# Oropharyngeal Cancer (OPC)- Base of Tongue

**Authors:**

Kelli B. Pointer MD, PhD

University of Chicago

Chicago, IL

Faculty: Aditya Juloori MD

# Case

- 57 year old male with cT4N0M0 p16+ SCC of the R BOT
- He presented after developing a persistent sore throat, dysphagia, right ear pain and a right sided headache

# Common Presentations

- **Most common presentation is a painless neck mass**
- Symptoms related to local invasion:
  - Sore throat
  - Dysphagia
  - Odynophagia
  - Otalgia →referred from cranial nerve IX via the tympanic nerve of Jacobson
  - Inability to protrude tongue/tongue fixation=deep musculature involvement
  - Trismus (normal opening from incisor to incisor is 3-4cm)= medial pterygoid invasion

# Differential Diagnosis of neck mass

- A persistent neck mass in an adult > 40 years old should prompt search for malignant source

| Acute | Subacute | Chronic |
|---|---|---|
| - CMV<br>- EBV<br>- staphylococcal/streptococcal infection<br>- Viral URI<br>- Hematoma<br>- HIV-related lymphadenopathy<br>- TB | - SCC of the upper aerodigestive tract<br>- Amyloidosis<br>- Lymphoma<br>- Metastatic cancer<br>- Parotid tumor<br>- Sarcoidosis<br>- Sjogren syndrome<br>- Castleman disease | - Thyroid pathology<br>- Brachial cleft cyst<br>- Carotid body tumor<br>-Glomus jugulare<br>- Lipoma<br>- Laryngocele<br>- Thyroglossal duct cyst |

# Work-up

- H&P
- Physical exam including complete head and neck exam, mirror and fiberoptic examination as clinically indicated.
- Biopsy of primary site or FNA of the neck
- IHC for p16
- CT with contrast and/or MRI with contrast of primary and neck
- As clinically indicated:
- EUA with endoscopy
- Pre-anesthesia studies
- FDG PET/CT
- Chest CT (+/- contrast)
- Dental evaluation including Panorex
- Nutrition, speech and swallowing evaluation/therapy, and audiogram
- Smoking cessation counseling
- Fertility/reproductive counseling

# Imaging

- MRI is preferred over CT
  - in patients with extensive dental amalgam (may obscure CT-based anatomy)
  - in patients with cranial nerve symptoms or radiographic perineural spread
- If imaging fails to reveal an obvious primary
  - PET/CT should be ordered before EUA, biopsies, and tonsillectomy, to help identify potential primary sites

# Imaging

- Evaluation of lymph node metastases should be conducted with CT or MRI of the neck
  - Use imaging study suitable for primary site evaluation
  - CT had higher sensitivity (77%) than MRI (72%)
  - MRI had a higher specificity (81%) than CT (72%)
- For patients with T3-4 primary tumors or N1+ disease, FDG PET/CT is preferred to evaluate for distant disease and thoracic metastases.

# Epidemiology

- Approximately 53,260 adults will be diagnosed with oral cavity or oropharyngeal cancers in the United States annually
- Average age of diagnosis is 62
- ~25% of cases occur in people younger than 55
- Male to female ratio- 4:1
- HPV prevalence by PCR/genotyping was 16.3% from 1984-1989 → 71.7% from 2000-2004. (Chaturvedi et al. (JCO 2011))
- **Population-level incidence of HPV+ OPC increased by 225% from 1988 to 2004.**
- Overall HPV prevalence in OPC increased from 40.5% before 2000 to 64.3% between 2000-2004 and 72.2% between 2005-2009 ($p<0.001$) (Mehanna et al. (Head Neck 2013)):
- Approximately 70-90% of newly diagnosed OPC cancers in the US are HPV+.

# Risk Factors

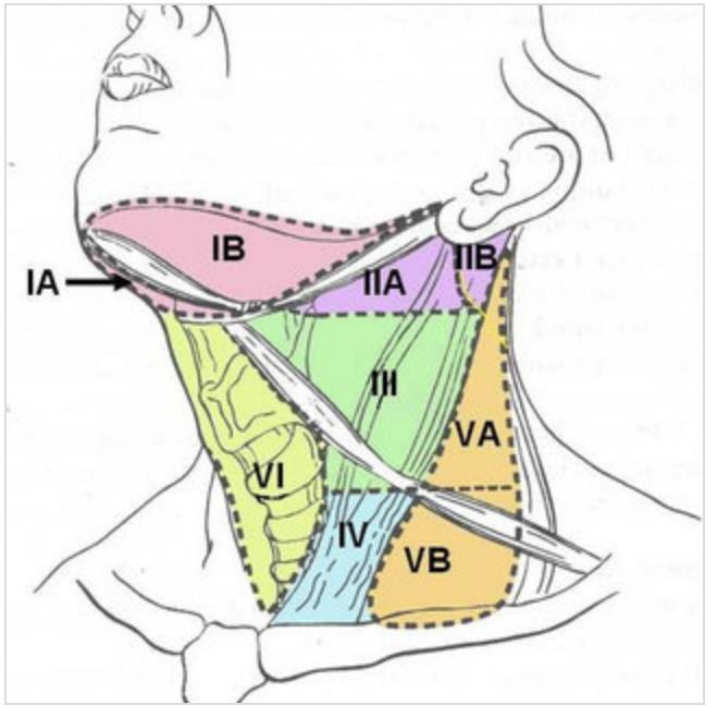
- Age
- High risk sexual behavior (HPV+)
- Smoking and alcohol (HPV-)

# Incidence of Positive Lymph Nodes

- Unilateral: 60-75%
- Contralateral: 20-30%
- Common drainage to level II and down to levels III and IV
- Levels IB, V and retropharyngeal lymph nodes (VIIa) can be involved- less common

# Nodal Distribution after Therapeutic Radical Neck Dissection

- I: 14%
- II:71%
- III:42%
- IV:28%
- V:9%

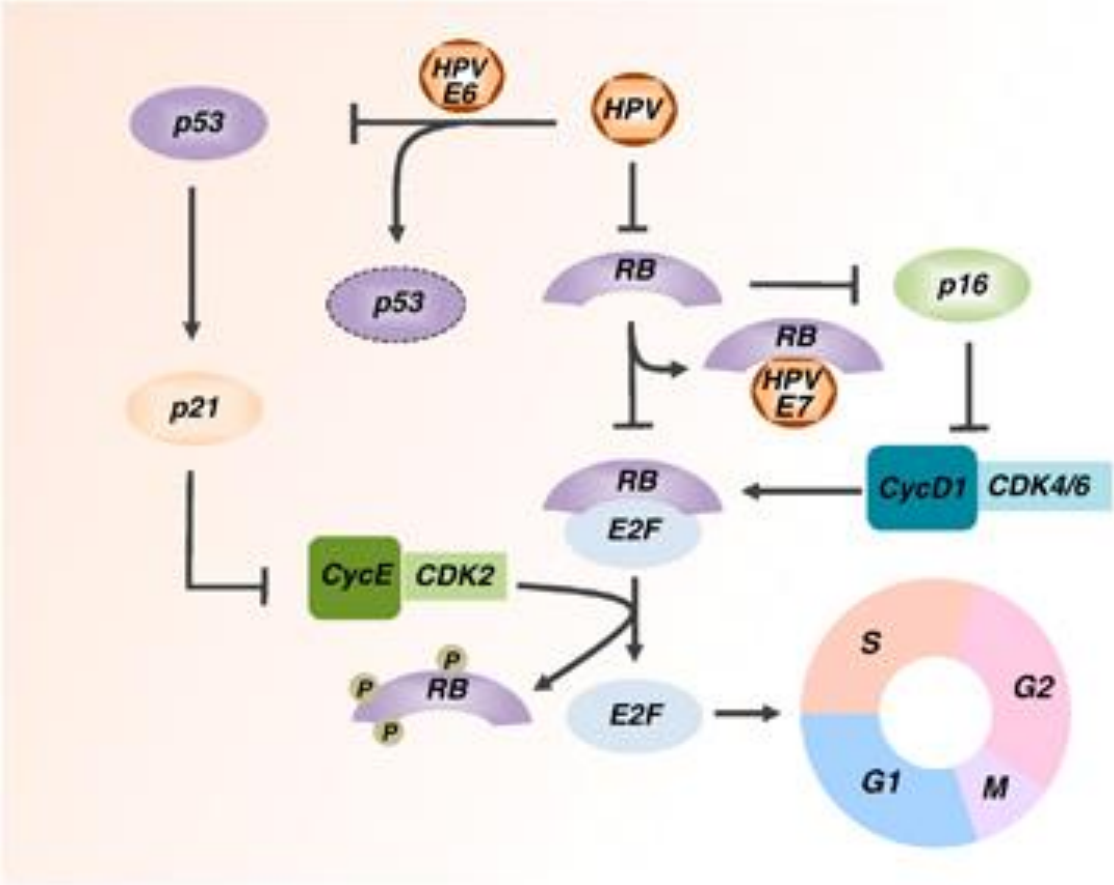



Neck dissections: Radical to conservative - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Diagrammatic-representation-of-the-neck-showing-various-nodal-levels-and-sublevels_fig1_7899995 [accessed 1 Aug, 2020]

Shah, J.P., Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg, 1990 160(4): 405-9

# HPV Mechanism of Oncogenesis

- Overexpression of p16 protein serves as surrogate marker of HPV integration into DNA.
- IHC for p16 is more sensitive but less specific than HPV DNA detection by FISH
- In HPV-endemic areas, the PPV of p16 positivity on IHC in OPC is ~90%.
- In areas where HPV is less common, PPV of p16 status can be <40%.
- EGFR is more commonly amplified in HPV-negative tumors and is associated with a poor prognosis




Suh, Y & Amelio, Ivano & Urbano, Teresa & Tavassoli, Mahvash. (2014). Clinical update on cancer: Molecular oncology of head and neck cancer. Cell death & disease. 5. e1018. 10.1038/cddis.2013.548

# HPV+ vs. HPV- (Huang et al. Oral Oncol 2013)

| | HPV+ | HPV- | |
|---|---|---|---|
| Age | Younger, less tobacco/EtOH | Older, more tobacco/EtOH | |
| **3-year OS:** | **82%** | **54%** | p<0.001 |
| LC | 94% | 82% | p<0.001 |
| RC | 94% | 84% | p<0.001 |
| 3-year DC | 89% | 85% | NS |
| 5-year DC | 87% (DC curve declines until 5 years after treatment ) | 85% (DC curve stable 2 years after treatment) | NS |
| 1-yr OS after DM:<br>3-yr OS after DM: | 28%<br>6% | 6%<br>0% | |
| Late toxicities | 16% | 27% | P=0.019 |
| 2nd primary rate | 9% | 20% | |
| Failure type | Predom. distant: 67% | Predom. LF: 53% | |
| Isolated DM | 48% | 27% | |
| Location of DM | More diffuse: lung, skin, brain, intra-abdominal nodes | lung, liver, and bone | |

# Standard of Care Treatment for definitive chemo-RT

- 70 Gy in 35 daily fx to high-risk PTV.
- Elective nodal volume should include bilateral neck for multi-level N disease.
- Select patients are candidates for TORS with adjuvant chemo-RT based on pathologic risk factors.
- SIB approach: 69.96 high-risk PTV (2.12 Gy/fx)/59.40 intermediate-risk PTV (1.8 Gy/fx) /54.12 low-risk PTV (1.64 Gy/fx)

# GORTEC 90-01 (Calais et al., JNCI 1999; Denis et al., JCO 2004)

- Prospective RCT of 226 patients with stage III-IV squamous cell carcinoma of the oropharynx
- Randomized to definitive RT alone (70 Gy/35 fx) with or without concurrent carboplatin and 5-FU for three cycles.
- 5-year outcomes included:
  - OS (22% vs. 16%), DFS (27% vs. 15%)
  - LRC (48% vs. 25%).
  - All were improved significantly with concurrent chemotherapy.
  - Grade 3+ late effects occurred in 30% vs. 56% of patients (p=0.12).
- **Conclusion: chemo-RT is better than radiation alone**

# MACH-NC Meta-analysis (Pignon et al., Lancet 2000; Update Radiother Oncol 2009)

- Patient-level meta-analysis of >17,000 patients from 93 trials
- OS benefit with the addition of chemotherapy to RT (4.5% at 5 years).
- Concurrent CRT showed absolute benefit of 6.5% at 5 years ($p<0.05$)
- Induction chemotherapy showed benefit of 2.4% at 5 years (p=NSS).
- Patients >70 did not benefit in terms of OS.
- Both concurrent and induction chemotherapy improved distant control (HR: 0.73 vs. HR 0.88, p=0.0001 and p=0.04, respectively).
- **Conclusion: chemo-RT improves OS compared to RT alone except in patients >70**

# MACH-NC Meta-analysis update-Blanchard et al., Radiother Oncol 2011).

- Blanchard update: 87 RCTs between 1965-2000 included with primary endpoint of HR of death or relapse.
- Divided patients into oral cavity, oropharynx, hypopharynx, and larynx.
- Analyzed individual patient-level data for 16,192 patients (5,878 oropharynx). Median f/u 5.6 years.
- Chemotherapy benefit higher for concomitant CRT for all tumor locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal site ($p<0.0001$) and laryngeal tumors ($p=0.05$).
- The 5-year absolute OS benefit for any chemotherapy was 5.3% (27.4% → 32.7%).
- Absolute OS benefit for adjuvant chemotherapy was -0.4% ($p>0.05$)
- 5-year absolute benefit for induction and concurrent chemotherapy was +1.4% ($p>0.05$) and +8.1% ($p<0.05$), respectively.
- **Conclusion there is a statistically significant improvement in OS with concurrent chemo-RT not seen with induction or adjuvant chemotherapy**

# Elective coverage of levels IB and V?

- Sanguineti et al. (Johns Hopkins, IJROBP 2009):
  - retrospective review of 103 patients with T1-2cN0 OPC staged with CT imaging who underwent initial neck dissection.
  - If CT negative, levels IB, IV, and V were involved 3%, 6%, and 1% of the time.
  - Levels IB and V were always pN+ <4% regardless of involvement of II-IV.
  - Level IV was 5% pN+ if level III not involved but 11% if level III involved.
  - **Conclusion: Levels IB and V are low-risk and can be spared in cT1-2 OPC.**
- Sanguineti et al. (Johns Hopkins, Acta Oncol 2014):
  - Retrospective review of 91 patients with HPV+ OPC and cN+ necks who underwent ipsilateral neck dissection between 1998-2010.
  - Risk of subclinical disease in both levels IB and V was <5% while it was 6.5% for level IV.
  - Level IB subclinical involvement >5% when 2+ ipsilateral levels besides IB are involved.
  - Risk of occult disease in level IV was <5% when level III was not involved.
  - Low number of events in level V did not allow analysis for RF for involvement.
  - **Conclusion: For HPV+ patients with cN+ disease, consider electively covering IB if 2+ other levels are involved. Level IV may be spared when level III is negative.**

# Coverage of contralateral retropharyngeal or contralateral high level II lymph node?

- Spencer at al. (WashU, Cancer 2014):
  - Prospective institutional database of patients treated to the oral cavity, oropharynx, hypopharynx, larynx ,and unknown primary with IMRT
  - Generation 1: comprehensive neck IMRT with parotid sparing
  - Generation 2: Eliminated contralateral high level II (HLII) lymph nodes
  - Generation 3: Further eliminated contralateral retropharyngeal lymph nodes
  - 488 patients received generation 2 and 3 treatment
  - No failures present in sparing contralateral retropharyngeal lymph nodes or high contralateral neck
  - Quality of life data comparing 44 patients in generation one and 51 patients in generation three
    - improvement globally and in all domains for generation three where reduced volumes were used ($p<0.007$)
  - **Conclusions: Sparing contralateral retropharyngeal lymph nodes and contralateral high level II lymph nodes for select patients improves quality of life with minimal failure risks**

# RT alone for definitive treatment?

- RTOG 0022 (Eisbruch et al. IJROBP 2010):
  - Investigated safety and efficacy of IMRT.
  - Prospective phase II trial of 69 T1-2N0-1 OPC cancer treated RT alone to 66 Gy/30 fx with IMRT.
  - IMRT was bilateral, chemotherapy was not permitted
  - Dose of 66 Gy in 2.2 Gy/fx over 6 weeks.
  - Subclinical PTV received SIB to 54-60 Gy in 1.8-2.0 Gy/fraction.
  - 2-year LRF was 9%
  - LRF was increased in those with major protocol deviations
  - **Conclusion: Patients with T1-2N0-1 can be considered for RT alone based on results of RTOG 0022.**
  - IMRT is feasible with encouraging acute and late toxicity. Quality of IMRT is important to avoid LRF.

# Should HPV+ OPC be treated differently than HPV- OPC?

# Why Consider De-Escalation for HPV+ OPC?

Gillison et al., JNCI 2000:

- Evidence for a causal association between human papillomavirus and a subset of head and neck cancers
- Investigated tumor tissue from 253 patients with newly diagnosed/recurrent HNSCC and tested for presence of HPV genome.
- HPV detected in 62 (25%) of 253 cases with 90% of HPV+ tumors having HPV16
- Oropharyngeal site (OR 6.2, 95% CI 3.1-12.1) independently increased HPV+
- HPV+ less likely among moderate-heavy drinkers and smokers. Also less likely to have TP53 mutations.
- **HPV+ had improved disease-specific survival (HR 0.26)**
- **After adjusting for lymph node disease, heavy EtOH consumption, and age 60+, all HPV+ tumors had 59% reduction in risk of death from cancer (HR 0.41)**

# Why Consider De-Escalation for HPV+ OPC?

Ang et al., NEJM 2010:

- Retrospective analysis of the association between HPV status and survival of patients on RTOG 0129, Median f/u was 4.8 years
- 215 p16+ (68% of known p16 status patients), 101 p16-, and 117 unknown p16 status
- HPV+ more common in non-smokers and patient's lower pack year history (PYH)
- HPV+ significantly associated with younger age, white race, better KPS, absence of anemia, and smaller primary tumors.

• 3-year OS similar in concomitant boost vs. standard fractionation arms (70.3% vs. 64.3%, p=0.18) as were rates of acute and late toxic events.

• 58% reduction in risk of death after adjusting for age, race, tumor/nodal stage, tobacco exposure, and treatment assignment

| | HPV+ | HPV- | P-value |
|---|---|---|---|
| 3-year OS | 82.4% | 57.1% | <0.001 |
| 3-year PFS | 73.7% | 43.4% | <0.001 |
| 3-year LRR | 13.6% | 35.1% | <0.001 |
| 3-year DM | 8.7% | 14.6% | 0.23 |
| 3-year second primary tumor | 5.9% | 14.6% | 0.02 |

# Ang et al., NEJM 2010 Continued

- RPA identified three risk groups for OPSCC based on HPV status:
- Patients with HPV+ tumors considered low-risk with exception of heavy smokers with high nodal burden (N2b-3).
- Patients with HPV- tumors were considered high-risk with exception of nonsmokers with tumors of stage T2-3.

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| HPV+ ≤10 PYH | HPV+ with >10 PYH AND N2b-N3 disease | HPV- with ≤10 PYH AND T4 disease |
| HPV+ with >10 PYH AND N0-N2a disease | HPV- with ≤10 PYH AND T2-3 disease | HPV- with >10 PYH |
| 3 year OS: 93% | 3 year OS: 70.8% | 3 year OS: 46.2% |

# De-Escalation Approaches for Definitive Chemo-RT for HPV+ OPC Summary

- **Substitution of cisplatin during chemo-RT with alternative, potentially less toxic radiosensitizers**
  - Cetuximab is inferior for OS and PFS compared to cisplatin
- **Dose-reduced chemo-RT**
  - HPV+ patients have excellent control with 60 Gy IMRT and concurrent cisplatin
- **Dose-reduced RT alone**
  - Cannot omit systemic therapy from dose-deescalated definitive chemo-RT for low-risk HPV+ OPC
- **Surgery +/- lower-dose or volume adjuvant RT**
  - RT or surgery are reasonable initial therapeutic options for early stage disease
  - High risk features are associated with relapse rates after TORS alone for HPV+ OPC suggesting adjuvant therapy is needed
  - PORT avoiding resected primary site and only targeting at the risk neck after TORS for low risk HPV+ OPC may be safe
  - Eliminating PORT to the PN0 neck has good control and global QOL similar to baseline
- **Induction chemotherapy followed by dose and/or volume de-escalated chemo-RT or surgery**
  - Induction chemotherapy with response and risk-stratified dose AND volume de-escalated RT/chemo-RT for HPV+ OPC is associated with favorable oncologic outcomes and reduced acute and chronic toxicity.

# Substitution of cisplatin during chemo-RT with alternative, potentially less toxic radiosensitizers

# RTOG 1016: Gillison et al., Lancet 2019

- Phase III, randomized, non-inferiority trial
- Eligibility: T1-2/N2a-N3 OR T3-4/N0-N3 HPV+ by p16 IHC
- Randomized to:
  1. 70 Gy in 6 fx/week with cisplatin 100 mg/m^2 on days 1 and 22
  2. cetuximab 400 mg/m^2 5-7 days pre-RT followed by 250 mg/m^2 weekly x 7 doses.
- RT for intermediate-risk elective CTV was 56 Gy including first-echelon lymph nodes and 40 Gy to lower-risk nodal regions
- N= 849
- 38% T3/4 disease, 38% >10 PYH, and 71% low-risk by RTOG 0129
- Primary outcome was 5-year OS
- Non-inferiority margin defined as ≤9% increase in death in cetuximab arm (upper limit of one-sided 95% CI for HR of death <1.4).
- Median f/u 4.5 years

# RTOG 1016: Gillison et al., Lancet 2019 Continued

- 5-year PFS: 67.3% cetuximab vs. 78.4% cisplatin (HR 1.72, p=0.0002)
- Of those with progression:
- LRF: 39% cetuximab vs. 30% cisplatin, DM: 35% cetuximab vs. 41% cisplatin
- **5-year OS: 77.9% cetuximab vs. 84.6% cisplatin** (HR for cetuximab 1.45, upper limit of one-sided 95% CI was 1.94, p=0.5056 for non-inferiority)
- **5-year LRF: 17.3% cetuximab vs. 9.9% cisplatin** (p=0.0005), **5-year DM: 11.7% cetuximab vs. 8.6% cisplatin (p=NSS)**
- Acute grade 3+ toxicity: 77.4% cetuximab vs. 81.7% (p=0.1586)
- Late grade 3+ toxicity: 16.5% cetuximab vs. 20.4% (p=0.1904)
- Grade 3+ mucositis: 41.5% cetuximab vs. 46.2% cisplatin; Grade 3+ dermatitis: 8.0% cetuximab vs. 12.4% cisplatin
- Early death 1.5% both arms
- PEG end of treatment: 57.3% cetuximab vs. 61.5% cisplatin
- 1-year PEG: 8.4% cetuximab vs. 9.2% cisplatin
- **Conclusion: For patients with HPV-positive OPC, RT+cetuximab demonstrated inferior OS and PFS compared to RT+cisplatin with similar toxicity rates.**

# Dose-reduced chemo-RT

# Chera et al. (UNC/UFlorida, Cancer 2018)

- Single-arm phase II trial with primary outcome of pathologic complete response
- null hypothesis: pCR = 87% in standard CRT
- IMRT to 60 Gy with concurrent weekly cisplatin 30 mg/m^2 with 54 Gy to low-risk PTV.
- Protocol-mandated primary site biopsy and selective neck dissection.
- 44 patients with median f/u of 36 months.
- Eligibility: T0-3, N0-2c, M0, p16+, minimal smoking history ≤10 PYH or >10 PYH and quit for ≥5 years
- **3-year OS: 95%**
- **3-year LC, CSS, RC, and DMFS: 100%**
- **pCR: 86%**
- 39% required feeding tube for mean duration of 15 weeks (range: 5-22, 0% at 1 year)
- Grade 3+ toxicity: 2% xerostomia, 39% dysphagia, 35% mucositis
- **Conclusions: Patients with favorable-risk HPV+ OPC have better preservation of quality of life with excellent 3 year tumor control and survival with 60 Gy IMRT with low dose cisplatin compared to standard therapies**

# Chera et al. (UNC/UFlorida, JCO 2019)

- Phase II trial of de-intensified chemoradiotherapy for human papillomavirus-associated oropharyngeal squamous cell carcinoma.
- Patients with AJCC 7th edition **T0-2N0-1 disease did not receive chemotherapy**. Cisplatin-ineligible patients received cetuximab preferentially (other options could have included carboplatin+/-paclitaxel)
- Enrolled 114 patients with T0-3N0-2 (AJCC 7th) OPC and minimal or remote tobacco history. Median f/u was 31.8 months
- 85% T1-2 tumors and 68% with ipsilateral neck disease.
- 11% had HPV- but p16+ disease
- 40% had HPV+/p16+
- 49% had p16+ with unknown HPV DNA status.
- 36% did not receive 6 cycles of cisplatin and 11% received cetuximab because they were cisplatin ineligible.
- PET was performed 10-12 weeks post-treatment with neck dissection only if indicated.
- Pathologically involved node from neck dissection triggered by post-RT PET was NOT considered a failure.
- Primary endpoint 2-year PFS.

# Chera et al. (UNC/UFlorida, JCO 2019) Continued

- **2-year PFS= 86%**
- **2-year LRC=95%,**
- **2-year DMFS= 91%.**
- Post-treatment PET response was 93% at primary site and 80% in the neck.
- 11 (9.6%) of patients had a neck dissection and 4 of these had pathologically confirmed residual disease.
- 9/14 recurrences (64.2%) had a component of distant failure (8 distant only, 1 local and distant)
- Of 14 patients with recurrence, 11 alive with salvage with only 2 having salvage surgery.
- All QOL items (EORTC QLQ30, HN35, and Eating Assessment Tool 10) returned to baseline by 6 months except for dry mouth and sticky saliva although these continued to improve beyond 1 year
- Notably, patients reported their swallowing function returning to baseline.
- **Conclusion: 60 Gy IMRT with low dose concurrent cisplatin is associated with favorable outcomes in HPV+ OPC**

# Dose-reduced RT alone

# NRG Oncology Cooperative Group HN002 presented at ASTRO 2019 (Yom et al.)

- Randomized Phase II Trial
- Patients with p16+, Non-Smoking Associated Locoregionally Advanced OPC
- Eligibility: OPC, ≤10 PYH, T1-2N1-2b; T3N0-2b with central path review for p16+ on IHC

Stratified by unilateral vs. bilateral neck RT (all RT was IMRT)

- Randomized to:

    **1) 60 Gy RT in 2 Gy/fx in 6 weeks + cisplatin 40 mg/m^2 weekly x 6 cycles**

    **2) 60 Gy RT in 2 Gy/fx at 6 fractions/week for 5 weeks (accelerated RT alone)**

- Primary hypothesis: 1 or both arms will achieve 2-year PFS rate ≥85% without unacceptable swallowing toxicity
- Null hypothesis: Neither arm achieves 2-year PFS ≥85%
- Alternative hypothesis: 1 or both arms results in 2-year PFS >91%
- At least 140 patients needed per arm for one-sided type I error of 10% and 80% power
- Co-primary endpoint: QOL defined as mean of the MDADI composite score at 1 year from baseline.
- If an arm reaches ≥85% PFS, acceptability bound for QOL is MDADI composite score ≥60
- 80% power to detect a 5-point difference between arms
- Total of 308 patients were randomized

# NRG Oncology Cooperative Group HN002 presented at ASTRO 2019 (Yom et al.)

- 2-year PFS estimate: CRT 90.5% vs. 87.6% for RT alone (p=0.035 for CRT to reject null but p=0.2284 for RT alone)
- 2-year LRF: 3.3% for CRT vs. 9.5% for RT alone arm
- 2-year DM: 4.0% for CRT vs. 2.1% for RT alone arm
- First failures: 17 in CRT arm vs. 24 in RT alone arm
- Local only: 1 (5.9%) for CRT vs. 10 (41.7%) for RT
- Regional only: 5 (29.4%) for CRT vs. 5 (20.8%) for RT
- Distant only: 6 (35.3% for CRT) vs. 4 (16.7%) for RT
- 2-year OS: 96.7% for CRT vs. 97.3% for RT alone
- 1-year mean MDADI 85.3 for CRT vs. 81.76 for RT alone (p=0.0755), mean change from baseline was -5.62 for CRT vs. -6.22 for RT alone. (Goal was for score ≥60)
- CRT met acceptability criteria for both PFS and MDADI.
- RT alone arm did not meet PFS acceptability criterion.
- Higher rates of acute grade 3-4 toxicity in CRT arm but late grade 3-4 toxicities and 2-year OS were not different. No grade 5 events.
- MDADI scores were high and not different between arms.
- **Conclusion: Does not appear that systemic therapy can be omitted from dose-deescalated definitive chemo-RT for low-risk HPV+ OPC**

# Surgery +/- lower-dose or volume adjuvant RT

# ORATOR (Nichols et al., Lancet Oncol 2019)

- **TORs vs. chemo-RT**
- Enrolled from 6 centers in Canada/Australia from 2012-2017.
- Eligibility: T1-2N0-2 OPC (size ≤4 cm)
- 68 patients with median follow-up=27 months
- Randomized to chemo-RT for N+ disease or TORS+ neck dissection (ND)
- 88% of patients p16+ , Smoking status not included in eligibility criteria
- RT was 70 Gy in 7 weeks with cisplatin for N+
- TORS+ND received adjuvant therapy based on pathologic risk factors
  - ~25% got surgery alone
  - 47% received adjuvant RT 60Gy for intermediate-risk features
  - 24% received adjuvant chemo-RT to 64 Gy for +SM or ECE
- **Primary endpoint: dysphagia-related QOL measured by 1-year MDADI score**

# ORATOR (Nichols et al., Lancet Oncol 2019) Continued

- Mean MDADI score better in RT arm vs. TORS+ND (86.9 vs. 80.1, p=0.42)
  - Difference did not meet pre-specified 10-point threshold for clinically meaningful decline
- Addition of adjuvant therapy did not account for worse QOL in TORS+ND arm.
  - Mean MDADI score for TORS+ND arm was 82.8 and minimally different from patients receiving adjuvant RT after TORS+ND (78.5) or even those receiving adjuvant CRT (80.4).
- In RT arm, addition of salvage surgery after CRT had significantly worse MDADI scores compared with RT alone or CRT alone (68.0 vs. 89.5 vs. 88.0, respectively, p=0.044).
- No difference in PFS between 2 arms (4 recurrences in each arm)
- **Conclusions: Lack of a significant difference in clinically meaningful MDADI decline suggests both RT and surgery are reasonable initial therapeutic options for early stage disease**

# Routman et al., IJROBP 2017

- 53 patients who underwent transoral surgery with unilateral/bilateral neck dissection but declined adjuvant RT despite the presence of risk factors.
- Risk factors were defined:
  1. **Intermediate-risk: PNI, LVSI, T3-4 disease, or N2+ disease**
  2. **High-risk: +SM or ECE**
- Majority of patients had pT1-2 disease (75% intermediate risk, 78.4% high-risk) and pN2 disease (68%).
- Median f/u of 42 months
- Cumulative incidence of relapse at 3 years was 26% (overall, 13 patients recurred).
- Risk of relapse in intermediate-risk patients was 11.8%
- Risk of relapse in high-risk patients was 52.4%
- Of the 13 patients who recurred, 10 underwent salvage therapy with a median follow-up of 20.6 months
- Successful salvage rate was 77%.
- **Conclusion: Risk category was associated with clinically significant relapse rates after TORS alone for HPV+ oropharyngeal cancer, comparable to historical data and traditional indications for adjuvant therapy for all oropharyngeal cancer.**

# Swisher-McClure et al. (Penn, IJROBP 2019)

- Investigation of deintensified adjuvant therapy by avoiding primary-site RT and treating bilateral neck only in patients with HPV+ OPC with R0 resections with TORS and ipsilateral neck dissection.
- Phase 2 clinical trial
- N=60 patients
- Eligibility: pT1-2N1-3 HPV+ OPCC with R0 primary site margin (≥2 mm)
- Most had T1 (73%) disease and limited history of tobacco use.
- RT indications: ENE (22%), N2-3 disease (42% N2a, 55% N2b, only 3% N2c-3 according to AJCC 7th). ENE received concurrent chemotherapy.
- RT: 60-66 Gy to involved neck and 54 Gy to uninvolved neck
- Resected primary site was treated as an active avoidance structure during treatment planning
- **Primary endpoint was 2-year primary-site LC. QOL included EORTC QLQ H&N35.**
- Median f/u 2.4 years

# Swisher-McClure et al. (Penn, IJROBP 2019) Continued

- 1 primary-site failure at 20 months post-RT
- 1 neck failure
- 3 distant failures
- 2 patients (3.3%) developed late soft tissue necrosis in primary site surgical bed resolving within 2 months
- Feeding tube dependence: 0% during RT, 3.3% temporarily during follow-up, 0% permanent
- 2-year LRFS 97.9%
- 2-year PFS: 92.1%.
- 2-year OS: 100%

**Conclusion: Post-op RT that avoids the resected primary tumor site and targets only the at-risk neck after TORS for selected patients with HPV+ OPC may be safe and is worthy of further study.**

**Note: Primary site received some dose- may be sufficient (in some cases) to control microscopic disease**

# Contreras et al. (WashU, JCO 2019)

- Avoid adjuvant RT to contralateral pathologically node-negative neck.
- Phase 2 trial
- **Primary endpoint: regional control in unirradiated pN0 neck.**
- 72 patients with multiple sites (51% OPC, 49% HPV+)
- RT: 60-66 Gy to primary tumor and involved nodal bed and adjacent pathologically positive nodal levels plus margin; 52-54 Gy to ipsilateral elective nodal basins.
- 88% of patients with 10+ lymph nodes removed in contralateral neck dissection
- 24% primary site RT only.
- Median f/u 53 months
- 2 failures in the unirradiated pN0 neck (both with concurrent primary site failure).
- Unirradiated neck control 97%
- 5-year LC: 84%; 5-year regional control: 93%
- 5-year OS: 64%; 5-year PFS: 60%
- QOL not significantly different from baseline at 12 and 24 months post-RT.
- Xerostomia worse 6 months post-RT but recovered to baseline by 12 and 24 months.
- **Conclusion : Eliminating PORT to the PN0 neck results in good control in the unirradiated neck and results in long term global QOL similar to baseline**

# Induction chemotherapy followed by dose and/or volume de-escalated C/RT or surgery

# Chen et al., Lancet Oncol 2017 (UCLA):

- Multi-center trial of induction chemotherapy (IC) followed by response-adapted, dose-reduced chemo-RT
- Single arm, Phase II trial
- Eligibility: Biopsy-proven stage III/IV OPC SCC, p16+, ECOG 0-1
- Treatment:
- Induction paclitaxel 175 mg/m^2 and carboplatin AUC 6 (TP) x 2 cycles followed by dose-reduced RT to 54 Gy or 60 Gy for responders or non-responders, respectively, with weekly paclitaxel 30 mg/m^2. IMRT was required.
- **Radiation dose determined by radiographic response to IC using RECIST criteria**.
  - Complete and partial response defined as 100% and ≥30% decrease in sum of the longest diameter of target lesions compared to baseline.
  - All patients had CT 2 weeks after induction chemotherapy.
  - **Patients with CR or PR by RECIST received 54 Gy in 27 fractions to primary and involved nodes. Uninvolved nodal areas received 43 Gy.**
  - **All others received 60 Gy in 30 fractions with a dose of 48 Gy to uninvolved areas**.
  - Surgical salvage required at primary site for all patients experiencing tumor progression at any time.
  - All patients with N1 or N2 disease not obtaining a CR by 2-3 months after treatment were generally required to undergo post-treatment neck dissection.
- **Primary endpoint: 2-year PFS (per-protocol), H0: 2-year PFS ≥72% to continue after first stage with ≥86% required to warrant further study.**

# Chen et al., Lancet Oncol 2017 (UCLA) Continued

- Enrolled 45 patients, Median f/u 30 months.
- 55% of patients received de-escalated RT to 54 Gy in 27 fractions with concurrent weekly paclitaxel based on IC response.
- **11% had CR at all disease sites and 43% had partial response.**
- At 3-month post-treatment PET 84% had radiographic CR. All had radiographic CR on subsequent follow-up imaging. One required post-therapy neck dissection.
- **2-year PFS: 92%**
- **2-year OS: 98%**
- **2-year LRC: 95%**
- **Only 1 distant failure**
- Grade 3+ neutropenia and leukopenia 11% and 39%. No cases of neutropenic fever. 7% required dose-reduction after cycle 1 of IC.
- Grade 3+ dysphagia 9%, mucositis 9%
- 7% had feeding tubes placed prophylactically in week 1 of chemo-RT and 7% had feeding tube placed during chemo-RT for high-grade dysphagia and weight loss.
- Late grade 3+ toxicity was 5%.
- Only 1 patient (2%) was G-tube dependent at 3-months post-treatment, but 0% G-tube by 6 months.
- **Conclusions: A phase III study is warranted based on 2-year PFS 92% (above 86% threshold) for induction chemotherapy followed by response-adapted, dose-reduced chemo-RT in HPV+ OPC**

# *Seiwert and Foster et al. (UChicago, Ann Oncol 2019)*

- Single institution, phase II trial
- N=62 patients enrolled with median follow-up=29 months.
- Eligibility: T1-4N2-3 OR T3-4anyN disease, p16+ on IHC
  - Low-risk (LR): ≤T3, ≤N2b, AND ≤10 PYH (N=28, 45%)
  - High-risk (HR): T4 OR ≥N2c OR > 10 PYH (N=34, 55%) 35% had >10 PYH
- **Primary endpoint: 2-year PFS (H0: 85% historical control with 11% margin**)
- Treatment: 3 cycles of induction chemotherapy using carboplatin/nab-paclitaxel followed by imaging for RECISTv1.1 response. **Then assigned to chemo-RT with TFHX based on response.**
  - **RT alone: 50 Gy in daily 2 Gy/fx for LR with ≥50% RECIST response (71% of LR)**
  - **Chemo-RT: 45 Gy in 1.5 Gy BID fx week on/week off TFHX for LR with 30-50% RECIST response (21% of LR) OR HR with ≥50% response (71% of HR)**
  - **Chemo-RT: 75 Gy in 1.5 Gy BID fx week on/week off with TFHX for all others (8% LR and 29% HR)**
  - Volume included pre-induction gross disease + 1.5 cm, involved nodal levels, and next echelon of uninvolved at-risk lymph nodes
- 82% of patients received de-escalation (92% of LR and 71% of HR).
- All were recommended to undergo neck dissection and biopsy of primary site at 4-8 weeks post-RT/CRT to confirm pathologic response

# *Seiwert and Foster et al. (UChicago, Ann Oncol 2019) Continued*

- ORR post-IC was 89%
- 71% experiencing ≥50% tumor size reduction after IC
- pCR rate: for all patients was 90% and 92% for those receiving 50 Gy RT alone/Chemo-RT of 45 Gy.
- pCR for patients receiving chemo-RT of 75Gy=80%.
- 2-year overall PFS = 94.5%
- 2-year overall OS= 98%.
- LR: 2-year PFS=95%
- LR: 2-year OS= 100%
- HR: 2-year PFS= 94%
- HR: 2-year OS = 97%
- 2-year LRC= 98%
- 2-year DC = 100%
- One high-risk patient experiencing pCR after chemo-RT of 45 Gy had a LF 11 months post enrollment with subsequent distant failure

**Conclusion: Induction chemotherapy with response and risk-stratified dose AND volume de-escalated RT/chemo-RT for HPV+ OPC is associated with favorable oncologic outcomes and reduced acute and chronic toxicity. Further evaluation in large multicenter studies is justified.**

# Treatment Patient Received

- Induction two cycles of induction chemotherapy with carboplatin and paclitaxel
- R BOT and bilateral neck
- 56 Gy in 1.6 Gy fractions with an SIB to 70 Gy in 2 Gy fractions with 40 mg/m2 of weekly cisplatin

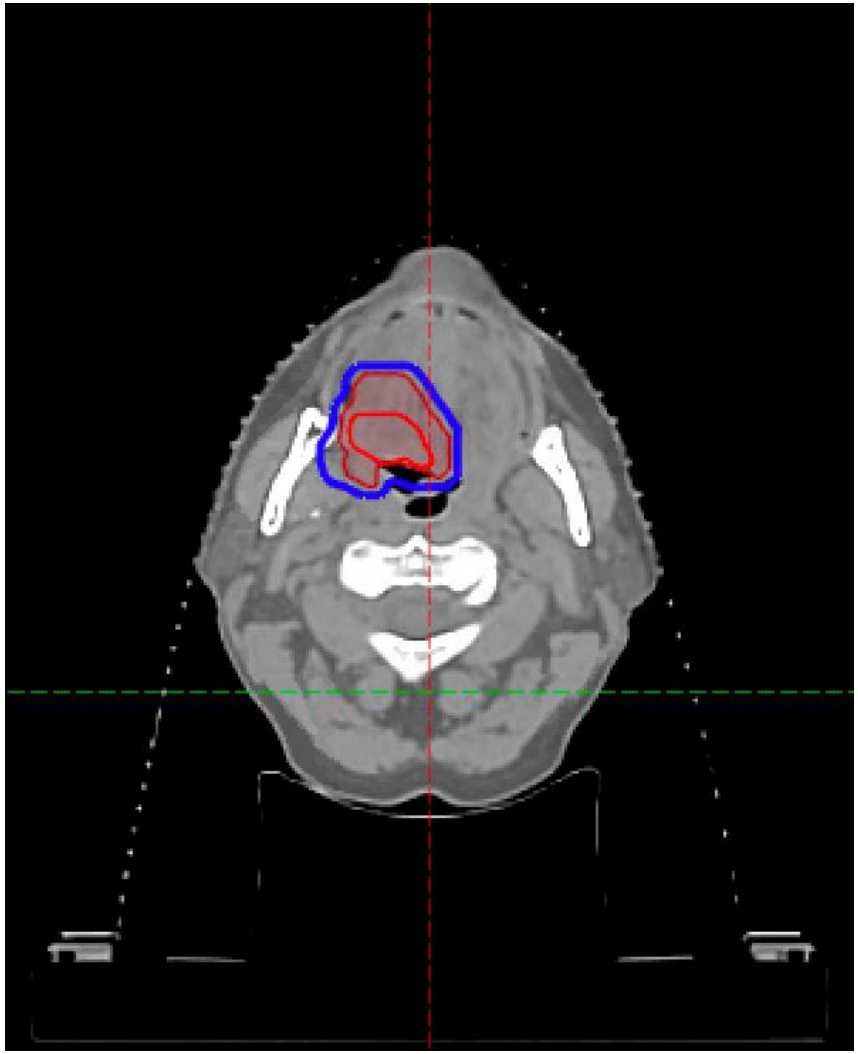
# Simulation

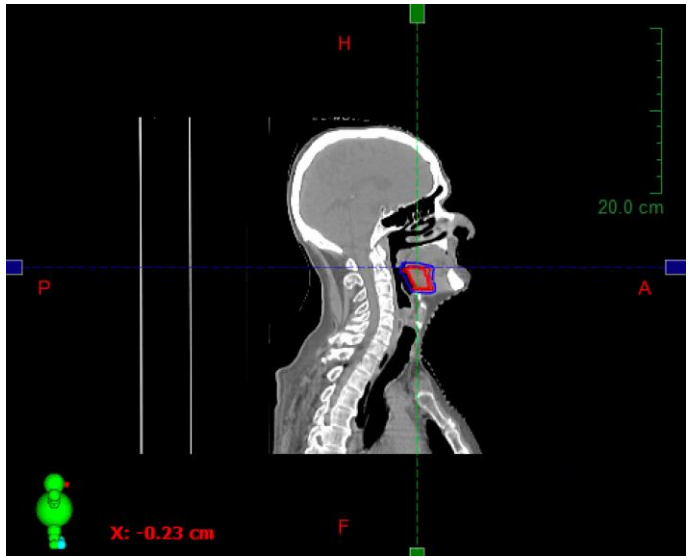
- Supine, arms down
- 5 point Head and neck mask
- IV contrast
- 2mm slice thickness

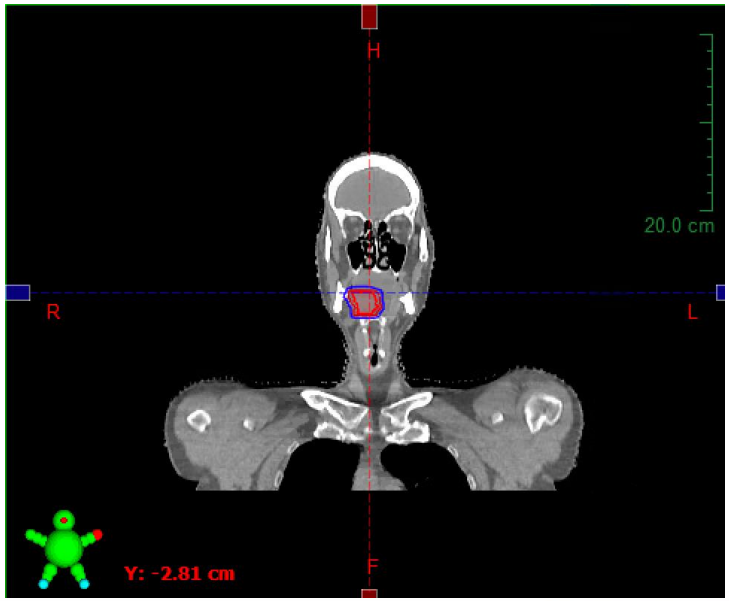
# Contouring

- Fusion of PET/CT and MRI used for GTV delineation
- 70 Gy CTV= 3 mm expansion of GTV respecting normal structures
- 70 Gy PTV= 3mm CTV expansion
- 56 Gy in 1.6 Gy
  - Bilateral level IB (due to T4 disease) and II-IV covered. IA covered due to deep extrinsic muscle involvement.
  - Ipsilateral RP nodes covered, but contralateral side spared due to negative neck

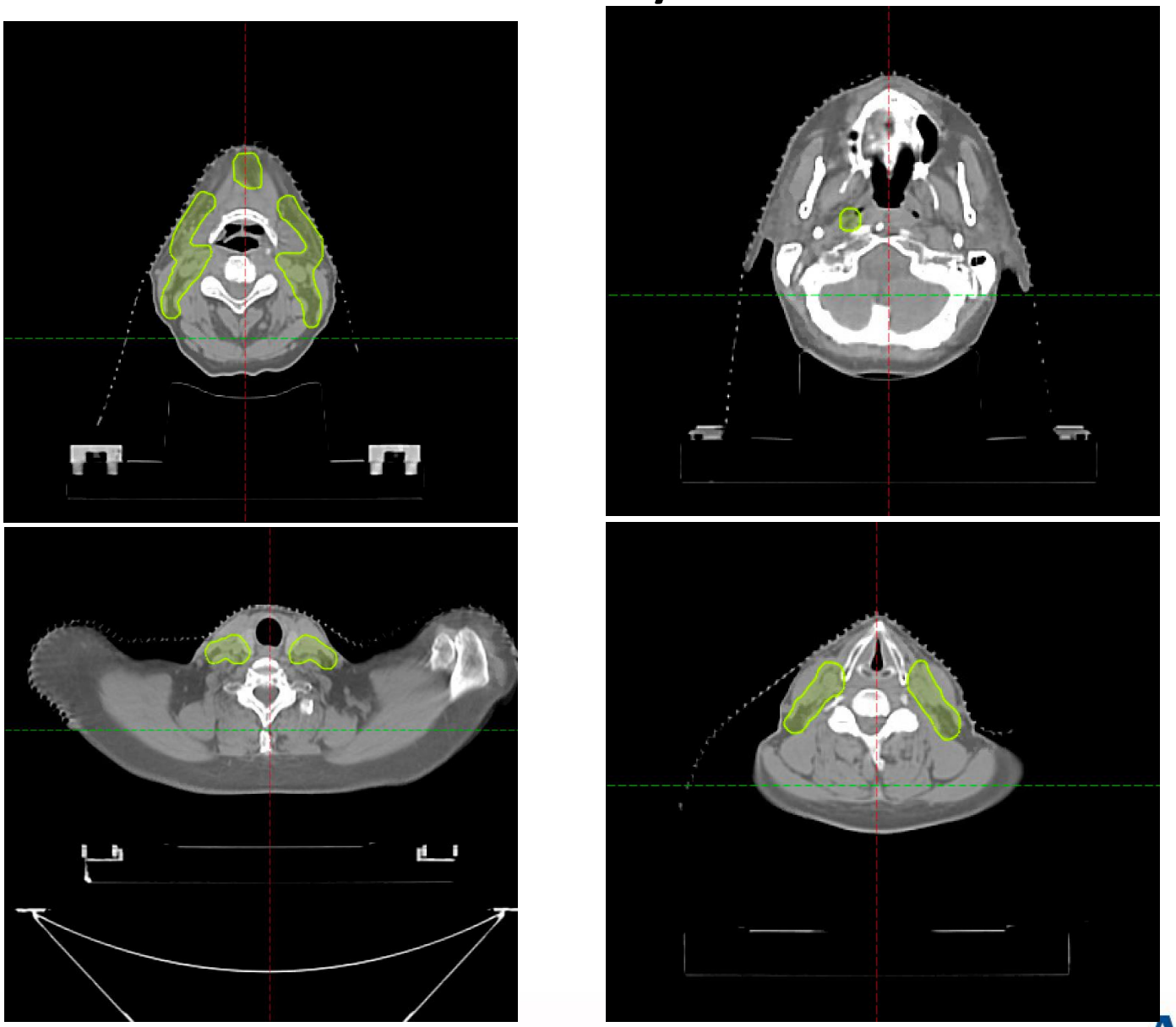
# GTV, CTV and PTV 70 Gy



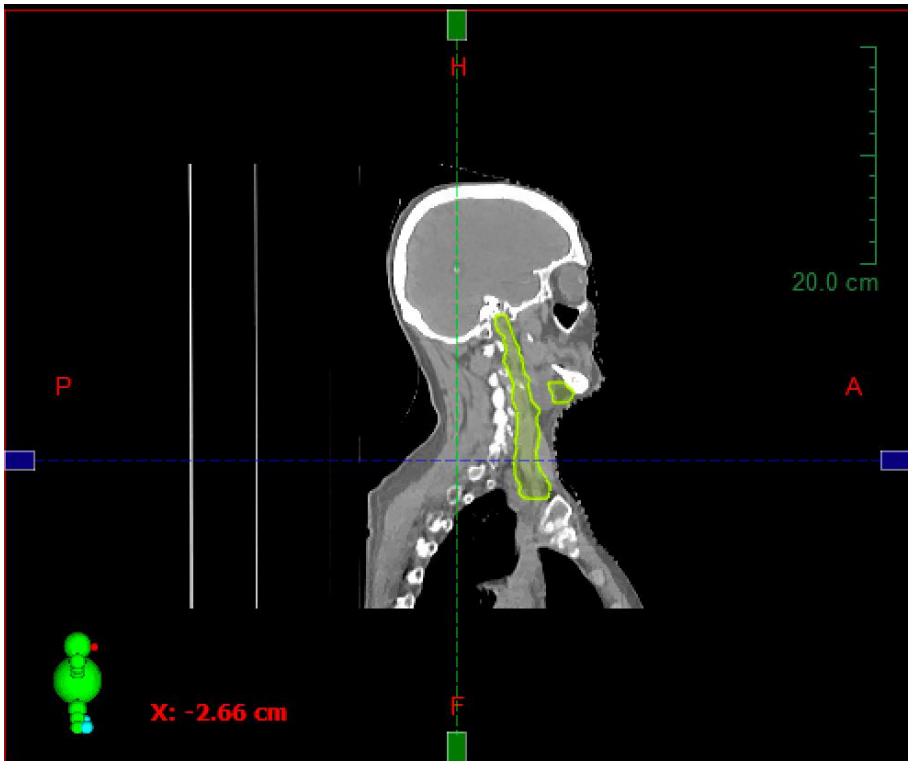


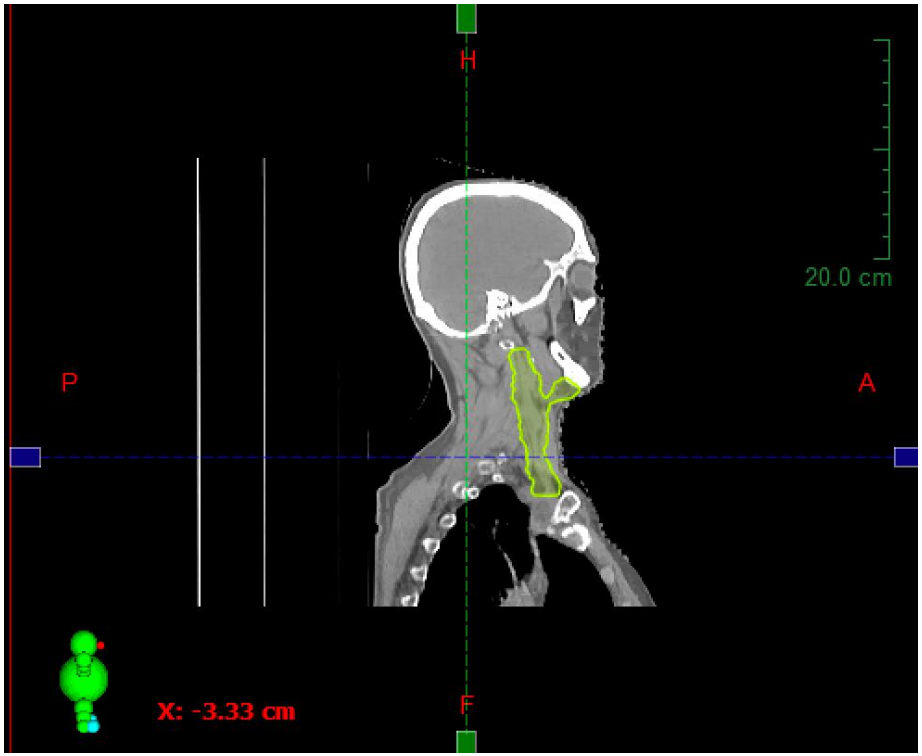



# 56 Gy

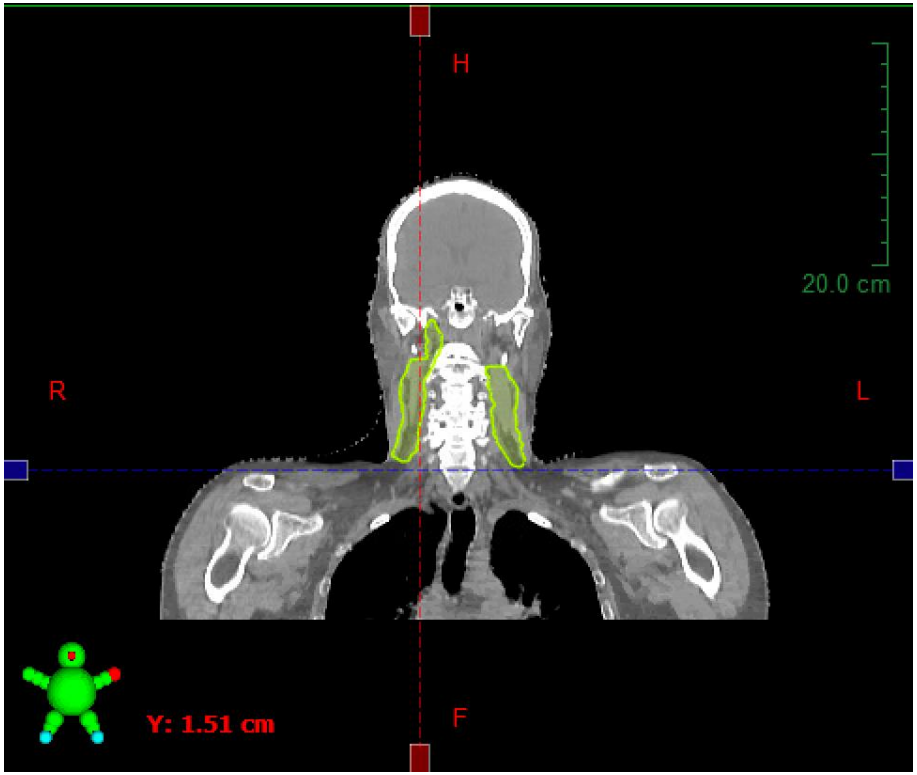


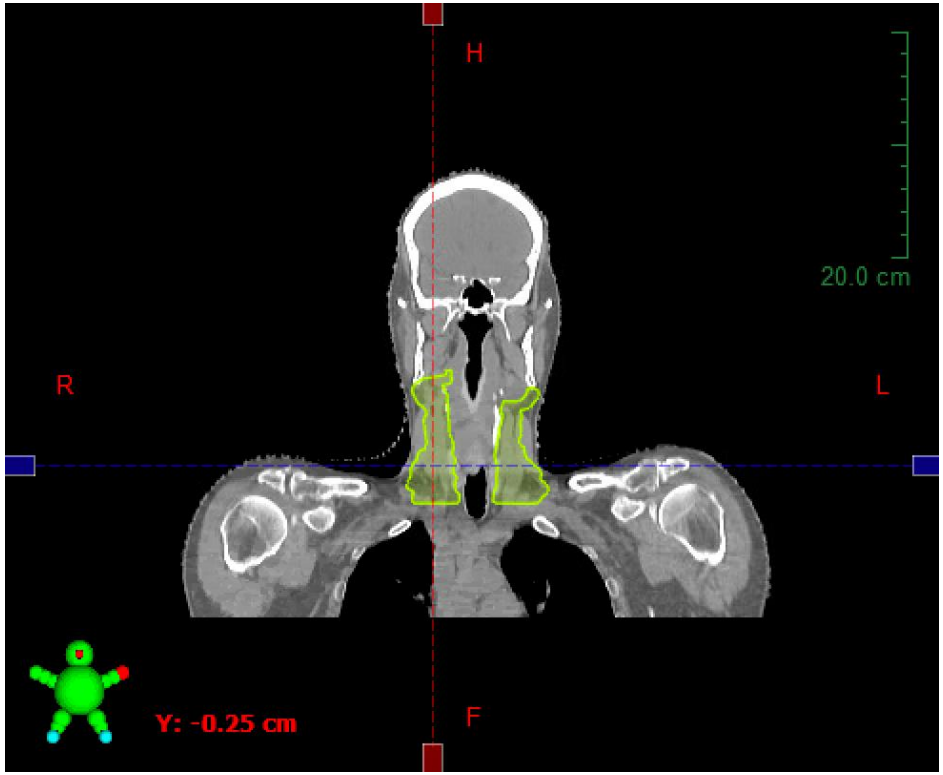
# 56 Gy



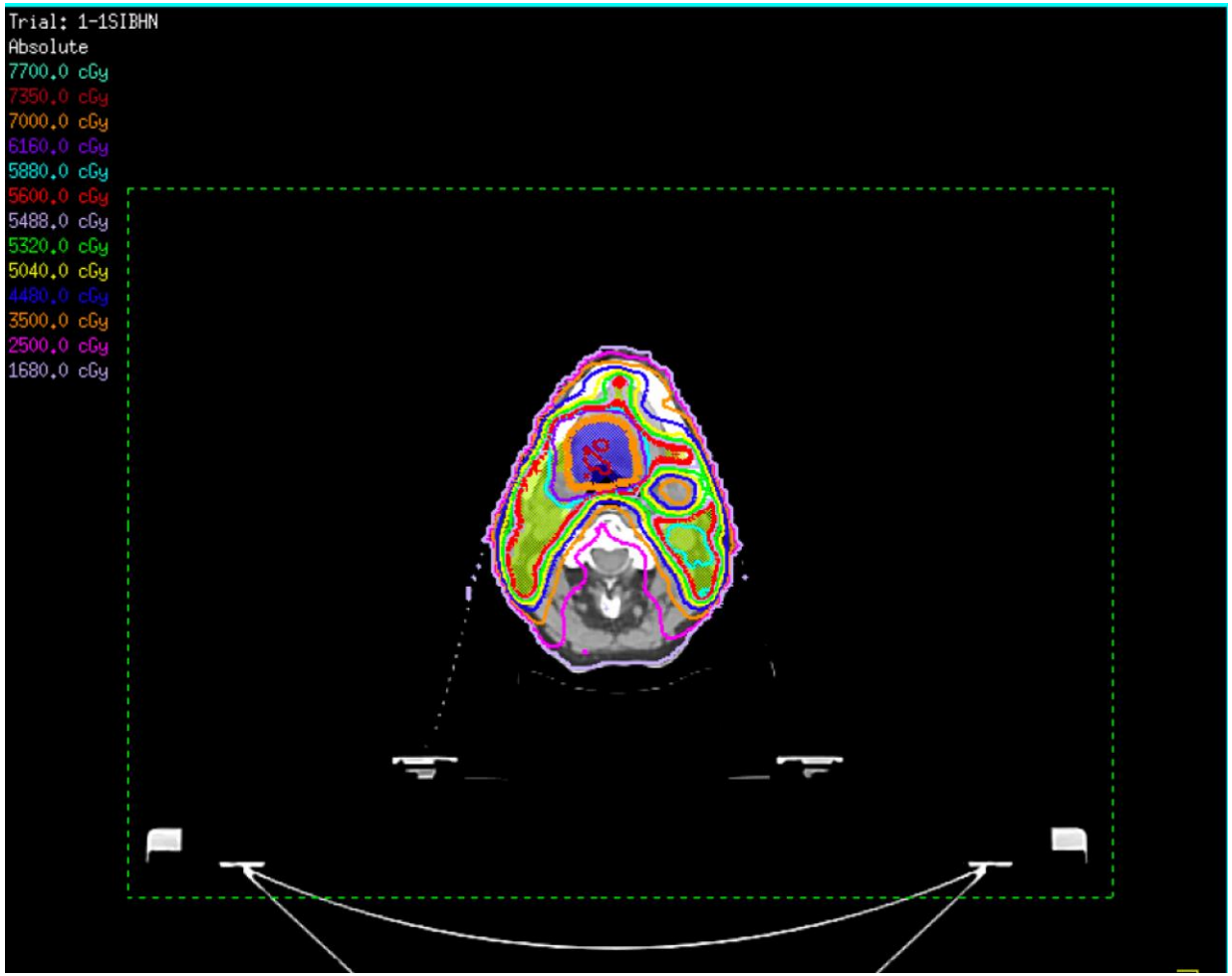



# 56 Gy

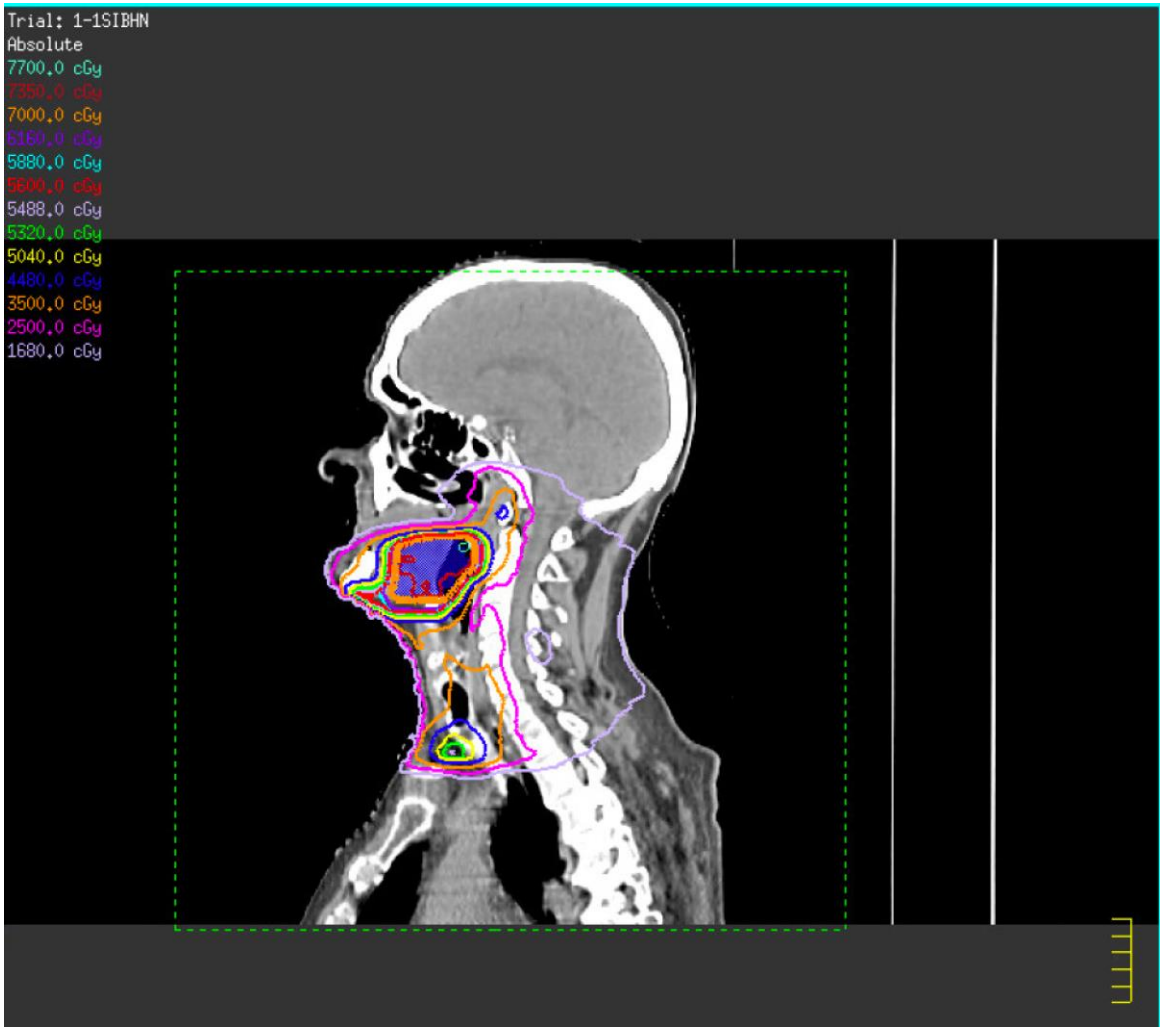


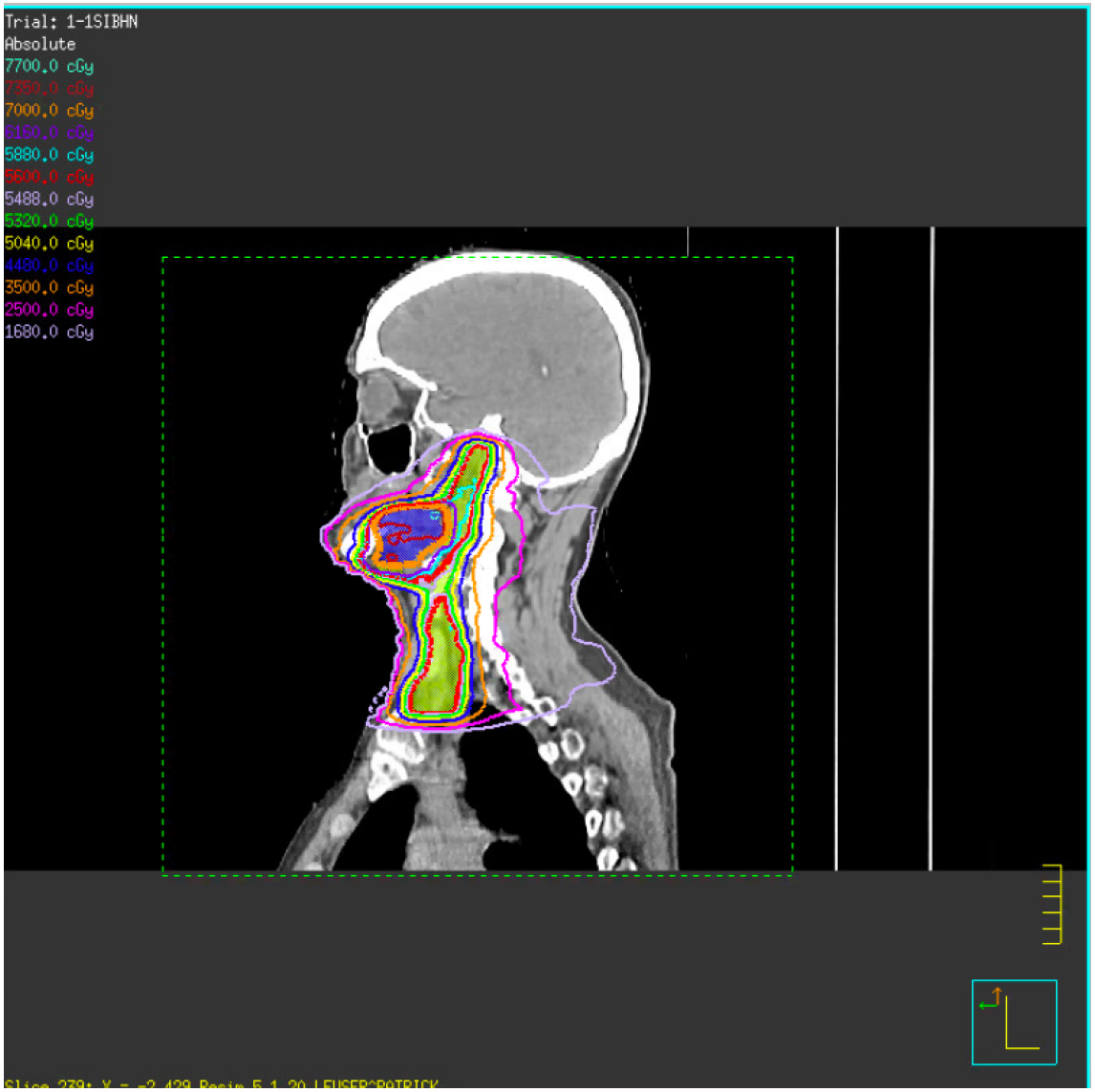
# Dose Distribution



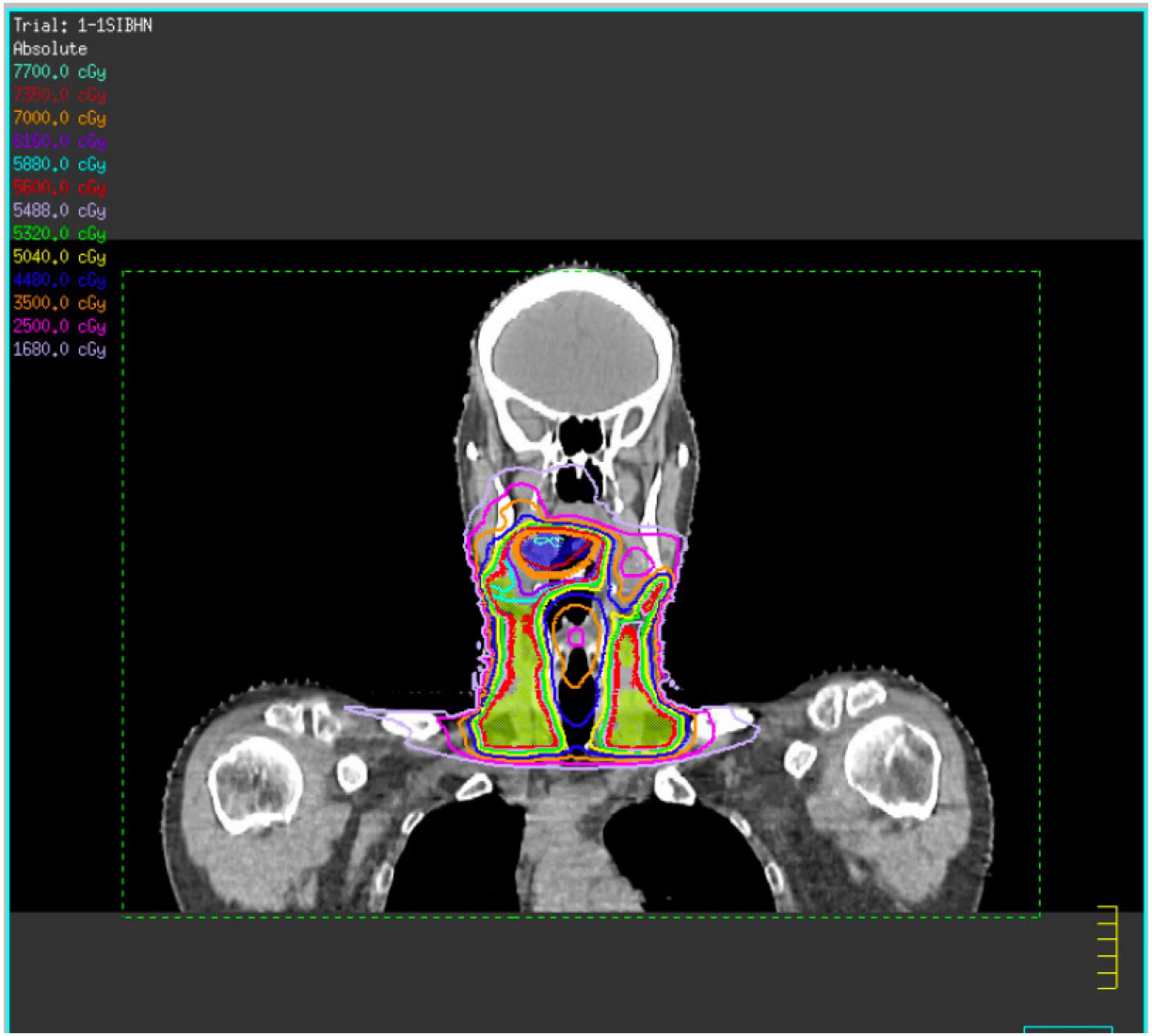
# Dose Distribution



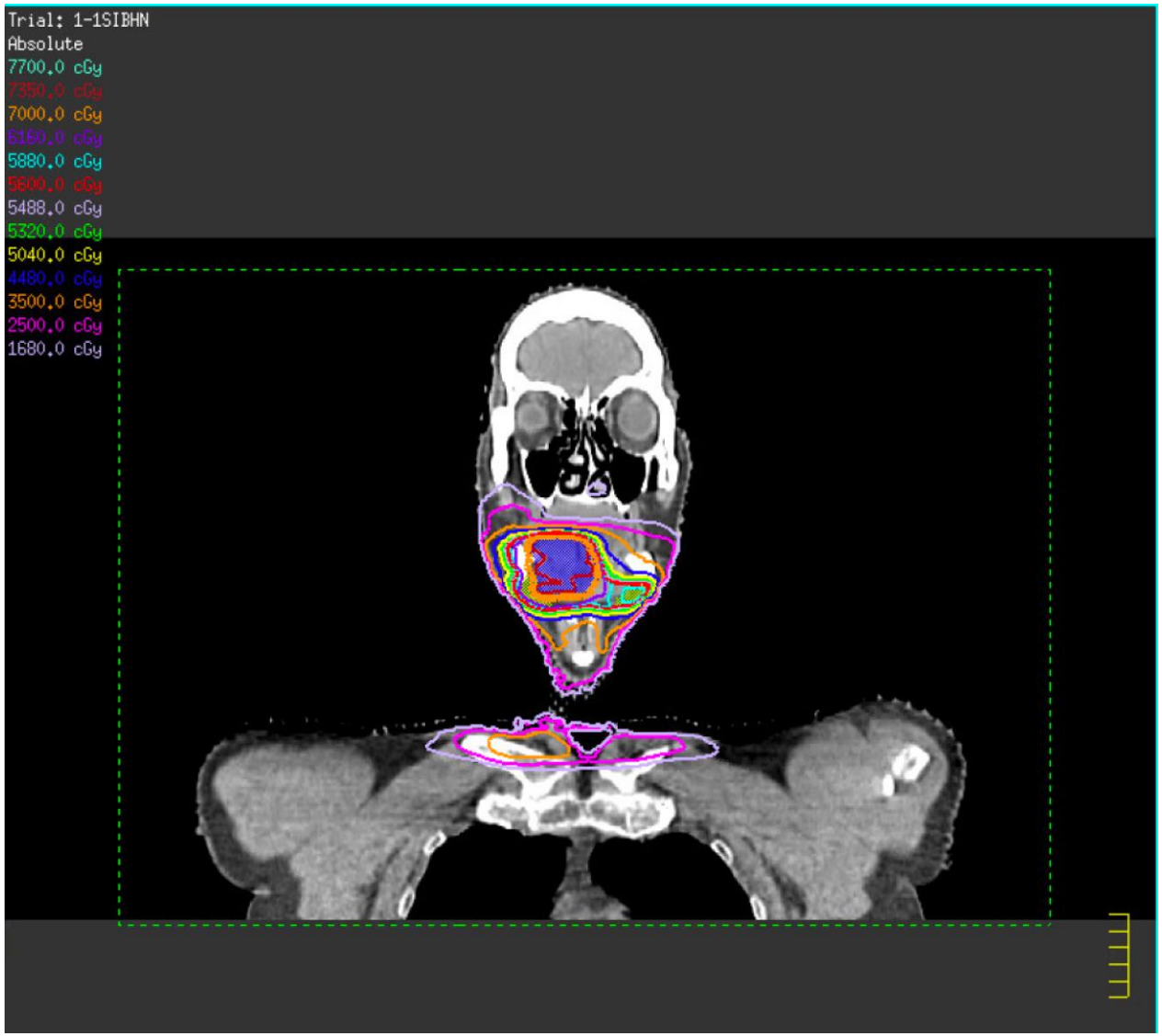
# Dose Distribution



# Dose Distribution



# Dose Distribution



# Dose Constraints
# General constraints based on HN-005

| OAR | Dose Constraint |
|---|---|
| Brachial Plexus_R/L | D0.03cc[Gy] <= 66 |
| Parotid_R/L (at least one gland) | Mean [Gy] <=26 |
| Larynx_SG | Mean [Gy] <=40 |
| Pharynx (uninvolved) | Mean [Gy] <=45 |
| Oral Cavity (uninvolved) | Mean [Gy] <=35 |
| Lips | Mean [Gy] <=20 |
| Esophagus_S | Mean [Gy] <=30 |
| Submandibular gland_R/L (contralateral) | Mean [Gy] <=39 |
| Cochlea_R/L | Mean [Gy] <=35 |
| Bone_Mandible | D0.03cc [Gy] <=73.5 |
| Thyroid | Mean [Gy] <=50 |
| Spinal Cord | D0.03cc [Gy] <=45 |

- Dose constraints can be individualized and provided to dosimetry based on what may be achievable (depending on the location and distribution of gross disease) in each case.

# Constraints used in case for treatment

| Structure | Goal | Plan |
|---|---|---|
| PTV 70<br><br>PTV 56 | | V100% = 98.60%<br>V95% = 99.80%<br><br>V100% = 95.50%<br>V95% = 99.23% |
| Oral cavity | Mean < 50Gy | 47.68 |
| Mandible | 0.03cc max <73.50Gy | 73.39Gy |
| Trachea | Mean < 20Gy | 16.03Gy |
| L Submandibular | Mean < 40Gy | 39.89Gy |
| R parotid | Mean < 20Gy | 18.34Gy |
| L parotid | Mean < 15Gy | 13.98Gy |
| Lips | Max < 25Gy | 32.79Gy |
| Constrictors | Mean < 40Gy | 38.98Gy |
| Supraglottis | Mean < 45Gy | 41.97Gy |
| Larynx | Mean < 35Gy | 30.73Gy |
| R cochlea | Mean < 15Gy | 8.83Gy |
| L cochlea | Mean < 5Gy | 3.54Gy |
| Brainstem | Max < 25Gy | 22.84Gy |
| Spinal cord | Max < 25Gy | 23.66Gy |
| Esophagus | Mean < 15Gy | 13.23Gy |

# Acute Toxicities

- Dermatitis
- Dysphagia- present in over 50% prior to treatment
- Feeding tube dependent
- Mucositis
- Xerostomia
- Ageusia
- Fatigue

# Long Term Toxicities

- Telangiectasias
- Dysphagia- ~20% with conventional RT, ~6% with IMRT (treatment to pharyngoesophageal constrictors impact outcomes
- Esophageal stricture- can present with feeling of something getting stuck in throat/chest or change in pattern of cough when swallowing food
- Xerostomia – maximum recovery 1-2 years, present in 64% of long term survivors at mean follow-up, decreased with IMRT to ~ 15%
- Ageusia
- Dental caries- increases 50-fold after RT, benefit from fluoride trays
- Osteoradionecrosis- 5-7%
- Trismus- up to 35% with conventional RT, 5-15% with IMRT
- Chronic mucosal pain/ sensitivity- can be exuberated by hot, spicy, acidic or dry foods
- Chronic feeding tube- 10-25%
- Ototoxicity ( from cisplatin)- 20-40% at 1 year
- Autonomic dysfunction- thought to be as a result of fibrosis in arterial walls and decreased baroreceptor sensitivity
- Neck fibrosis
- Lymphedema

# Follow-up

- **First year after treatment:**
  - Baseline post-treatment imaging of primary site and regional nodes recommended within 6 months after treatment
  - After the first post-RT imaging, routine imaging is not required unless if there is clinical suspicion
  - Detailed physical exam every 1-3 months
  - Direct/indirect examination every 3 months
- **Second year after treatment:**
  - Detailed physical exam every 2-6
  - direct/indirect examination every 6 months
- **3-5 years after treatment:**
  - Detailed physical exam every 4-8 months during
  - Direct/indirect examination every 6 months
- **5 years +**
  - Detailed physical exam with direct/indirect examination yearly
- TSH levels every 6-12 months or earlier if symptomatic
- Speech, hearing, swallow examinations, and GI consult as needed
- Chest imaging based on smoking risk factors

# Conclusions

- Consider dental evaluation, nutrition, speech/swallow evaluation, and audiogram for all patients
- Standard definitive treatment of OPC is 75 Gy in 35 fractions with concurrent chemotherapy (standard of care at some institutions is surgery followed by adjuvant radiation)
- TORs +/- neck dissection may be appropriate for some patients with early well lateralized OPC
- Adjuvant therapy after TORS is warranted for patients with high risk features of positive surgical margins, ECE, PNI, LVSI, T3-4 disease or multi-site N disease

# Conclusions

- HPV+ OPC patients tend to be younger, have less smoking history, and have better prognoses than patients with HPV- OPC
- Treatment de-escalation of HPV+ OPC may beneficial
  - Cisplatin is still the radiosensitizer chemotherapy of chose over cetuximab
  - Decreased radiation dose or fields may be warranted or considered as further de-escalation trials emerge

# Conclusions

- Cover bilateral Levels II-IV
- Level IA is at risk with deep intrinsic muscle invasion
- For T3-T4 disease consider covering level IB, optional for T1-T2 disease
- Consider ipsilateral or no RP coverage with node negative neck

# References


1. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24-35.

2. Bensadoun RJ, Riesenbeck D, Lockhart PB, et al. A systematic review of trismus induced by cancer therapies in head and neck cancer patients. Support Care Cancer 2010;18:1033-8.

3. Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33-40.

4.Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91:2081-6.

5.Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294-301.

6.Chen AM, Felix C, Wang PC, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. Lancet Oncol 2017;18:803-11.

7.Chera BS, Amdur RJ, Green R, et al. Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus-Associated Oropharyngeal Squamous Cell Carcinoma. J Clin Oncol 2019;37:2661-9.

8.Chera BS, Amdur RJ, Tepper JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2018;124:2347-54.

9.Contreras JA, Spencer C, DeWees T, et al. Eliminating Postoperative Radiation to the Pathologically Node-Negative Neck: Long-Term Results of a Prospective Phase II Study. J Clin Oncol 2019;37:2548-55.

10.Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69-76.

11.Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol 2010;28:2732-8.

12.Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA 2012;307:693-703.

13.Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 2000;92:709-20.

14.Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet 2019;393:40-50.

15.Haynes J, Arnold KR, Aguirre-Oskins C, Chandra S. Evaluation of neck masses in adults. Am Fam Physician 2015;91:698-706.

16.Huang SH, Perez-Ordonez B, Weinreb I, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. Oral Oncol 2013;49:79-85.

17.Hutcheson KA, Lewin JS, Barringer DA, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer 2012;118:5793-9.

18.Krabbe CA, Balink H, Roodenburg JL, Dol J, de Visscher JG. Performance of 18F-FDG PET/contrast-enhanced CT in the staging of squamous cell carcinoma of the oral cavity and oropharynx. Int J Oral Maxillofac Surg 2011;40:1263-70.

19.Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582-9. 20.Mehanna H, Wong WL, McConkey CC, et al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med 2016;374:1444-54.

21.Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. Int J Oral Maxillofac Surg 2011;40:229-43.

22.Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. Lancet Oncol 2019;20:1349-59.

# References


23.Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.

24.Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. 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.

25.Routman DM, Funk RK, Tangsriwong K, et al. Relapse Rates With Surgery Alone in Human Papillomavirus-Related Intermediate- and High-Risk Group Oropharynx Squamous Cell Cancer: A Multi-Institutional Review. Int J Radiat Oncol Biol Phys 2017;99:938-46.

26.Sanguineti G, Califano J, Stafford E, et al. Defining the risk of involvement for each neck nodal level in patients with early T-stage node-positive oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2009;74:1356-64.

27.Sanguineti G, Pai S, Agbahiwe H, et al. HPV-related oropharyngeal carcinoma with Overt Level II and/or III metastases at presentation: The risk of subclinical disease in ipsilateral levels IB, IV and V. Acta Oncol 2014;53:662-8

28.Seiwert TY, Foster CC, Blair EA, et al. OPTIMA: a phase II dose and volume de-escalation trial for human papillomavirus-positive oropharyngeal cancer. Ann Oncol 2019;30:1673.

29.Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg 1990;160:405-9.

30.Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.

31. Spencer CR, Gay HA, Haughey BH, et al. Eliminating radiotherapy to the contralateral retropharyngeal and high level II lymph nodes in head and neck squamous cell carcinoma is safe and improves quality of life. Cancer 2014;120:3994-4002.

32. Sun J, Li B, Li CJ, et al. Computed tomography versus magnetic resonance imaging for diagnosing cervical lymph node metastasis of head and neck cancer: a systematic review and meta-analysis. Onco Targets Ther 2015;8:1291-313.

33. .Swisher-McClure S, Lukens JN, Aggarwal C, et al. A Phase 2 Trial of Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID): Omission of the Resected Primary Tumor Bed After Transoral Robotic Surgery for Human Papilloma Virus-Related Squamous Cell Carcinoma of the Oropharynx. Int J Radiat Oncol Biol Phys 2020;106:725-32.

34.Yom SST-S, P.; Caudell J.J.; Waldron, J.N.; Gillison, M.L.; Truong, M.T.; Jordan, R.; Subramaniam, R.; Yao, M.; Chung, C.; Geiger, J.L.; Chan, J.; O'Sullivan, B.; Blakaj, D.M.; Mell, L.K.; Thorstad, W.L.; Jones, C.U.; Banerjee, R.N.; Lominska, C.E; and Le, Q.T. NRG-HN002: A Randomized Phase II Trial for Patients With p16-Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer. Int J Radiat Oncol Biol Phys 2019.

35.Zuur CL, Simis YJ, Lansdaal PE, et al. Ototoxicity in a randomized phase III trial of intra-arterial compared with intravenous cisplatin chemoradiation in patients with locally advanced head and neck cancer. J Clin Oncol 2007;25:3759-65.


Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com