

# Oral Cavity Squamous Cell Carcinoma

**Jeremy Price, MD, PhD**

**Faculty Advisor: Yvonne Mowery, MD, PhD**

**Duke University, Durham, NC, USA**

# Case: History

- HPI: 81F presents with **left facial swelling, difficulty chewing, dentures no longer fitting, & weight loss x 3 months**. 30 PY smoking hx.
- PE:
  - **ECOG: 2**, dementia but independent in ADLs
  - HEENT: Edentulous, **white left intraoral mass, exophytic and firm arising from left buccal mucosa**.
  - Lymphatic: No cervical, submandibular, submental, or supraclavicular lymphadenopathy



# Common Presentations:

- Oral cavity pain
- Facial swelling
- Dysgeusia, tongue immobility/deviation
- Dysphagia
- Trismus
- Speech changes
- Loose teeth
- Poorly fitting dentures
- Hx of alcohol, tobacco, betel nut use
- Cranial nerve deficits:
  - CN V2-V3 – Trismus, impaired sensation of middle and/or lower third of face, paresthesias, impaired muscles of mastication

# Case: Imaging + Biopsy



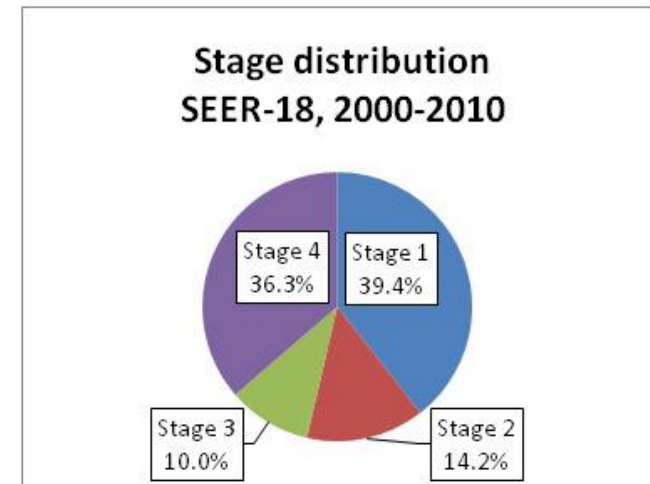
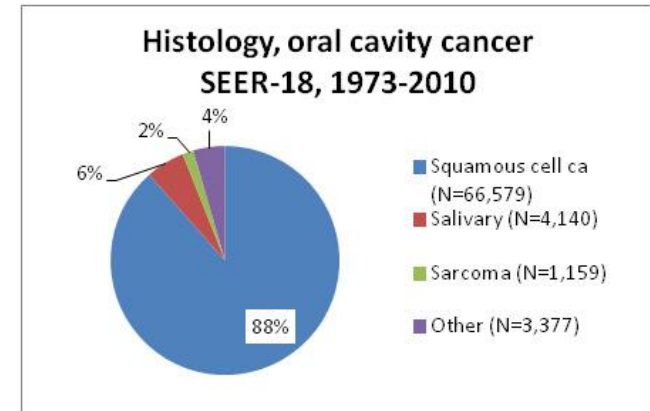
- CT neck w/ contrast: 4.6 x 3.2 x 3.9 cm left inner cheek heterogeneously enhancing mass eroding into the left mandible
- CT chest: No metastatic disease
- ENT performed incisional biopsy: well-differentiated, keratinizing invasive SCC

# Workup & Evaluation

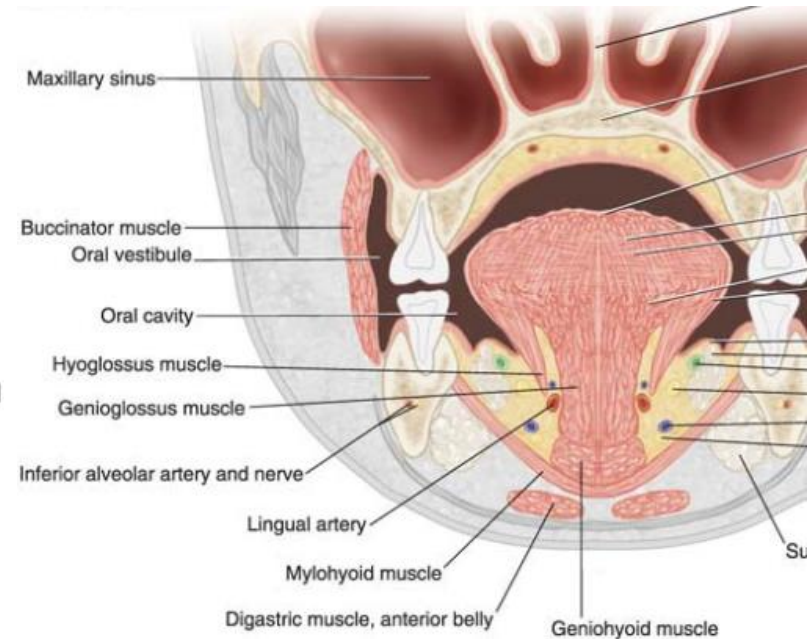
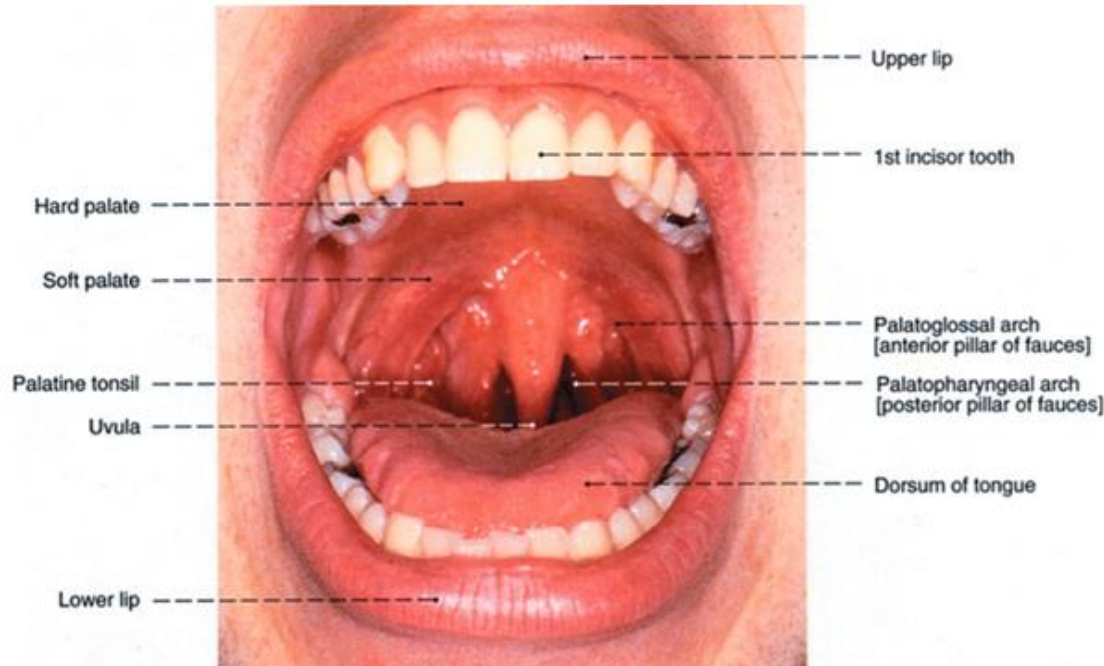
- H&P: complete H&N exam, FOL as clinically indicated (eg, BOT involvement), tobacco/EtOH use
- CT neck with contrast and/or MRI
- CT chest; consider PET systemic staging
- Core or incisional bx of primary tumor vs FNA of palpable nodes; consider exam under anesthesia
- Dental, speech therapy, nutrition evaluations
- Multidisciplinary consultation: ENT, oral surgery, radiation oncology, medical oncology, nutrition
- Tobacco cessation counseling
- Psychosocial evaluation
- HPV etiology rare and not typically tested

# Oral Cavity Cancer: Epidemiology

- Oral cavity cases: 51,540 (2018) in US
- Deaths: 10,030 in US
- 80% due to tobacco and EtOH
  - Tobacco: 3x higher risk
  - EtOH + tobacco: 10-15x higher risk
- Most commonly oral tongue in US (40-50%)
- Buccal cancer common in Asia due to betel/tobacco chewing
- Median age at diagnosis: 62
  - Most cases at age  $\geq 50$
- Median age at death: 68

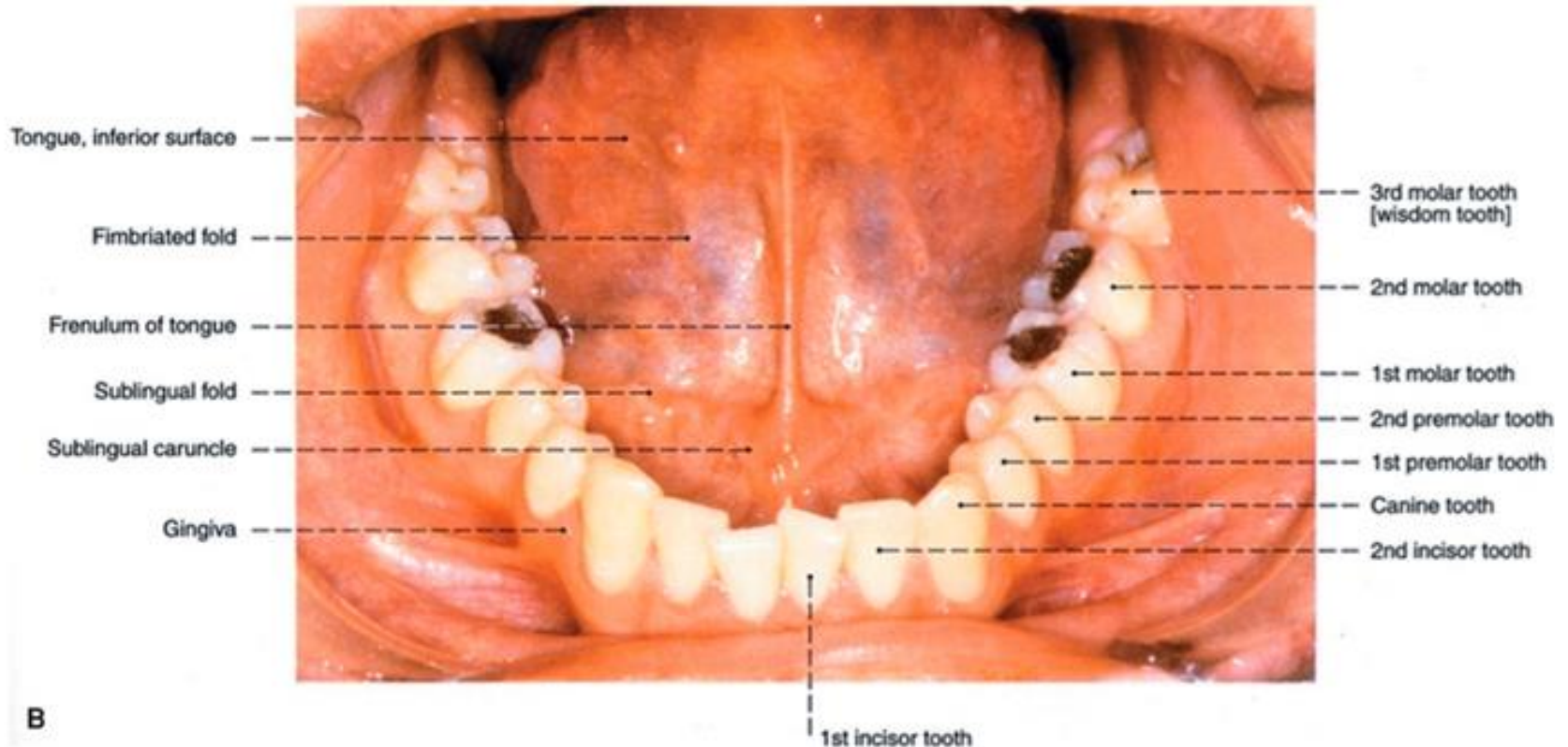


# Anatomy: Oral Cavity



- Oral cavity = Cavity bounded by alveolar margins of maxilla and mandible
- Roof: hard palate anteriorly and soft palate posteriorly
- Floor: mylohyoid muscle; anterior 2/3 of tongue on floor

# Anatomy: Oral Cavity



- See also for radiographic anatomy:  
<https://radiopaedia.org/cases/tongue-and-floor-of-mouth-neoplasm>



# Oral Cavity Cancer: T Staging

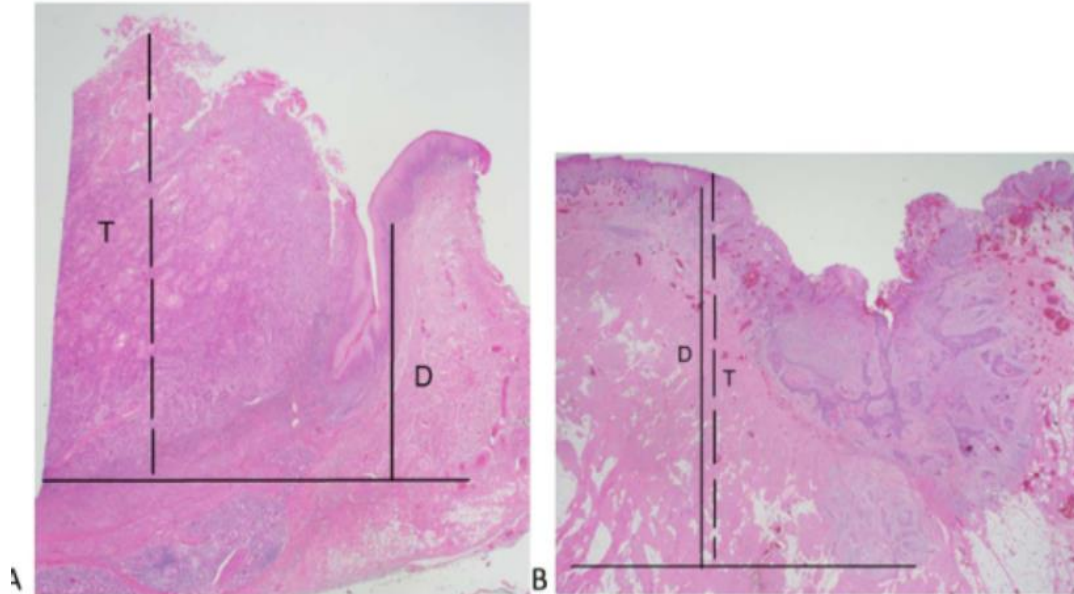
## T stage, AJCC 8<sup>th</sup> edition

T0	No evidence of primary tumor
T1	$\leq 2$ cm size <b>AND</b> * $\leq 5$ mm depth
T2	$\leq 2$ cm size AND depth $> 5$ mm but $\leq 10$ mm <b>OR</b> $> 2$ cm but $\leq 4$ cm with depth $\leq 10$ mm
T3	Tumor $> 4$ cm <b>OR</b> $> 10$ mm depth
T4	Locally advanced disease
T4a	Moderately advanced local disease (e.g. invades through cortical bone, inferior alveolar nerve, FOM/intrinsic tongue muscles, skin of face, maxillary sinus)
T4b	Very advanced local disease (e.g. invades masticator space, pterygoid plates/space, skull base, encases internal carotid artery)

\*AJCC 8th edition includes depth of invasion (DOI)

# Oral Cavity Cancer: T Staging

- Depth of invasion (DOI) versus Tumor Thickness
  - DOI = perpendicular distance from the basement membrane region to the deepest point of the infiltrative front of the tumor
  - Tumor Thickness = perpendicular distance between the highest point of the tumor surface to the deepest point of the infiltrative front of the tumor



# Oral Cavity Cancer: N Staging

N stage, AJCC 8 <sup>th</sup> edition	
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, $\leq 3$ cm, ENE-
N2	Single ipsilateral LN ( $> 3$ cm but $\leq 6$ cm) or multiple LN ( $\leq 6$ cm)
N2a	Metastasis in single ipsilateral lymph node ( $> 3$ cm but $\leq 6$ cm)
N2b	Metastasis in multiple ipsilateral lymph nodes (all $\leq 6$ cm)
N2c	Metastasis in bilateral or contralateral lymph nodes (all $\leq 6$ cm)
N3*	Metastasis in a lymph node $> 6$ cm and ENE- <b><u>OR</u></b> clinically overt ENE+
N3a	Metastasis in a lymph node $> 6$ cm and ENE-
N3b	Clinically overt ENE+

\*N3 in AJCC 8th edition is now N3a and N3b

# Oral Cavity Cancer: Stage Grouping

AJCC 8 <sup>th</sup> Edition Stage Grouping			
<b>0</b>	Tis	N0	M0
<b>I</b>	T1	N0	M0
<b>II</b>	T2	N0	M0
<b>III</b>	T3	N0 or N1	M0
	T1 or T2	N1	M0
<b>IVA</b>	T4a	N0, N1, or N2	M0
	T1, T2, or T3	N2	M0
<b>IVB</b>	Any T	N3	M0
	T4b	Any N	M0
<b>IVC</b>	Any T	Any N	M1a or M1b

# Case: Management

- Early stage lesions (T1-2, N0-1)
  - Surgery preferred
  - Definitive (chemo)radiation therapy for inoperable patients
- Locally advanced lesions (T3-4, N+)
  - Surgical resection +/- radiation
    - Add concurrent chemotherapy for ECE or + Margins
  - Definitive chemoradiation if unresectable

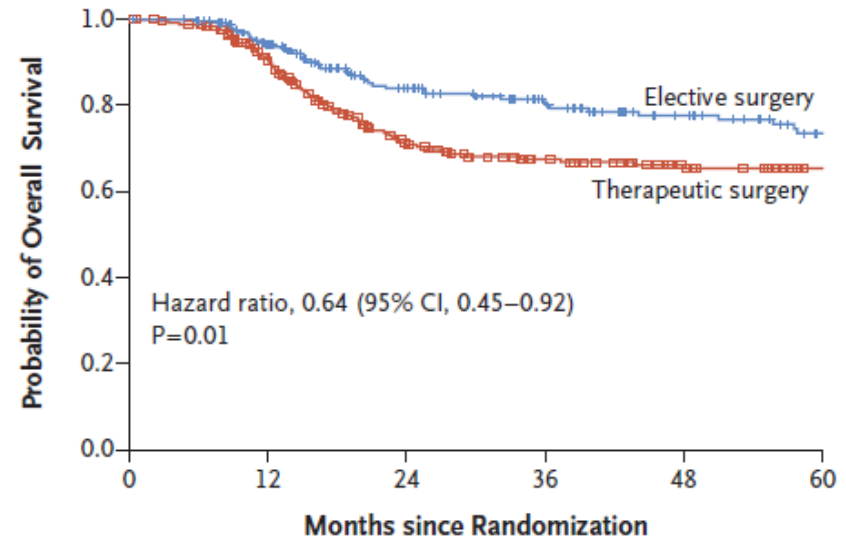
# Case: Surgical Management

- Stage IVA disease (cT4aN0M0) based on mandibular cortical bone invasion
- Surgery:
  - Radical resection of left buccal mucosa, FOM, and segmental mandibulectomy with sLND (IA, left IB-III, 0/22 LN) with **indeterminate** margins, 14 mm depth of invasion
- Neck dissection routinely includes **1<sup>st</sup> echelon nodes in level I-III**; levels IV-V may be dissected if nodal disease discovered in surgery
- Ipsilateral dissection for well cN+ lateralized primary sites; for midline primary or invasion of a midline OAR consider bilateral neck dissection
- Neck dissection when cN+
  - Consider for N0 patients if DOI > 3mm

# Oral Cavity Cancer: Surgical Management

- Should patients with oral cavity cancer have up front neck dissection?

- D’Cruz et al, NEJM 2015:
  - n=496 patients with T1-T2, cN0 SCC
- Randomized:
  - Oral excision (> 5 mm margin) w/ modified neck dissection (levels 1 – 4) if nodal relapse
  - Oral excision + ipsilateral selective neck dissection (levels 1 – 3) + included levels 4 – 5 if LN+ during surgery
  - PORT as clinically indicated

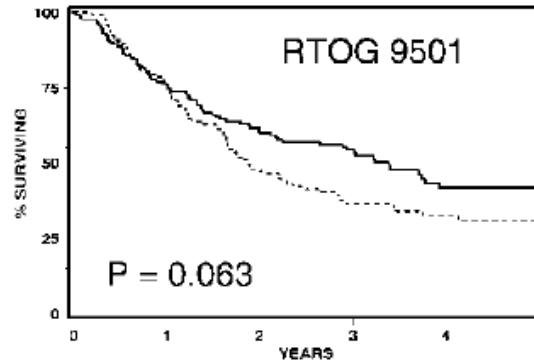
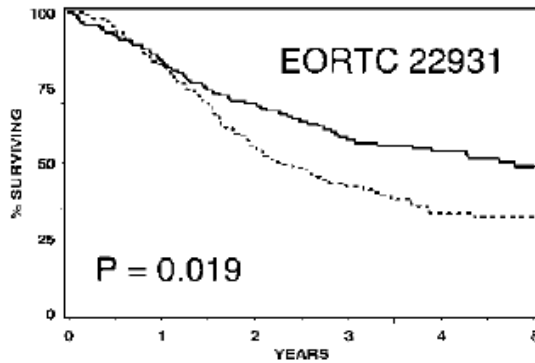


No. at Risk						
Elective surgery	243	195	143	110	86	67
Therapeutic surgery	253	197	129	105	86	74

**Improved OS with planned neck dissection**

# Case: Post-Operative Management

- What is the role of adjuvant chemoradiation vs RT alone for this patient?
  - Bernier, Cooper et al. *Head and Neck* 2005:



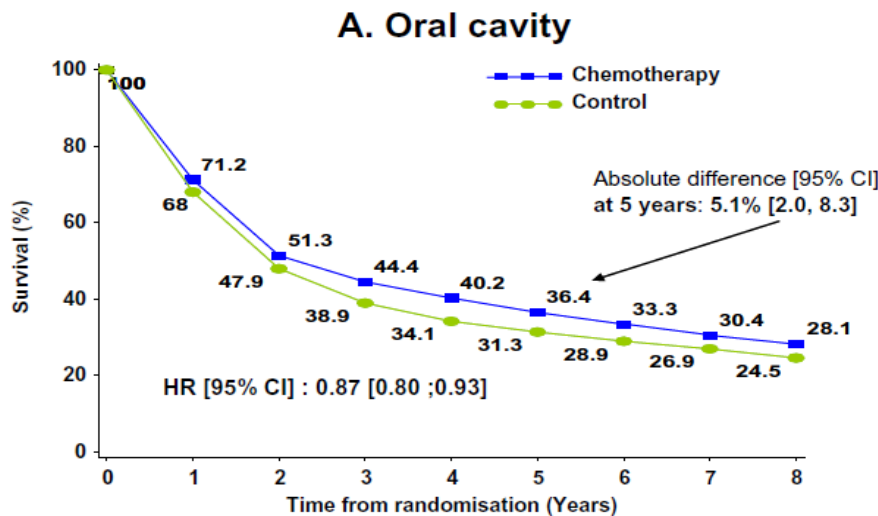
Pooled analysis of EORTC 22931 and RTOG 9501: OS improved with RT + concurrent chemo (RCT) vs RT alone for patients with +Margin and/or +ENE

# at Risk		EORTC 22931			RTOG 9501		
Year		0	2	5	0	2	5
RCT	—	122	82	31	130	80	16
RT	---	111	59	16	116	55	11



# Case: Post-Operative Management

- What is the role of chemoradiation vs RT alone for this patient?
  - MACH-NC Meta-Analysis (Pignon et al, Radiother Oncol 2009):



Significant OS benefit with addition of chemotherapy per MACH-NC. **Absolute difference at 5 years = 5.1%**

Number of deaths/person-years:

	Years 0-2	Years 2-5	Years >=6
LRT+CT	1008/3031	253/2165	139/1620
LRT	1070/2846	280/1771	99/1204

LRT+CT  
LRT

# Case: Post-Operative Management

- What is the role of chemoradiation vs RT alone for this patient?
  - HOWEVER:
    - Poor performance status (ECOG 2)
    - Advanced age (81)
    - Comorbid dementia
- Therefore, **post-operative RT alone** was utilized despite indeterminate margin
- Typical **PORT Indications:**
  - + Margins / Gross residual disease
  - T3/T4
  - LVS1
  - PNI
  - >1-3 LNs
  - DOI > 3mm

# Radiation Technique

- Post-operative RT with a composite IMRT/VMAT plan
- Prescription:
  - 50 Gy in 2.5 Gy/fraction to the high risk CTV (tumor bed with margin)
  - 40 Gy in 2.5 Gy/fraction to low risk CTV (tumor bed with additional margin) + undissected right level IB
- **Conventional fractionation (most commonly utilized)** dose prescription = 60-66 Gy to high/intermediate risk CTVs and 54 Gy to low risk CTV at 2 Gy/fraction
- Alternative techniques include protons & brachytherapy

# Radiation Simulation

- Position: Supine in short thermoplastic mask, bite block
  - If treating neck, utilize long thermoplastic mask
- CT with IV contrast
- Consider wiring scars, bolus, based on high risk features
- Fuse pre-op CT/MRI to delineate initial tumor bed for CTV design

# Radiation Technique: Hypofractionation

- **Goal:** Deliver accelerated treatment without chemotherapy to provide maximal local control benefit with minimized acute toxicity → **hypofractionation**
- Common at our institution for smaller PTV volume and pN0 disease
- Langendijk JA et al, IJROBP 2003.
- 46 – 50 Gy at 2 Gy/fx + boost at **2.5 Gy/fx without chemotherapy**
  - Total 55 Gy (neg. margin)
  - Total 62.5 Gy (pos. margin)
- 3 year LRC =
  - 87% intermediate risk
  - 66% high risk
- Hypofractionation experiences with concurrent chemotherapy:
  - Jacinto et al, BMC Cancer 2018 & Sanghera et al, IJROBP 2007

<b>Intermediate risk</b>	ECE or Microscopic + margin + 1 risk factor
<b>High risk</b>	ECE and Microscopic + margin; or ECE or +margin and $\geq 2$ risk factors

# Radiation Technique: Elective Nodal Coverage

- Pathologic nodal disease by T Stage and site for cN0 neck
  - Byers et al. *Head Neck Surg* 1988

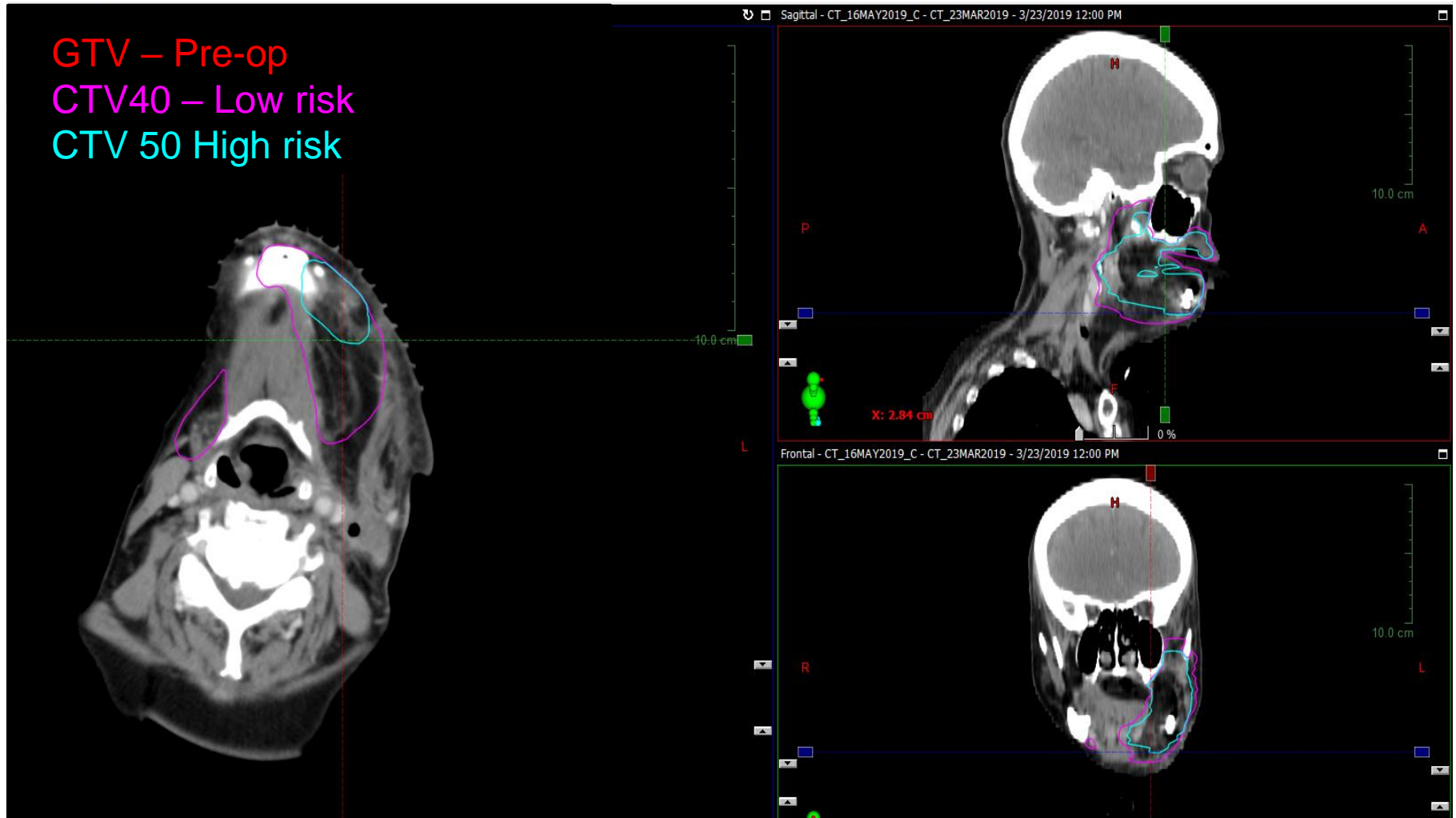
Site	Tx-T1-T2	T3-T4	Total
Oral tongue (n=48)	18.6%	31.6%	25%
FOM (n=62)	18.6%	26.3%	21%
Lower gum (n=41)	11.5%	13.3%	12.2%
Buccal mucosa (n=10)	0%	0%	0%
Retromolar trigone (n=23)	36.4%	33%	34.8%

- Should the undissected level IV be included in RT fields?
  - Warshavsky et al, JAMA OHNS 2019
  - Rate of level IV involvement in cN0 neck is 2.53% in fixed-effects model  
→ therefore omitted in this patient

# Radiation Contouring

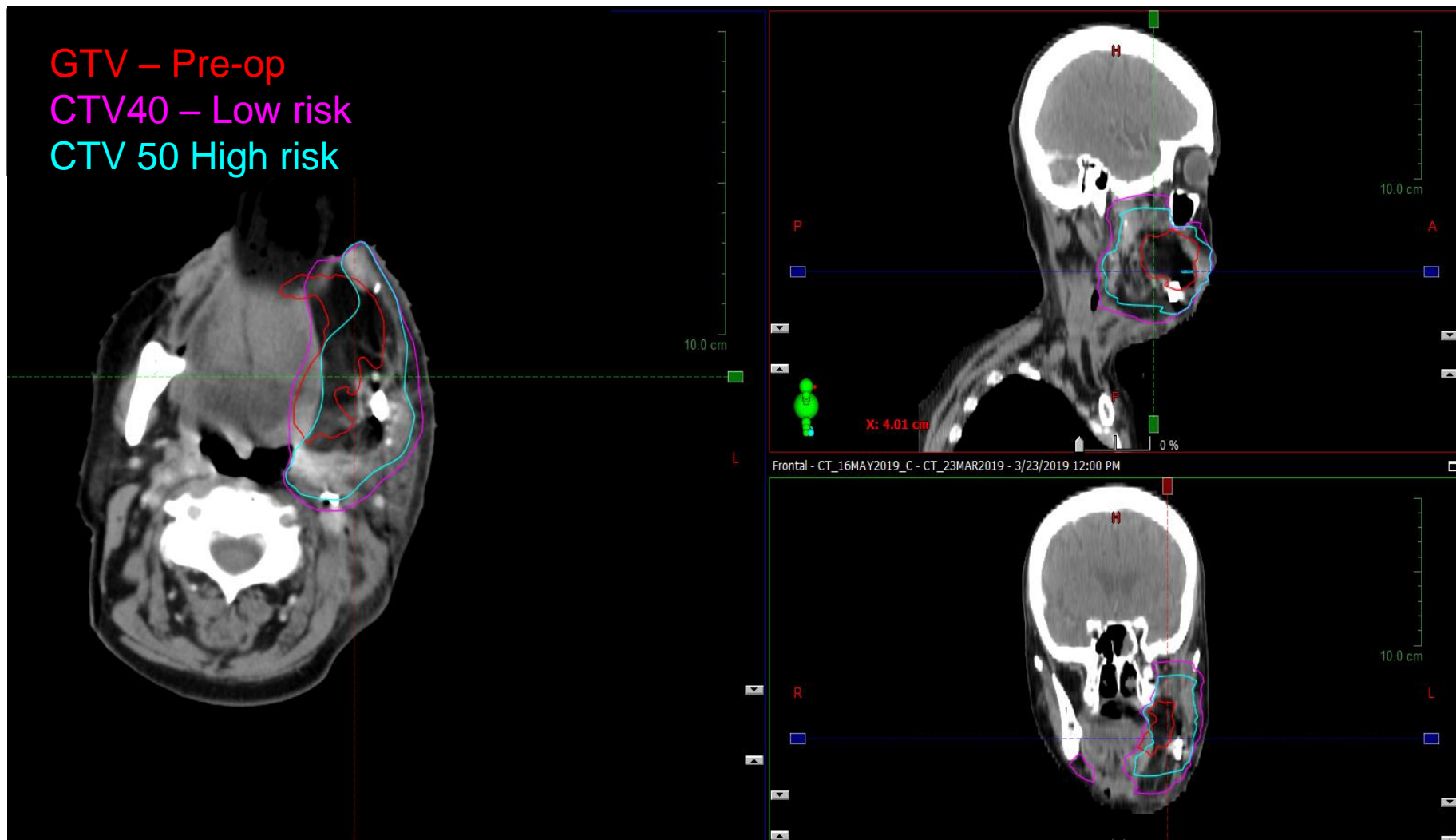
- GTV-Preop = initial site of gross disease as estimated by preoperative imaging
- CTV50 (high risk) = Pre-op GTV / tumor bed with margin (5-10 mm)
- CTV40 (low risk) = CTV50 + 5-10 mm expansion based on clinical suspicion and uncertainty due to post-op anatomical changes and encompassing surgical clips + undissected right IB
- PTV = CTV + 3mm margin, based on daily image guidance and immobilization
- For contouring/dose guidelines with conventional fractionation/SIB see: <https://econtour.org/cases/28>

# Case: Target Volumes



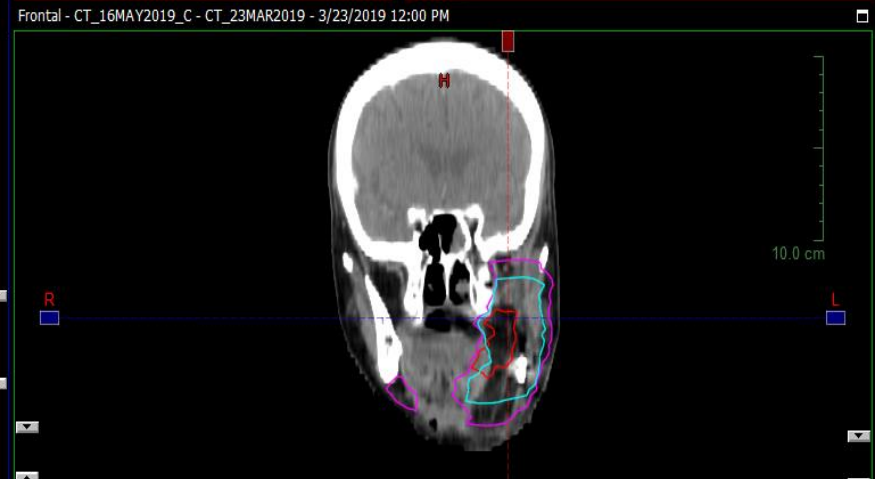
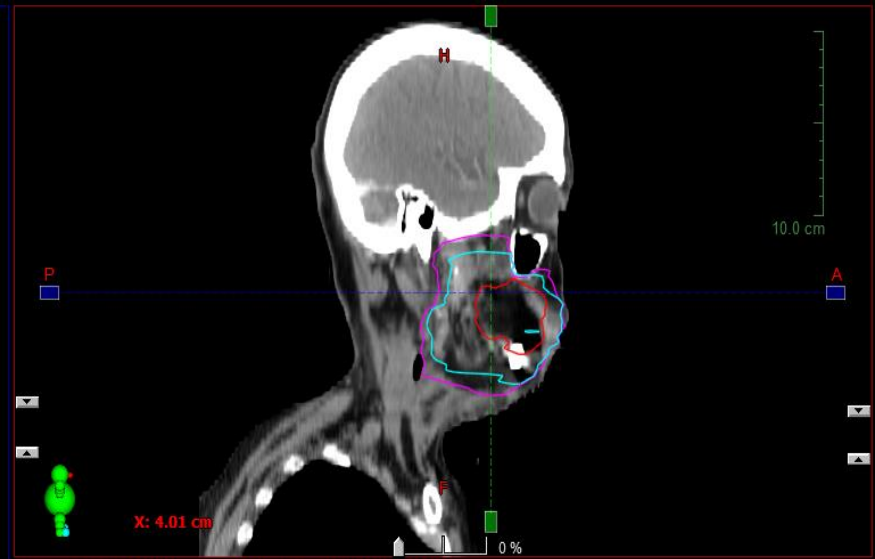
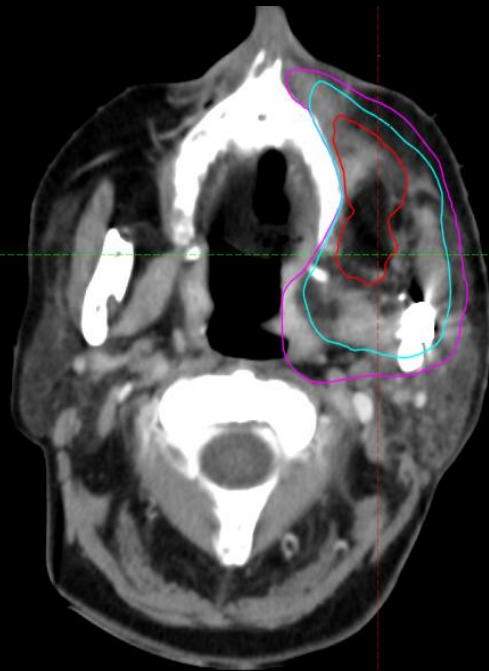


# Case: Target Volumes



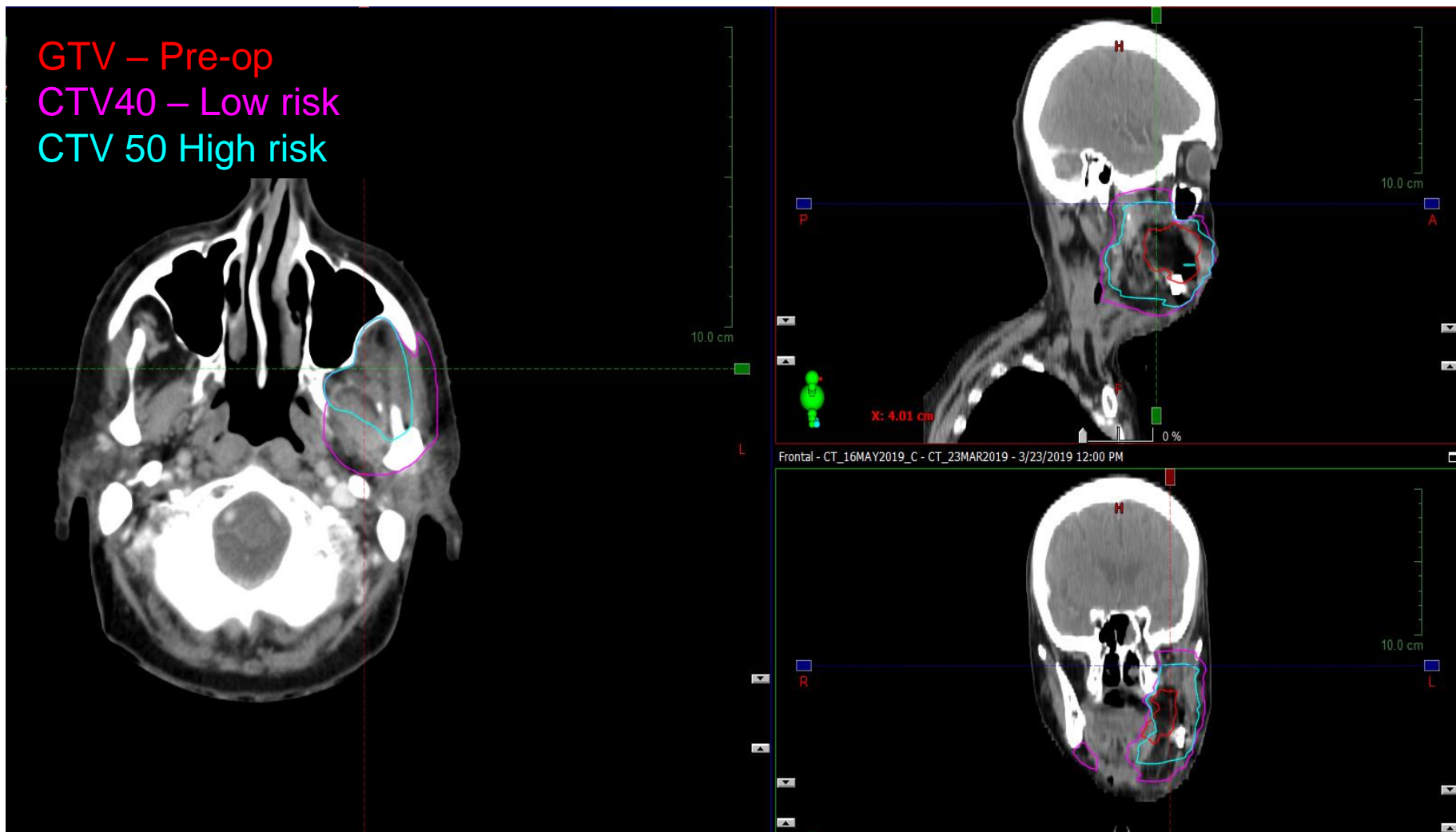
# Case: Target Volumes

GTV – Pre-op  
CTV40 – Low risk  
CTV 50 High risk



Frontal - CT\_16MAY2019\_C - CT\_23MAR2019 - 3/23/2019 12:00 PM

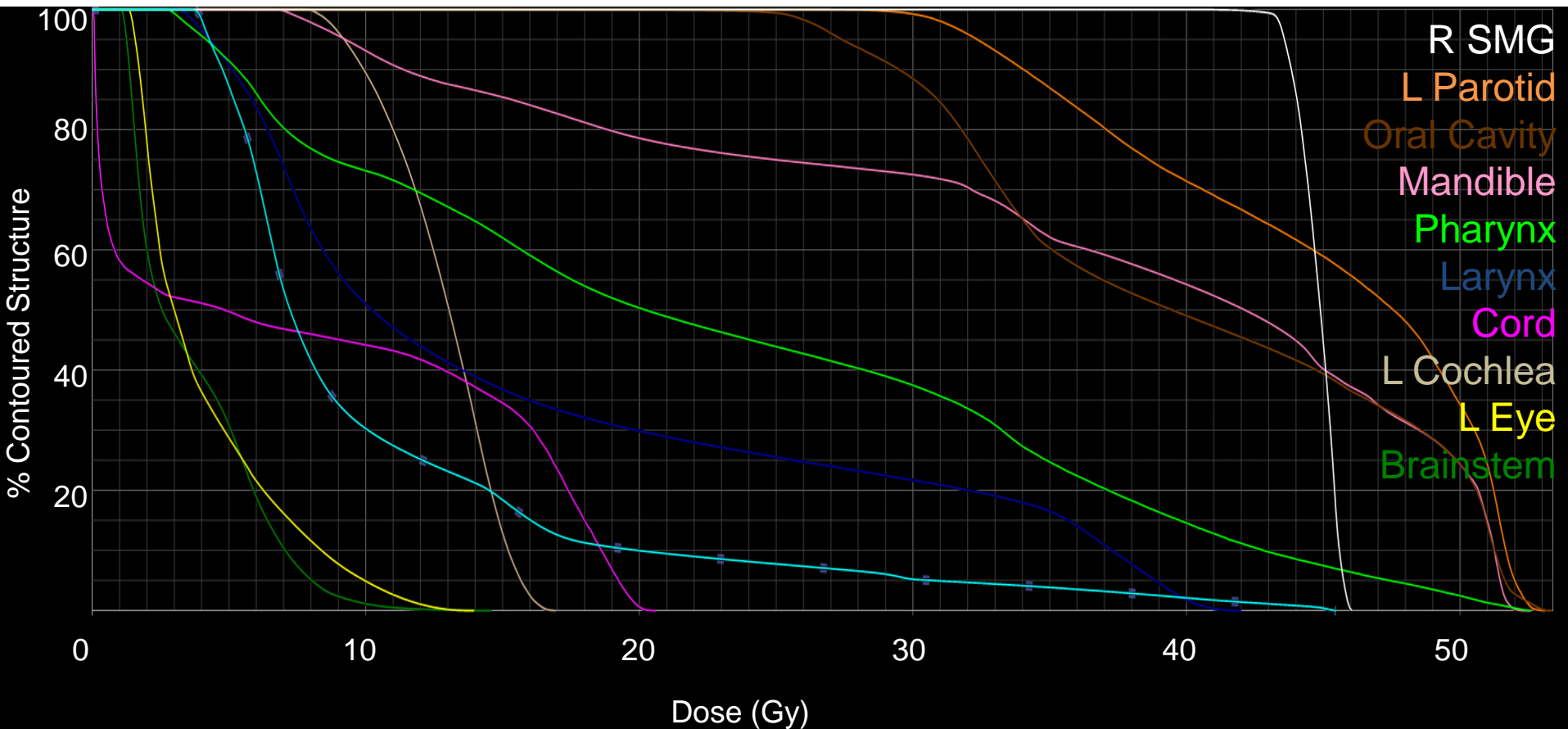
# Case: Target Volumes



# Key Dose Constraints: Hypofractionation

Constraints			
OARs	Dose		Rationale?
Rt Parotid	5-8 Gy	Median	Preserve major salivary gland
Oral cavity	30-35 Gy	Median	Mucositis, pain
Larynx	15 Gy	Median	Wound healing around tracheostomy, hoarseness
Pharynx	25-30 Gy	Median	Mucositis, pain
Mandible	56 Gy	Max	Osteoradionecrosis
Cochlea, left	30 Gy	Max	Ototoxicity
Left eye	30 Gy	Max	Vision loss
Pharyngeal constrictors	25-30Gy	Median	Post-op swallowing
Rt SMG	No constraint		In PTV 40 target volume

# Case: Dose Volume Histogram OAR



# Case: On Treatment Management

## Surgical

- Tracheostomy
  - Airway protection post-op
- Dobhoff/NGT or PEG
  - Allow intra-oral healing post-op and with RT induced mucositis
  - Speech & swallow evaluation for aspiration risk
- Wound healing
  - Ensure flap is well healed prior to RT to minimize wound complication and RT breaks

## Radiation / Chemoradiation

- Pain management
  - Secondary to post-op pain and RT-induced mucositis
- Xerostomia
  - Rx xylitol, flax seed oil, copious fluid intake to minimize
- Dysgeusia
  - Counseling patient to avoid minimized PO intake (if no PEG/NGT)
- Dermatitis
  - Ensure proper skin/wound care and analgesia
- Labs Abnormalities
  - Monitor electrolytes if decreased PO intake and/or chemotherapy. Monitor CBC if chemotherapy.

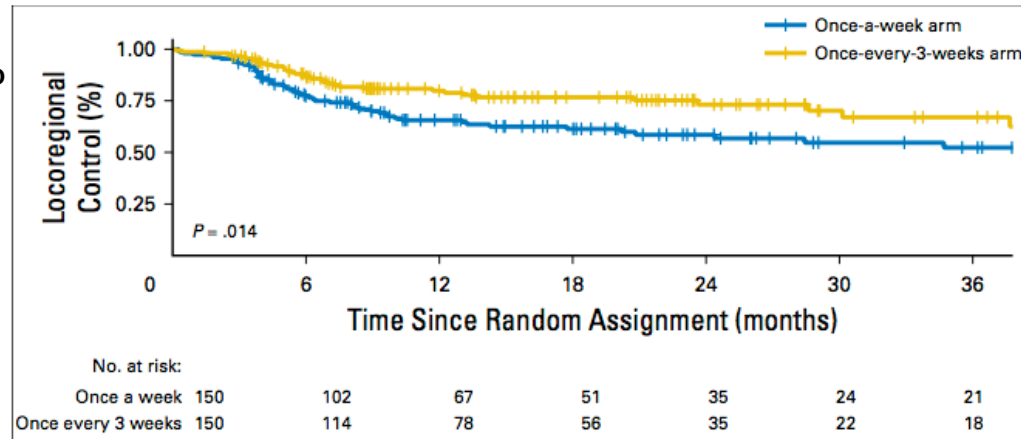
# Case: Follow-Up

- H&P + complete H&N physical exam +/- FOL
  - q1-3 months for year 1
  - q2-6 months for year 2
  - q4-8 months for years 3 –5
  - Yearly for years > 5
- Baseline post-op CT at 3 months adjuvant treatment
  - Additional imaging practices vary per institution or as indicated by symptoms/exam
- TSH yearly (if thyroid irradiated)
- Speech/swallowing/dental/hearing evaluations
- Smoking cessation
- Depression screening

# Oral Cavity Cancer: Clinical Pearls

## • What is the ideal regimen of concurrent cisplatin?

- Noronha et al, JCO 2018:
  - n=300 patients with LAHNC (87% oral cavity, 93% PORT)
- Randomized:
  - Weekly cisplatin 30 mg/m<sup>2</sup>
  - Q3 Week 100 mg/m<sup>2</sup>
  - As administered with RT delivered by opposed portals



Improved LRC with Q3 week cisplatin but with more toxicity; no difference in OS

- OCAT Trial (Laskar et al, ASCO 2016): Conventional RT (56-60 Gy/6 wk) vs CRT (56-60 Gy/6 wk + weekly cisplatin 30 mg/m<sup>2</sup>) vs Accelerated RT (56-60 Gy/5 wk) for high-risk oral cavity patients → showed similar locoregional control for all three arms



# References

1. Brady LW, Wazer DE, Perez CA. *Perez & Brady's Principles and Practice of Radiation Oncology*. Lippincott Williams & Wilkins; 2013.
2. NCCN: Clinical Practice Guideline Head and Neck Cancers.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J. Clin.* 2018;68:7–30.
4. Chinn SB, Myers JN. Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions. *J. Clin. Oncol.* 2015;33:3269–3276.
5. Dirven R, Ebrahimi A, Moeckelmann N, Palme CE, Gupta R, Clark J. Tumor thickness versus depth of invasion – Analysis of the 8<sup>th</sup> edition AJCC Staging for oral cancer. *Oral Oncology*. 2017.
6. Bernier J, Cooper JS, Pajak TF, *et al.* 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). *Head Neck*. 2005;27:843–850.
7. Pignon J-P, le Maître A, Maillard E, *et al.* Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother. Oncol.* 2009;92:4–14.
8. Langendijk JA, de Jong MA, Leemans CR, *et al.* Postoperative radiotherapy in squamous cell carcinoma of the oral cavity: the importance of the overall treatment time. *Int. J. Radiat. Oncol. Biol. Phys.* 2003;57:693–700.
9. Jacinto AA, Batalha Filho ES, Viana L de S, *et al.* Feasibility of concomitant cisplatin with hypofractionated radiotherapy for locally advanced head and neck squamous cell carcinoma. *BMC Cancer*. 2018;18:1026.
10. Sanghera P, McConkey C, Ho K-F, *et al.* Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. *Int. J. Radiat. Oncol. Biol. Phys.* 2007;67:1342–1351.
11. Warshavsky A, Rosen R, Nard-Carmel N, *et al.* Assessment of the Rate of Skip Metastasis to Neck Level IV in Patients With Clinically Node-Negative Neck Oral Cavity Squamous Cell Carcinoma: A Systematic Review and Meta-analysis. *JAMA Otolaryngol. Head Neck Surg.* 2019;145:542–548.
12. D’Cruz AK, Vaish R, Kapre N, *et al.* Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *N. Engl. J. Med.* 2015;373:521–529.
13. Noronha V, Joshi A, Patil VM, *et al.* Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. *J. Clin. Oncol.* 2018;36:1064–1072.
14. Laskar S, Chaukar D, Deshpande M, *et al.* Phase III randomized trial of surgery followed by conventional radiotherapy (5 fr/Wk) (Arm A) vs concurrent chemoradiotherapy (Arm B) vs accelerated radiotherapy (6fr/Wk) (Arm C) in locally advanced, stage III and IV, resectable, squamous cell carcinoma of oral cavity- oral cavity adjuvant therapy (OCAT): Final results (NCT00193843). *J. Clin. Oncol.* 2016; 34(15 sup):6004.

**Please provide feedback regarding this case or other ARROcases to [arrocase@gmail.com](mailto:arrocase@gmail.com)**