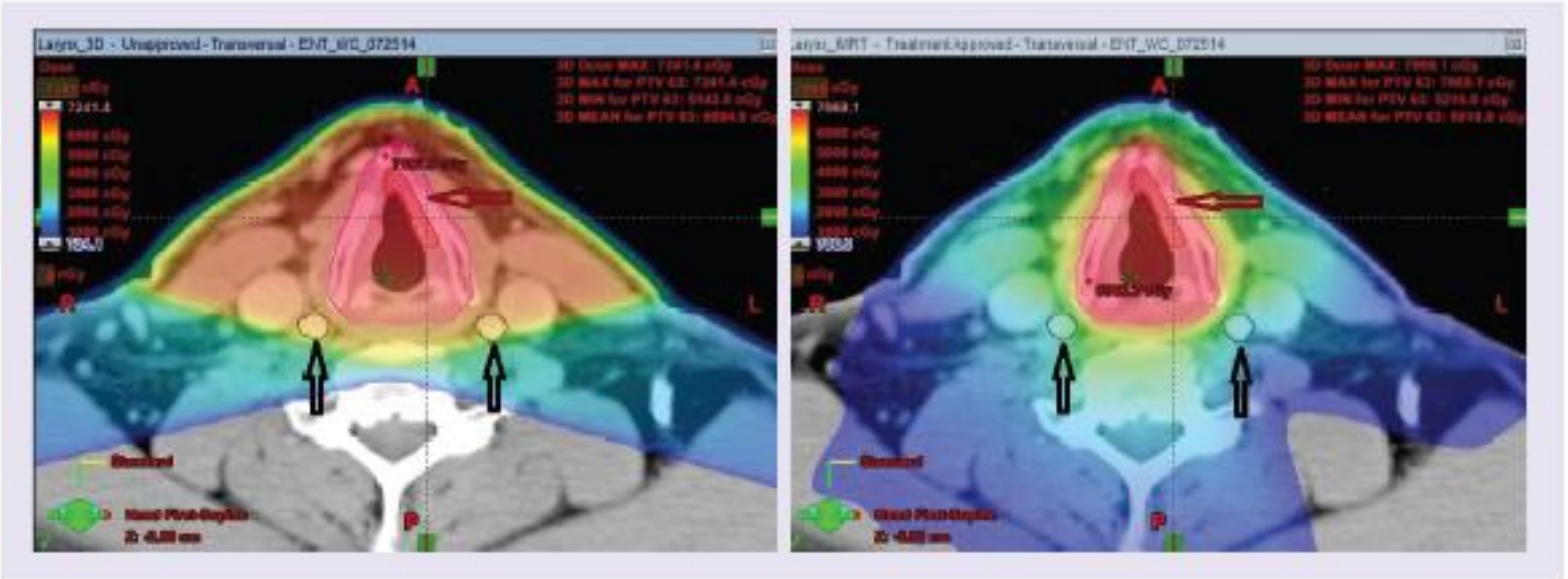

Figure 2. Comparative radiation dose distributions comparing conventional radiotherapy (left) and intensity-modulated radiotherapy (right). The colorwash display indicates higher dose in red and lower dose in blue. The carotids are indicated with black arrows and the vocal cord tumor with dark red arrows.

T3 Glottic Larynx: Treatment Approach

- Larynx preservation is the central concept for T3
- VA Larynx Trial
  - Total laryngectomy vs. induction chemo followed by RT
  - Equal survival with 2/3 of patients in chemoRT arm able to preserve larynx
- RTOG 91-11
  - Sequential chemoRT vs. concurrent chemoRT vs. RT alone
  - Concurrent chemoRT had best larynx preservation and locoregional control
- To be a candidate for larynx preservation, patient must have a functional larynx (able to breathe and swallow)
- UF criterion of tumor volume <3.5 cc with no airway compromise to qualify for larynx preservation

(N Engl J Med 1991; 324:1685-90.)

INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*

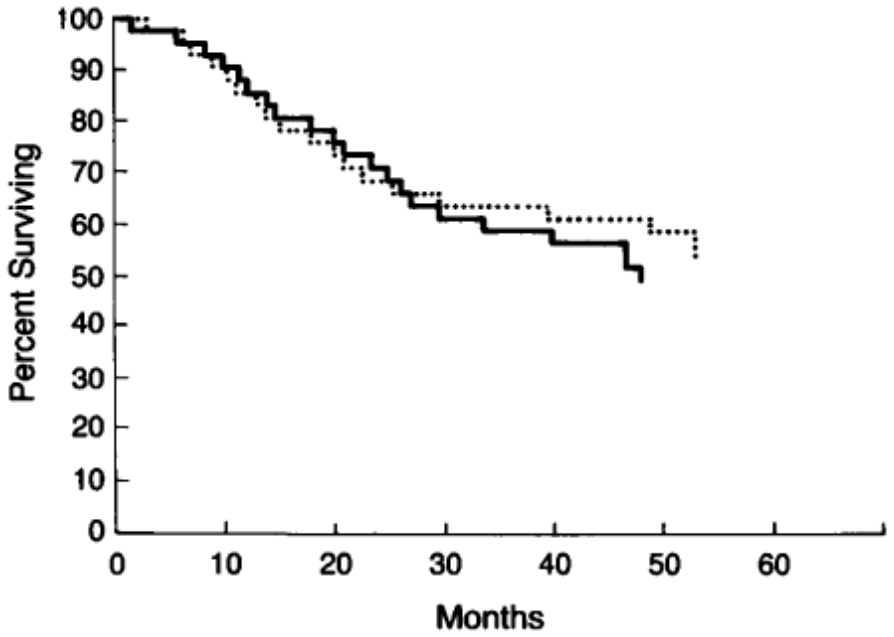

Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

Survival rates at two years were 68 percent for both groups (P = 0.9846). The median follow-up was 33 months.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak, William Morrison, Bonnie Glisson, Andy Trotti, John A. Ridge, Wade Thorstad, Henry Wagner, John F. Ensley, and Jay S. Cooper

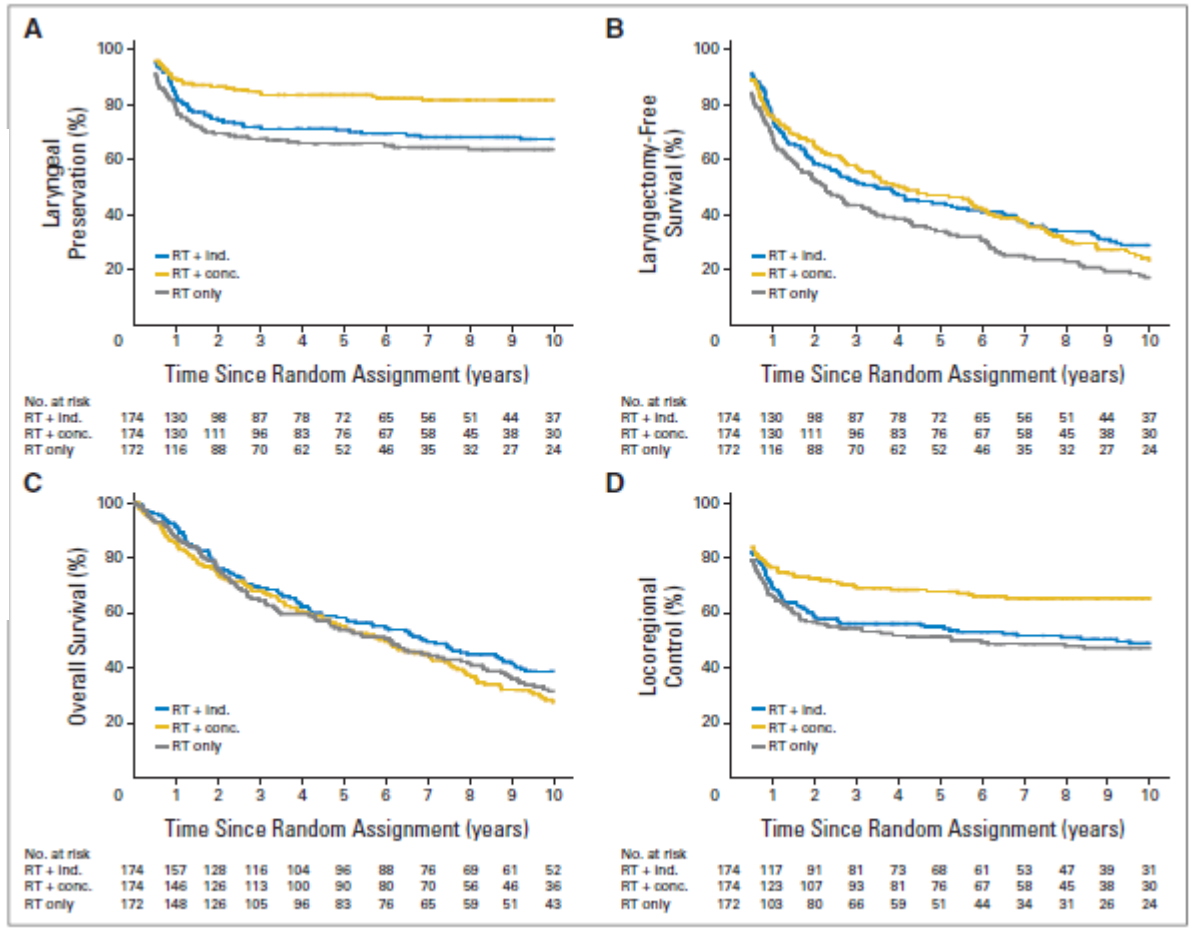
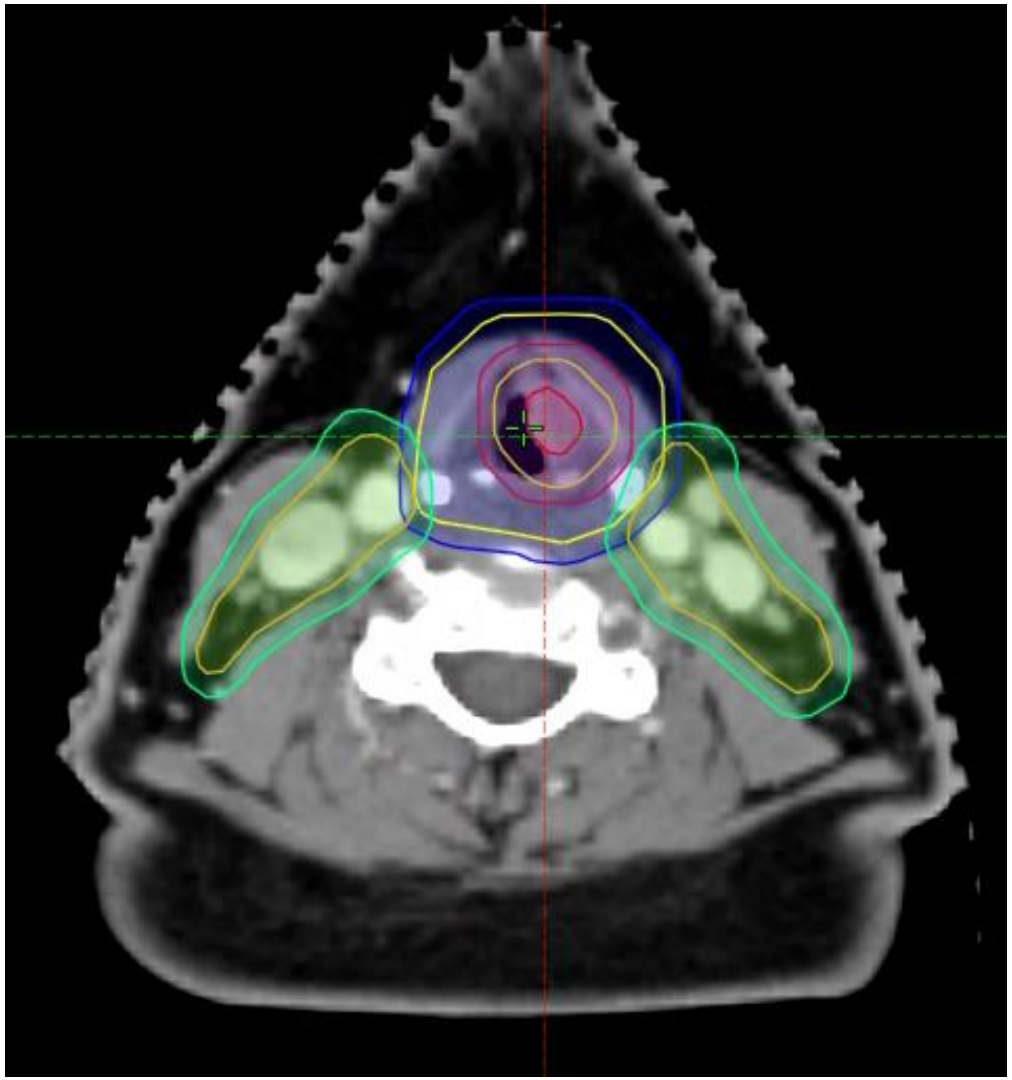


Fig 2. (A) Laryngeal preservation, (B) laryngectomy-free survival, (C) overall survival, and (D) locoregional control according to treatment group. conc., concomitant; Ind., induction; RT, radiation therapy.

T3 Glottic Larynx: Planning

- GTV70 defined by imaging and fiberoptic exam
- CTV70 is 5 mm expansion
- PTV70 is 3 mm expansion
- CTV60 is entire larynx
- PTV60 is 3 mm expansion
- Nodal coverage is usually levels 2-4
- Concurrent cisplatin chemotherapy



T4 Glottic Larynx: Treatment Approach

- T4 glottic larynx cancer is a “surgical disease” based on poor outcome of T4 cases in VA larynx trial
- Beware of the trap of offering T4 patients larynx preservation with the idea of saving total laryngectomy for salvage—not all recurrences can be salvaged.

“Olsen Hypothesis”

- Larynx cancer is the only major cancer in which survival is falling
- This is due to the substitution of chemoRT in T4 cases with inability to salvage some failures

REEXAMINING THE TREATMENT OF ADVANCED LARYNGEAL CANCER

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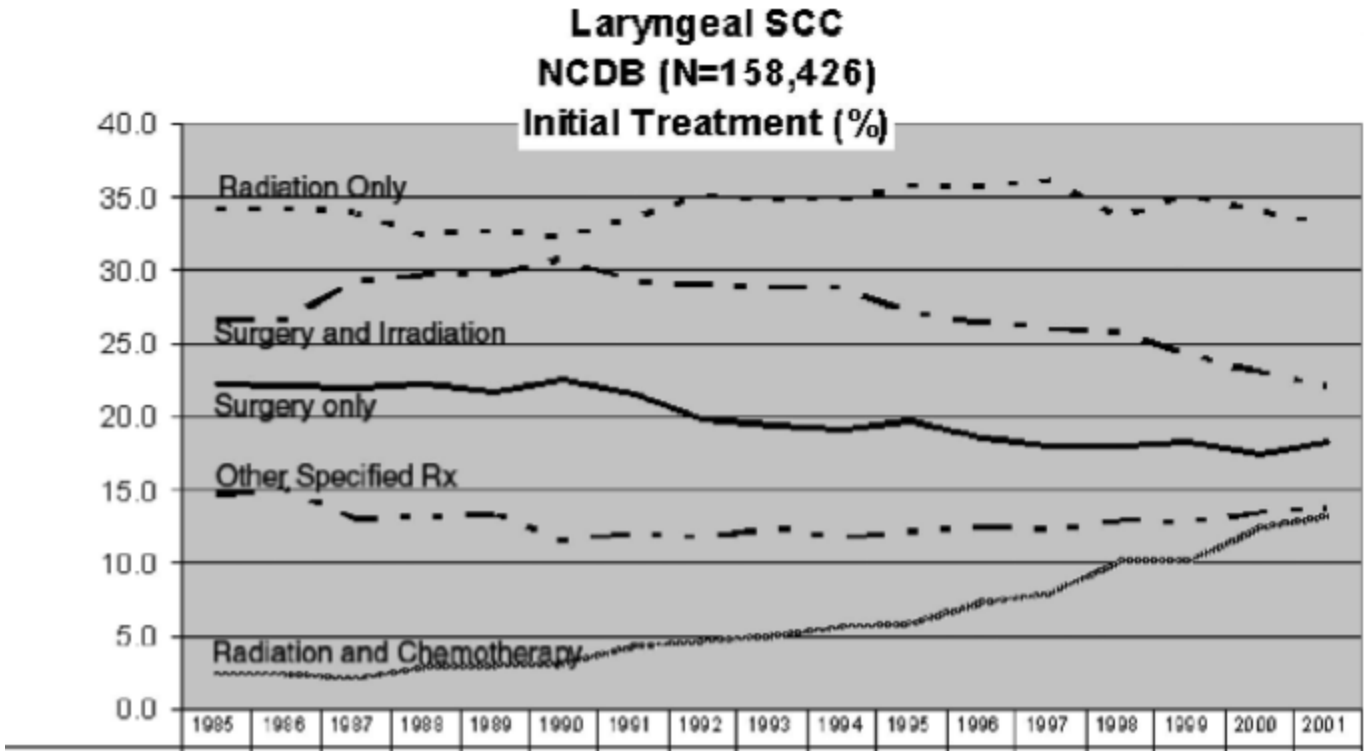
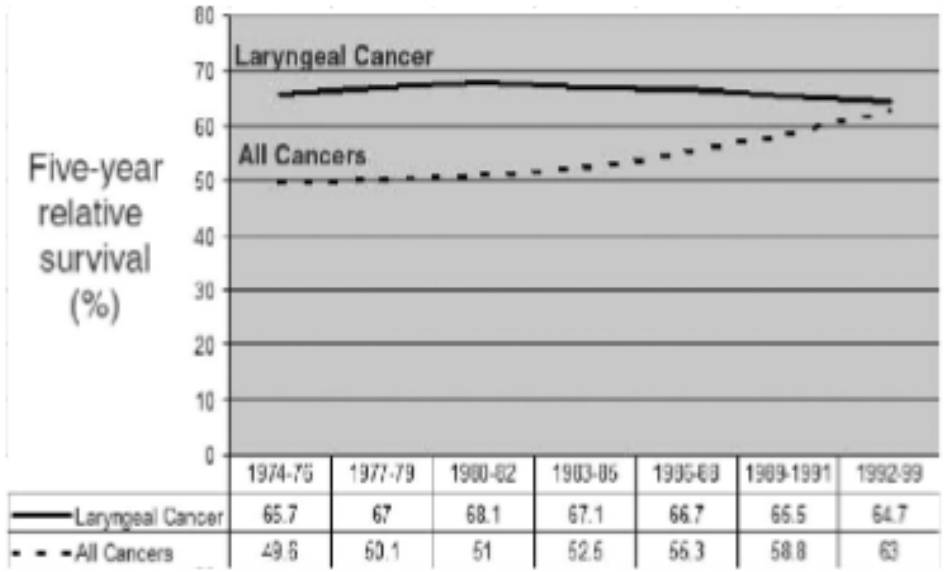
Laryngeal Cancer in the United States: Changes in Demographics, Patterns of Care, and Survival

Henry T. Hoffman, MD, MS, FACS; Kimberly Porter, MPH; Lucy H. Karnell, PhD; Jay S. Cooper, MD; Randall S. Weber, MD; Corey J. Langer, MD; Kie-Kian Ang, MD, PhD; Greer Gay, PhD; Andrew Stewart, MA; Robert A. Robinson, MD, PhD

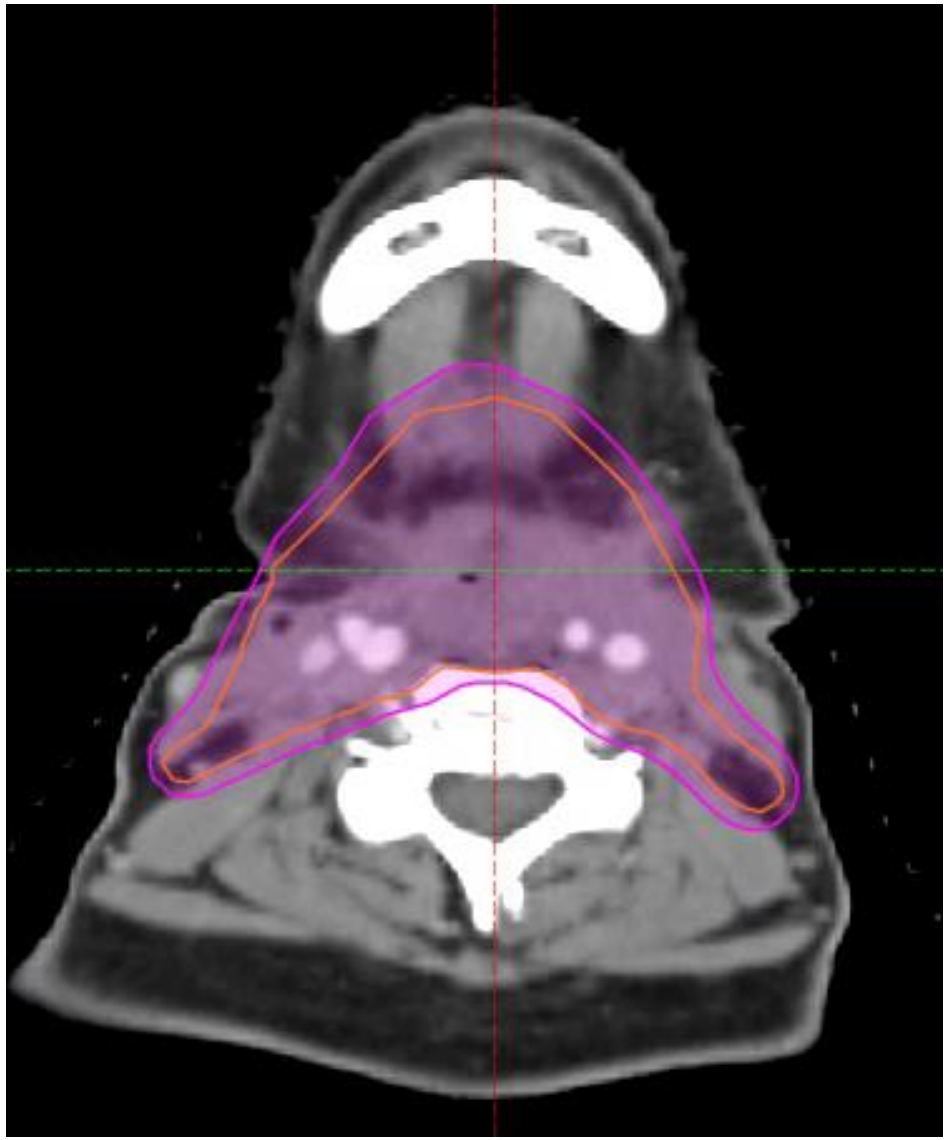
Laryngoscope, **116(Suppl. 111):1–13, 2006**





T4 Glottic Larynx: Postoperative RT

- Based on pathologic evidence of cartilage invasion, treat the tumor bed with neopharynx from the distal tongue base to the upper esophagus with margin
  - 60 Gy/30 fxs
- Cover draining nodes bilaterally at levels II-IV
  - 54-60 Gy depending on nodal involvement
- Level VI for subglottic extension
- ChemoRT for positive margins or ENE



Supraglottic Larynx: Treatment Approach

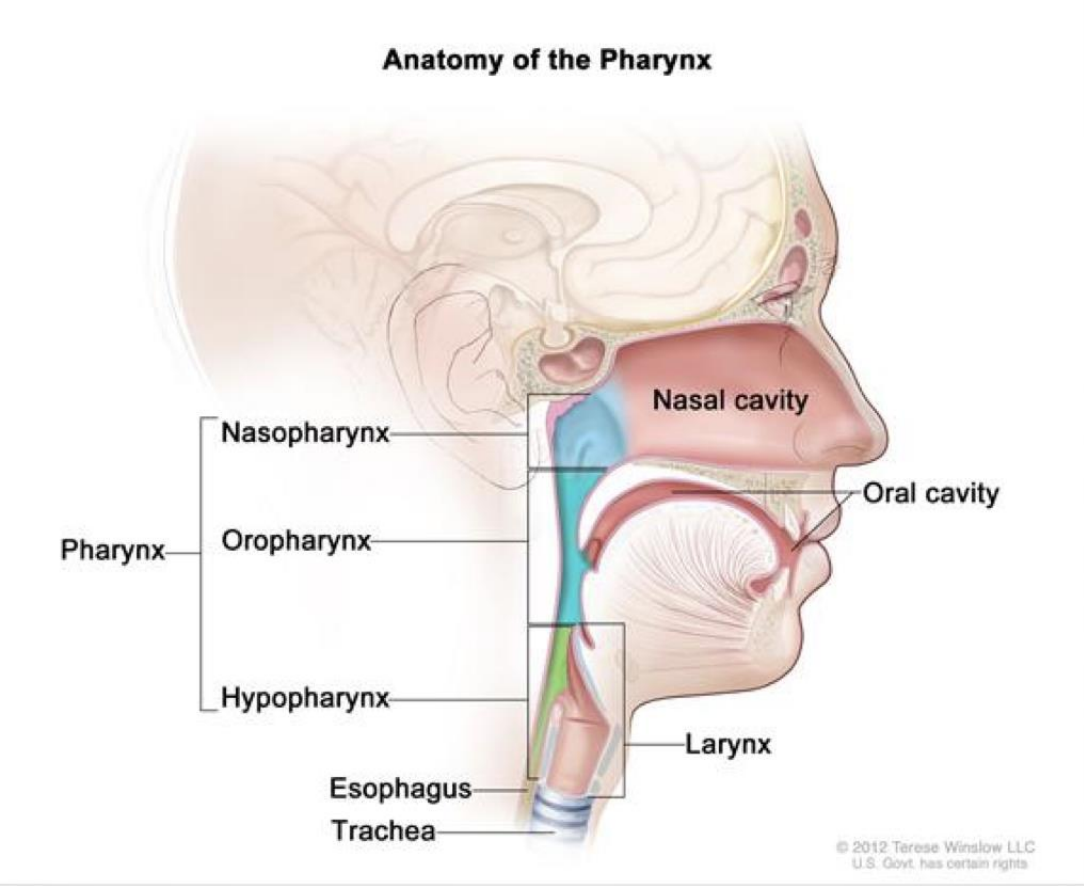
- Supraglottic laryngectomy appropriate for selected early cases
  - pT1-2N0-1
  - Good pulmonary status—aspiration is a risk after supraglottic laryngectomy
- Otherwise, main approach is definitive RT or chemoRT
- Must have functional larynx (breathe and swallow)
- 70/63/56 with chemo or accelerate if RT alone
- Cover levels II-IV bilaterally
- ChemoRT for
  - >T2N1 disease, OR
  - Tumor volume >6 cc (UF approach)

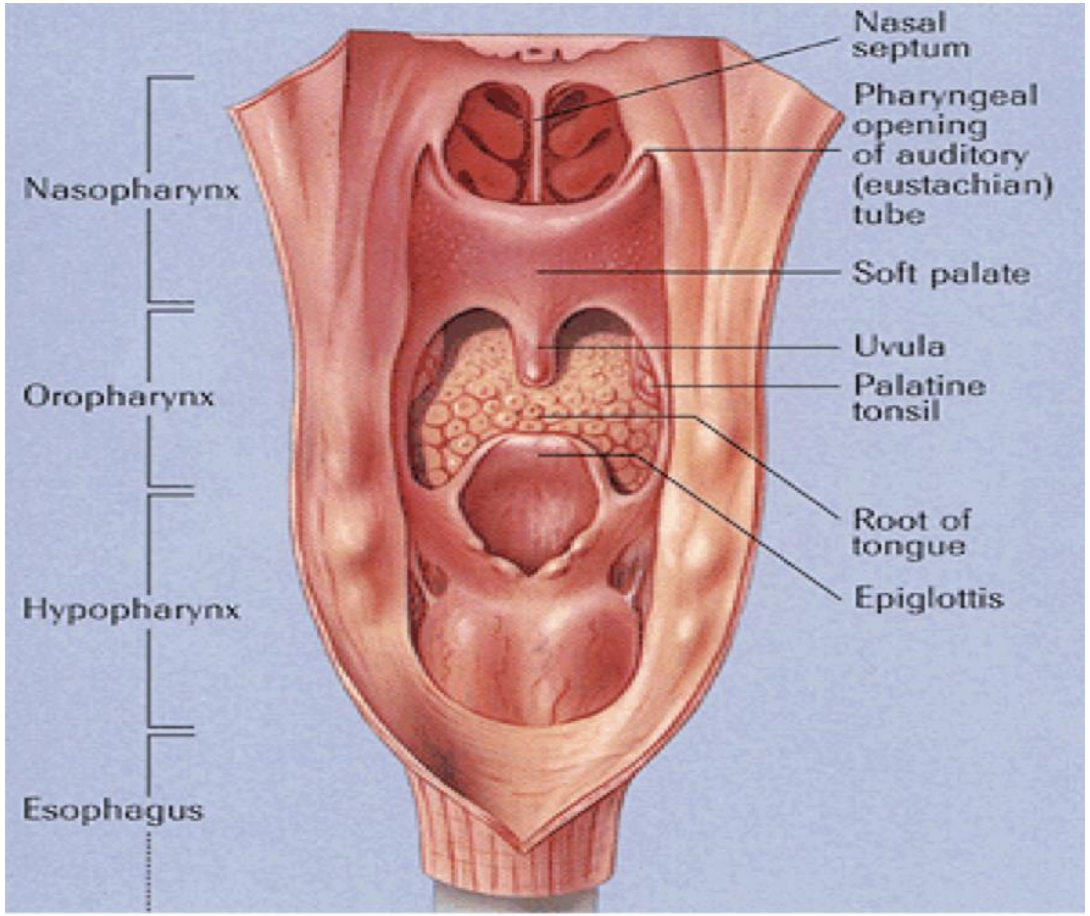
Subglottic Larynx: Treatment Approach

- These are rare compared to glottic and supraglottic tumors
- Tend to have clinically aggressive behavior
- Access to tracheal lymphatics
- May cause airway obstruction
- Can be treated with definitive chemoRT, but salvage can be difficult
- More advanced tumors often treated with total laryngectomy, low tracheostomy and postoperative RT/chemoRT
- Cover levels II-IV, VI

Hypopharynx

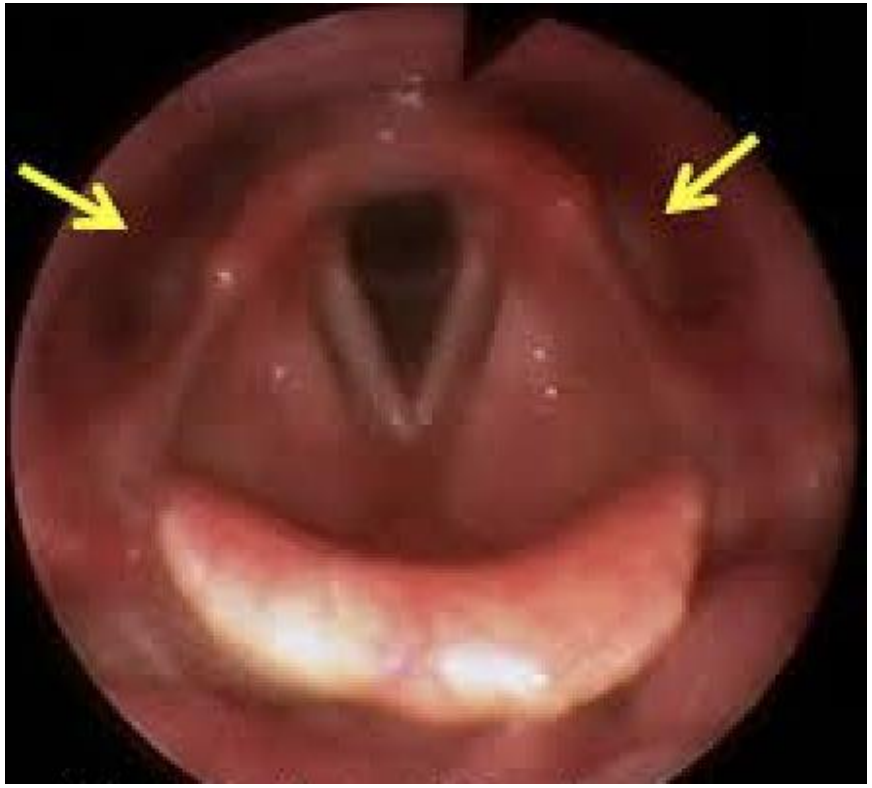
Hypopharynx: Anatomy





Hypopharynx: Subsites

- Pyriform sinuses (seen at left)
- Post-cricoid
- Posterior hypopharyngeal wall

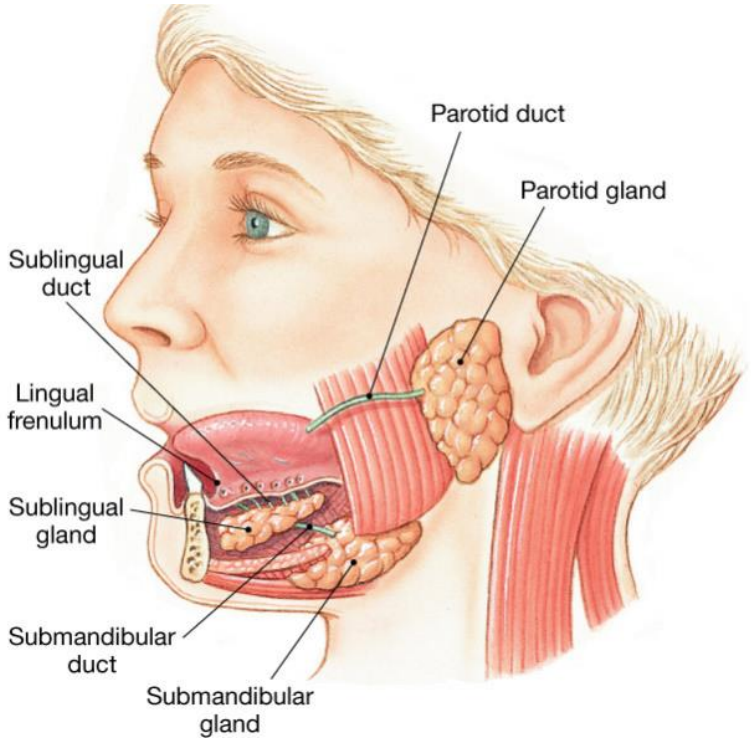


Hypopharynx: Treatment Approach

- Generally seen as a “surgical disease.”
- Usually present late
- Often involve lymphatics
- Often irreversibly compromise swallowing function
- Primary surgical approach is total laryngectomy + partial pharyngectomy with flap reconstruction followed by RT or chemoRT
- T1 cases (very rare) may be managed with RT alone; T2 cases (also very rare) with chemoRT
- Cover RP, level VI

Salivary Tumors

Salivary Gland Tumors



- Divided into major and minor salivary glands
- Major
  - Parotid
  - Submandibular
  - Sublingual
- Minor
  - Scattered nests of salivary tissue throughout the upper aerodigestive tract
  - Hard palate is the most common site

Salivary Histologies

- Many different histologies, each with an expected behavior related to grade and other characteristics
- Low Grade
  - Pleomorphic adenoma
  - LG mucoepidermoid
  - Acinic cell
- High Grade
  - HG mucoepidermoid
  - Adenoid cystic
  - Adenocarcinoma
  - Carcinoma ex-pleomorphic adenoma
  - Squamous cell carcinoma
  - Salivary duct carcinoma

Salivary Tumors: Treatment Approach

- Salivary tumors are a “surgical disease.” Unless unresectable, all cases begin with an attempt at complete surgical resection.
- Postoperative RT indicated for
  - High grade
  - Close or positive margins
  - Perineural invasion (all adenoid cystic cases)
  - Lymph node involvement (proof of high grade behavior)
  - Recurrence
  - Tumor spillage

Salivary Tumors: Chemotherapy

- Role of chemotherapy not well-defined
- Consider for multiple positive nodes
- Patients should be enrolled on RTOG 1008
  - Postoperative RT +/- weekly cisplatin for high-grade salivary tumors

Additional Topics

Altered Fractionation

- Very confusing area for many practitioners
- RTOG 90-03
- DAHANCA
- RTOG 0129

Final Results of Local-Regional Control and Late Toxicity of RTOG 9003: A Randomized Trial of Altered Fractionation Radiation for Locally Advanced Head and Neck Cancer

Jonathan J. Beitler, MD, MBA,* Qiang Zhang, PhD,† Karen K. Fu, MD,‡ Andy Trotti, MD,§ Sharon A. Spencer, MD,‖ Christopher U. Jones, MD,¶ Adam S. Garden, MD,# George Shenouda, MD,** Jonathan Harris, MS,† and Kian K. Ang, MD, PhD (deceased)#

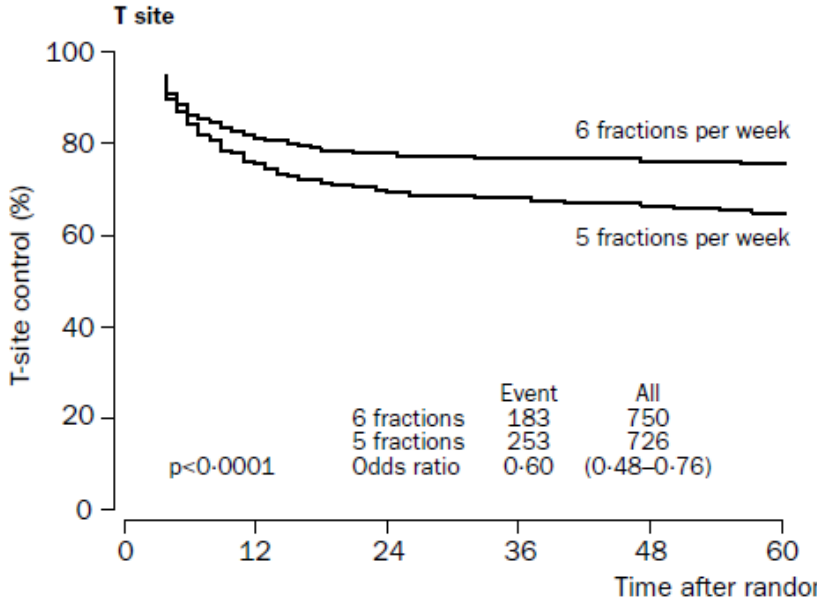
Int J Radiation Oncol Biol Phys, Vol. 89, No. 1, pp. 13–20, 2014

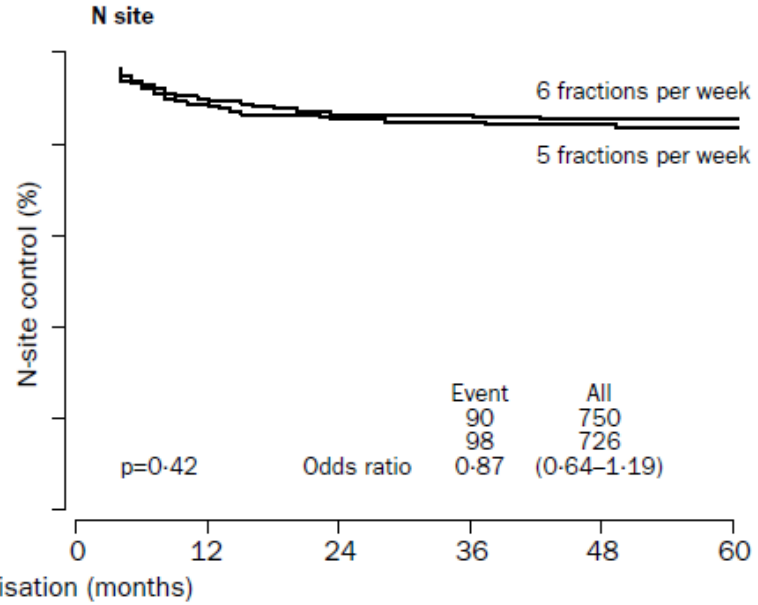
- 4-arm radiation-only study
- 3 hyperfractionated arms with once-daily radiation control arm
- Improved local control with pure hyperfractionated and concommitant-boost arms
- Improved overall survival with pure hyperfractionated arm

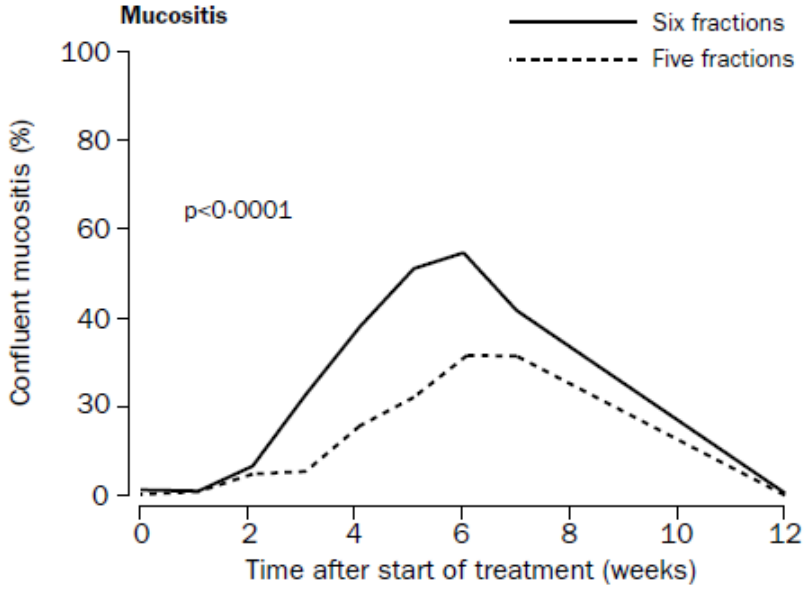
Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Lancet 2003; **362:** 933–40

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group





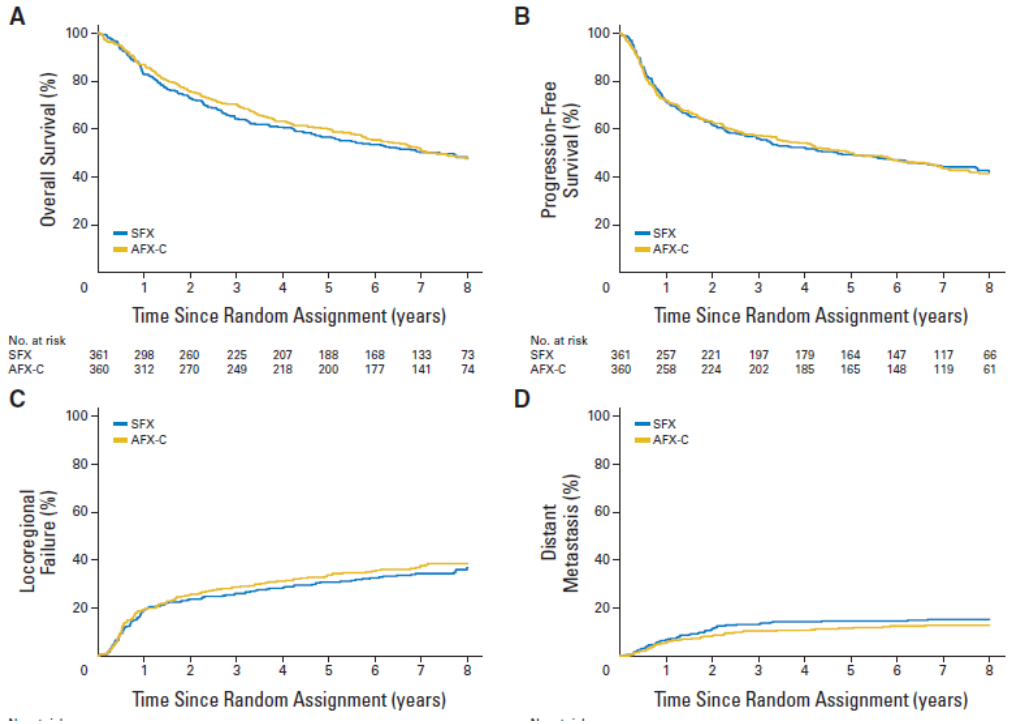


Randomized Phase III Trial to Test Accelerated Versus Standard Fractionation in Combination With Concurrent Cisplatin for Head and Neck Carcinomas in the Radiation Therapy Oncology Group 0129 Trial: Long-Term Report of Efficacy and Toxicity

J Clin Oncol 32:3858-3867. © 2014 by American Society of Clinical Oncology

Phuc Felix Nguyen-Tan, Qiang Zhang, K. Kian Ang, Randal S. Weber, David I. Rosenthal, Denis Soulieres, Harold Kim, Craig Silverman, Adam Raben, Thomas J. Galloway, André Fortin, Elizabeth Gore, William H. Westra, Christine H. Chung, Richard C. Jordan, Maura L. Gillison, Marcie List, and Quynh-Thu Le

In the setting of concurrent chemotherapy, there was no benefit to accelerated fractionation compared to standard fractionation.



Chemotherapy for Head/Neck Patients

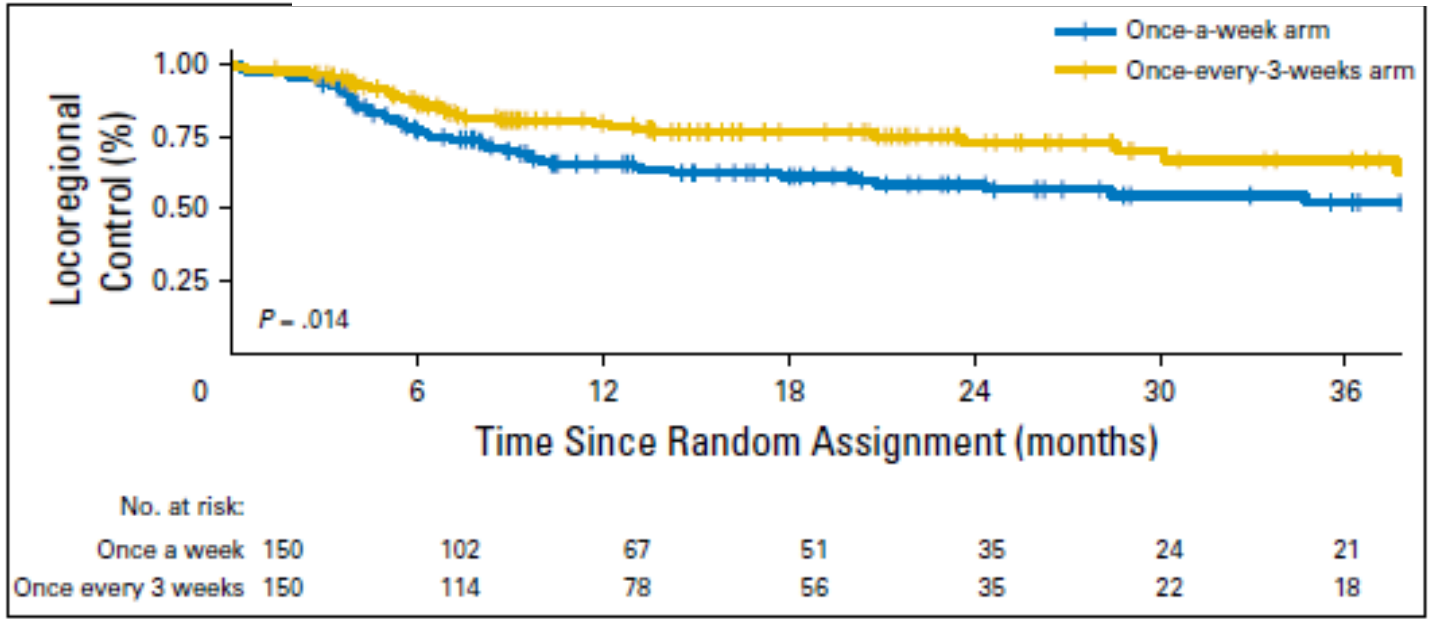
- Mainstay of chemotherapy in the definitive and postoperative settings is cisplatin
  - Both high/dose (bolus) at 100 mg/m^2 and weekly at 30-40 mg/m^2 are used widely
  - Recent Indian randomized study demonstrated improved locoregional control with bolus treatment

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial

Vanita Noronha, Amit Joshi, Vijay Maruti Patil, Jaiprakash Agarwal, Sarbani Ghosh-Laskar, Ashwini Budrukkar, Vedang Murthy, Tejpal Gupta, Anil K. D'Cruz, Shripad Banavali, Prathamesh S. Pai, Pankaj Chaturvedi, Devendra Chaukar, Nikhil Pande, Arun Chandrasekharan, Vikas Talreja, Dilip Harindran Vallathol, Vijayalakshmi Mathrudev, Aparna Manjrekar, Kamesh Maske, Arati Sanjay Bhelekar, Kavita Nawale, Sadhana Kannan, Vikram Gota, Atanu Bhattacharjee, Shubhada Kane, Shashikant L. Juvekar, and Kumar Prabhash

J Clin Oncol 35. *© 2017 by American Society of Clinical Oncology*



Cetuximab

- What about cetuximab?
  - Bonner trial demonstrated OS advantage of RT/cetuximab over RT alone
  - Only large, randomized comparison of RT/cetuximab vs. RT/cisplatin is RTOG 1016 in HPV+ population—no results yet
  - Retrospective 2011 trial from MSKCC for locally advanced HNSCC showed significant improvements in LRC, FFS and OS for concurrent cisplatin vs. concurrent cetuximab
  - Retrospective 2015 trial from MDACC for p16+ oropharynx patients showed no differences in survival for concurrent cisplatin, carboplatin or cetuximab
  - As of now, concurrent cisplatin remains SOC for all groups. Cetuximab reserved for patients who cannot receive cisplatin.

Chemotherapy, cont.

- How many cycles of bolus cisplatin are indicated?
  - In previous RTOG studies, about half of patients did not receive the third planned cycle of bolus cisplatin due to toxicity
  - For definitive treatment of HPV+ disease, RTOG 1016 used 2 cycles
  - For definitive or postoperative treatment of HPV-negative disease, 3 cycles is generally indicated

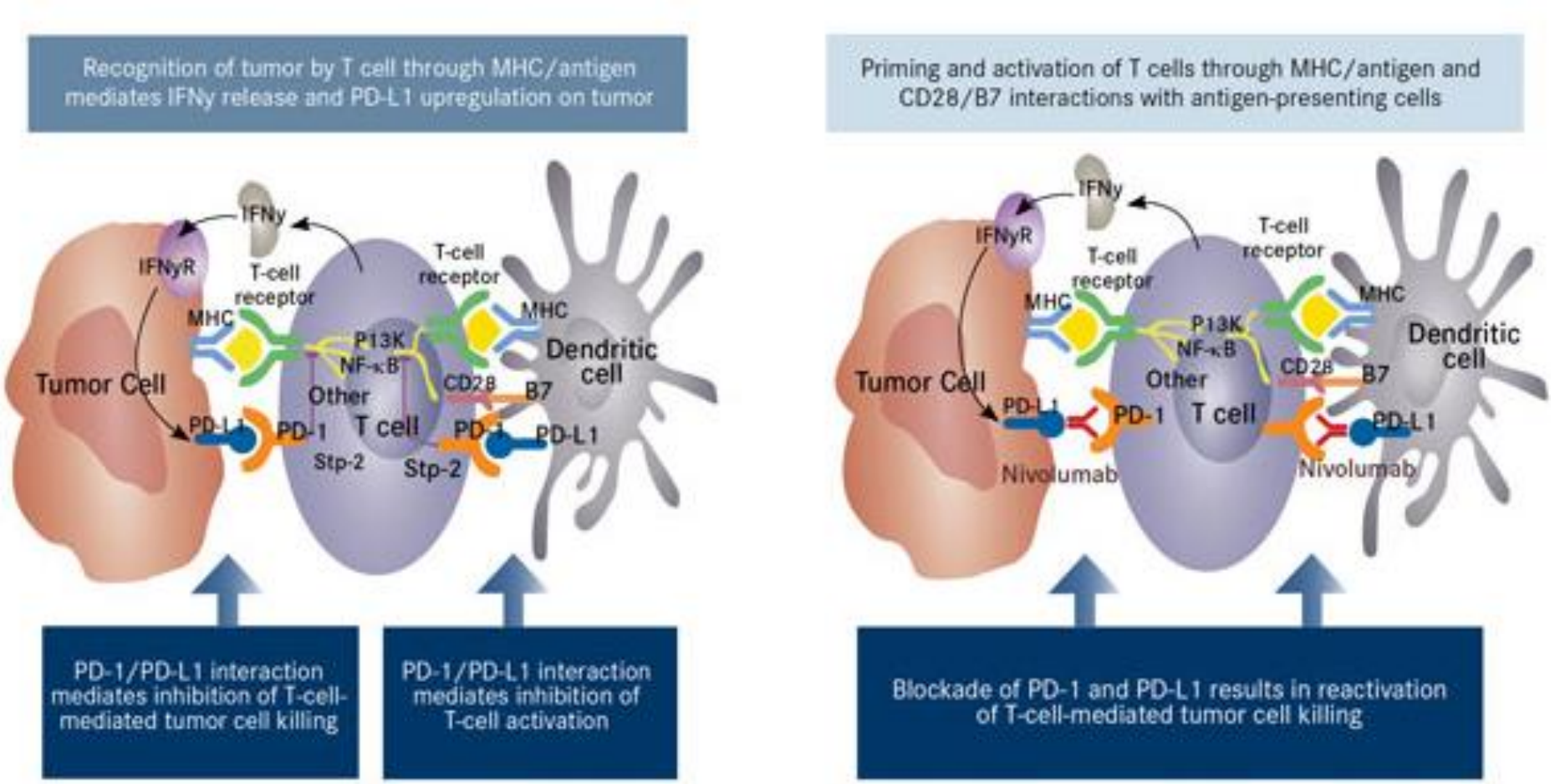
Chemotherapy, cont.

- What about induction chemotherapy?
  - Popularized by the TAX324 trial
    - Trial showed advantage of a taxane (docetaxel) added to PF used for induction compared to the same induction without the taxane
    - The study did not compare an induction strategy to a pure concurrent strategy
    - This was the role of the DECIDE and PARADIGM trials
      - Both finished early and showed no advantage for induction
  - Where might induction have an advantage?
    - Prevent tracheostomy in patient with impending airway compromise
    - Rapidly-progressing disease with need to start therapy immediately, before IMRT can be planned

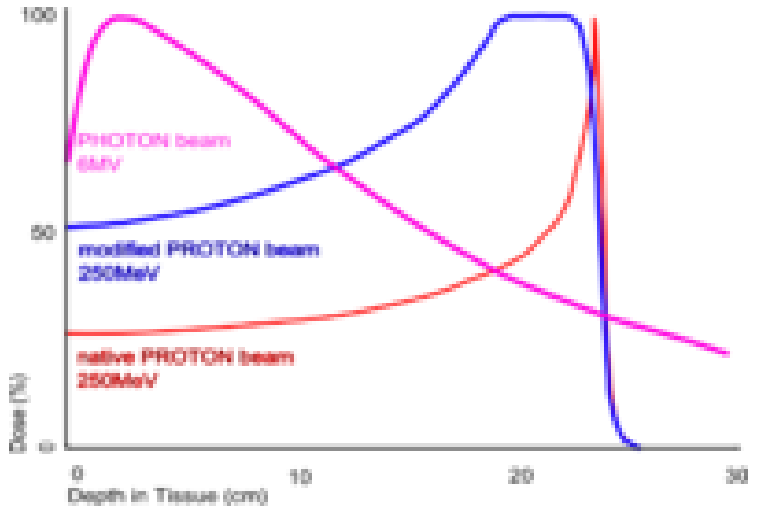
Immunotherapy

- Pembrolizumab and nivolumab are FDA-approved for recurrent/metastatic HN cancers after failure of platinum-containing chemotherapy
- Both are PD-1 (programmed death receptor 1) blocking antibodies
- Pembrolizumab is given IV every 3 weeks and nivolumab is given IV every 2 weeks
- Multiple PD-1 and PDL-1 agents are in current trials in combination with standard chemoRT for high-risk locally advanced HN cancers, but none is currently approved for that indication

PD-1/PD-L1 Inhibitor Mechanism



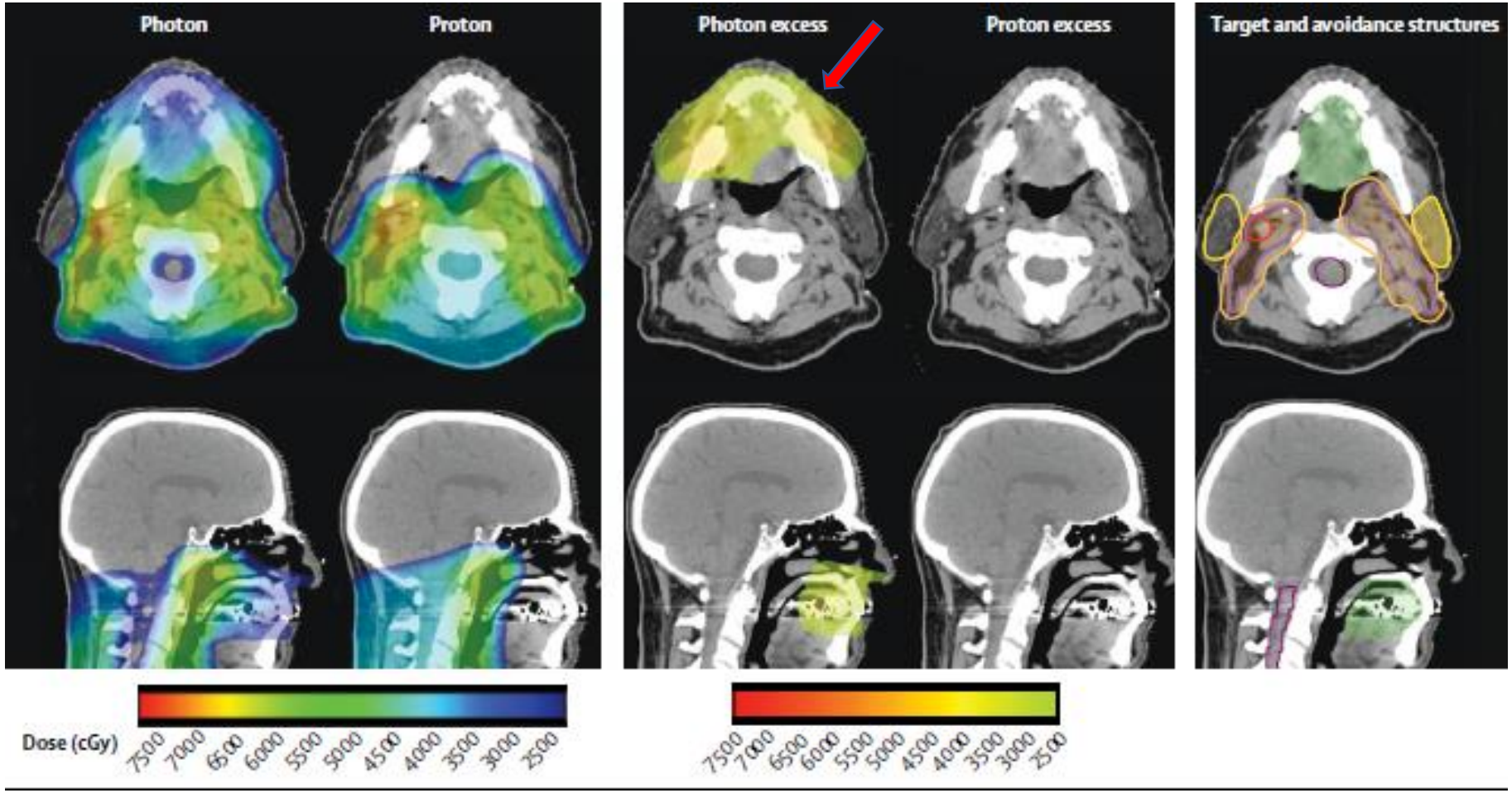
Proton Therapy



Proton Therapy

- Focus of research on proton therapy for HN cancer relates to reduction in normal tissue toxicity from dosimetric advantage of IMPT.
- Essentially no dose beyond Bragg peak tends to reduce or eliminate dose to normal structures beyond target, in contrast to IMRT.
- Advantages are greatest for unilateral cases
- No prospective, randomized data yet

Protons, cont. (Post-TORS tonsil case)



Proton Data (all retrospective comparisons)

- Multiple published studies showing statistically significant reductions in toxicity:
  - Mucositis
  - Nausea
  - Dysgeusia
  - Fatigue
  - Feeding tube dependence
  - Pain
  - Xerostomia

Recommended Proton Review

Head and neck cancer 1

Proton therapy for head and neck cancer: expanding the therapeutic window

Jonathan E Leeman, Paul B Romesser, Ying Zhou, Sean McBride, Nadeem Riaz, Eric Sherman, Marc A Cohen, Oren Cahlon, Nancy Lee

Lancet Oncol 2017; 18: e254–65

Coverage of Tracheostomy Site

- Tracheostomy site is at elevated risk for recurrence when
  - Tumor involved the subglottis
  - Tracheostomy was placed with primary tumor still present (possibility of seeding the tracheostomy wound)
- How to prevent recurrence at this location?
  - If IMRT is used to treat low neck, contour tissues around tracheostomy to receive 60 Gy
    - Unlike traditional AP supraclav field, IMRT may provide enough surface dose to make bolus unnecessary
    - Can check with surface dosimeter
  - If conventional AP supraclav field is used, consider “donut” bolus to prevent skin sparing in this area

Treatment of Retrostyloid and Retropharyngeal nodes

- Retrostyloid
  - Treat whichever side has level 2 nodal involvement
- Retropharyngeal
  - Cover both lateral RP volumes in any pharyngeal primary case (safest broad recommendation), OR
  - Cover ipsilateral RP volume only if the pharyngeal wall is involved in an oropharynx case, but bilateral RPs for all nasopharyngeal and hypopharyngeal cases
  - Cover medial RP volumes only if the lateral RP nodes are involved

Re-Irradiation

- Acceptance of re-irradiation for HN tumors has increased markedly from the late 1990s (RTOG 96-10) to 2018
  - Previous standard of considering re-irradiation only for cases in which surgical salvage with negative margins was impossible has now shifted
  - Current SOC has migrated to
    - Post-op re-irradiation for similar indications as any other post-op case
    - Definitive re-irradiation for unresectable cases
    - 6-month disease-free interval
    - Concurrent chemotherapy is used in almost all non-SBRT re-irradiation settings
  - Usual fractionation is 2 Gy/d to 60-70 Gy
  - RFS 42% at 2 years in one report, 25% risk of severe late effects
  - SBRT is an alternative for well-localized, unresectable recurrences

Follow-Up Imaging

- Since the Yao publication in 2008, use of a PET-CT scan at 3 months post definitive RT has been accepted as the key imaging study to assess response (negative predictive value 99% at primary and neck)
- Previous algorithms using routine 6 month imaging after the 3-month PET are no longer current.
  - No data exists showing a benefit of routine imaging after 6 months
  - NCCN no longer recommends routine imaging after 6 months unless site difficult to visualize or symptoms prompt imaging
- Imaging should always be obtained if signs/symptoms merit or if tumor site is not amenable to examination

Support of the Head/Neck ChemoRT Patient

- Head/neck chemoRT is a highly toxic treatment, with 95% of patients suffering grade 3 acute toxicity and 75% suffering grade 3 late toxicity
- Most of the acute toxicity relates to radiation treatment, especially to oral mucositis
  - It is the responsibility of the radiation oncologist to manage these toxicities, often in coordination with other members of the treatment team
- What are key elements of this toxicity management strategy?

Support, cont.

- The most important element is PHYSICIAN/MIDLEVEL TIME
  - One weekly on-treatment visit may not suffice
  - OTVs often require 20-30 minutes or more
  - Follow-up visits need to be frequent if acute toxicity is severe
  - Assistance can be very important
    - Nutrition
    - Speech Pathology
    - Audiology
    - Pain management
    - Nursing
    - Social Work

Support, cont.

- Pain control deserves specific discussion
  - Head/neck chemoRT may be the most painful form of cancer therapy, primarily due to oral mucositis
  - There is no current drug that significantly reduces oral mucositis, so the pain must be managed
    - Oral hygiene/rinsing
    - Magic mix (liquid antacid/diphenhydramine/viscous lidocaine/antifungal/hydrocortisone)
    - NSAIDS
    - Gabapentin
    - Narcotics
  - Generally, patients without a pre-existing substance abuse history can be treated with adequate doses of narcotics for pain control and will taper off successfully when oral mucositis resolves.

Follow-up/Rehabilitation Issues

- Frequency of visits
- Pain management/narcotic taper
- Swallowing evaluation/advancing diet/indications for pharyngeal dilation
- Recovery of taste and saliva
- Fluoride treatment
- Edema/dewlap
- Fibrosis/musculoskeletal issues

Rehab, cont.

- Osteoradionecrosis vs. soft tissue necrosis
  - Potential influence of fraction size
  - Evaluation by oral surgeon for ORN cases
  - Use of HBO
  - Addition of pentoxyfylline ER (400 mg tid) and Vitamin E (1000 u qd)

Summary

Summary

- Management of head/neck cancer is a complex area of radiation oncology
  - Limited incidence compared to lung/breast/prostate cases
  - Anatomy
  - Patterns of spread
  - Use of fiberoptic laryngoscope
  - IMRT planning
  - High levels of acute and long-term toxicity

Summary, cont.

- Multidisciplinary assessment is key
  - Close relationships with HN surgeon and medical oncologist
    - Combined HN clinic arrangement is ideal
  - Regular HN tumor conference
    - Case review
    - Ongoing learning for all participants
- Incorporation of biomarkers
  - p16
  - p53
- Proton therapy
- Immunotherapy
  - Treatment for metastatic disease
  - Incorporation into trials for definitive therapy