Neoadjuvant Radiation and Immunotherapy in Head and Neck Cancer

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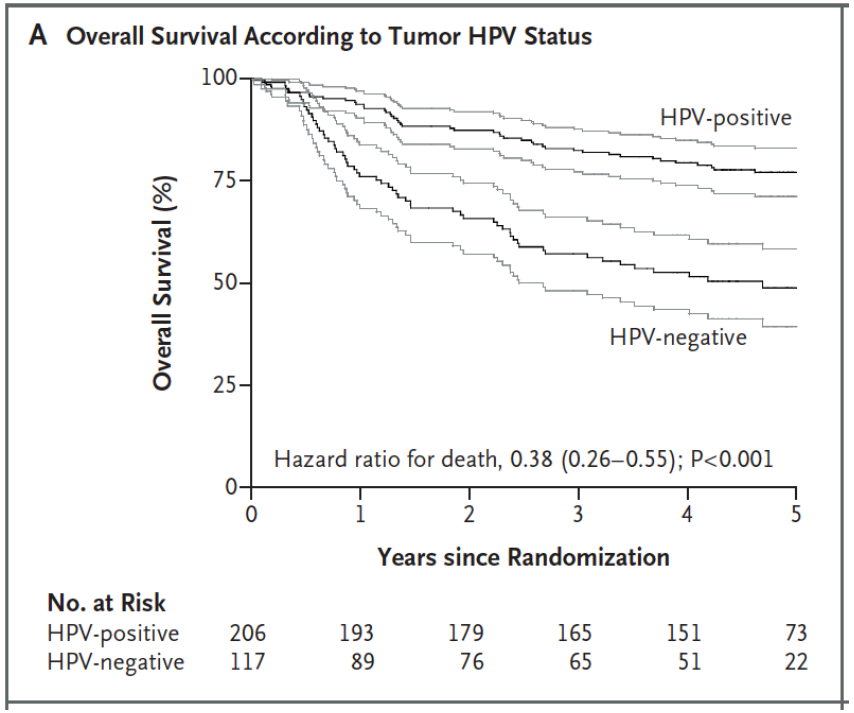
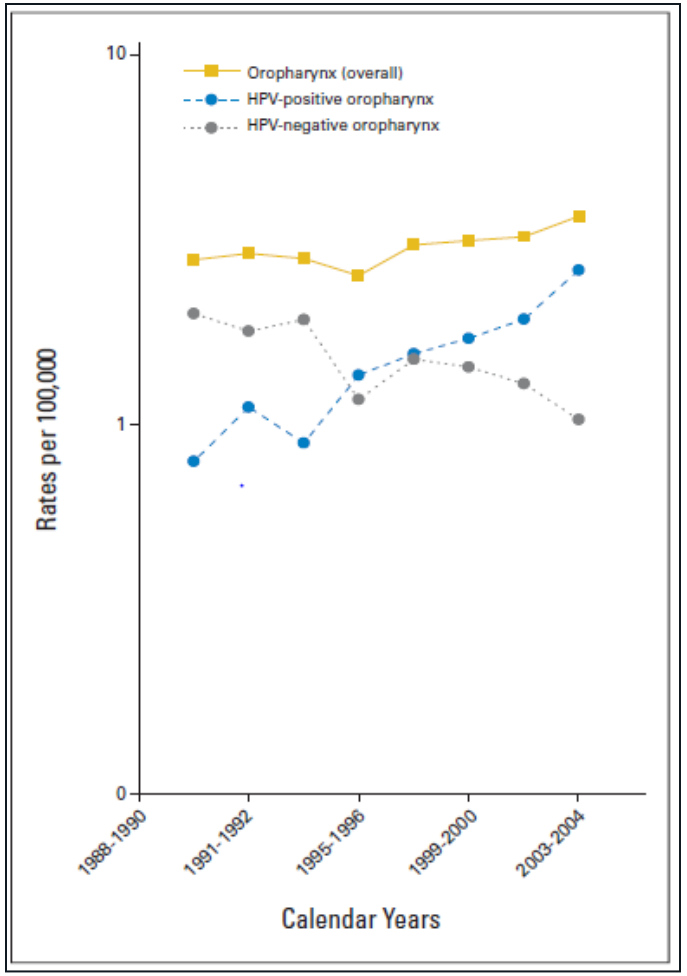
Oropharyngeal SCC

- Rates of many types of HNSCC are declining
  - HPV associated oropharyngeal SCC are increasing
- Favorable prognosis in comparison
  - Still up to 20% mortality at 3 years





Toxicity

- Significant side effect rates up to 40%

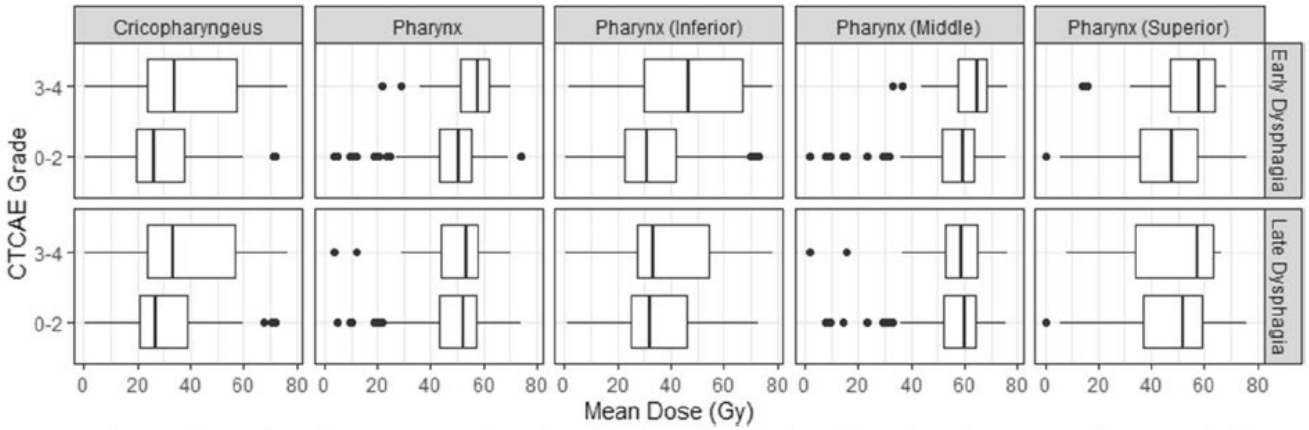
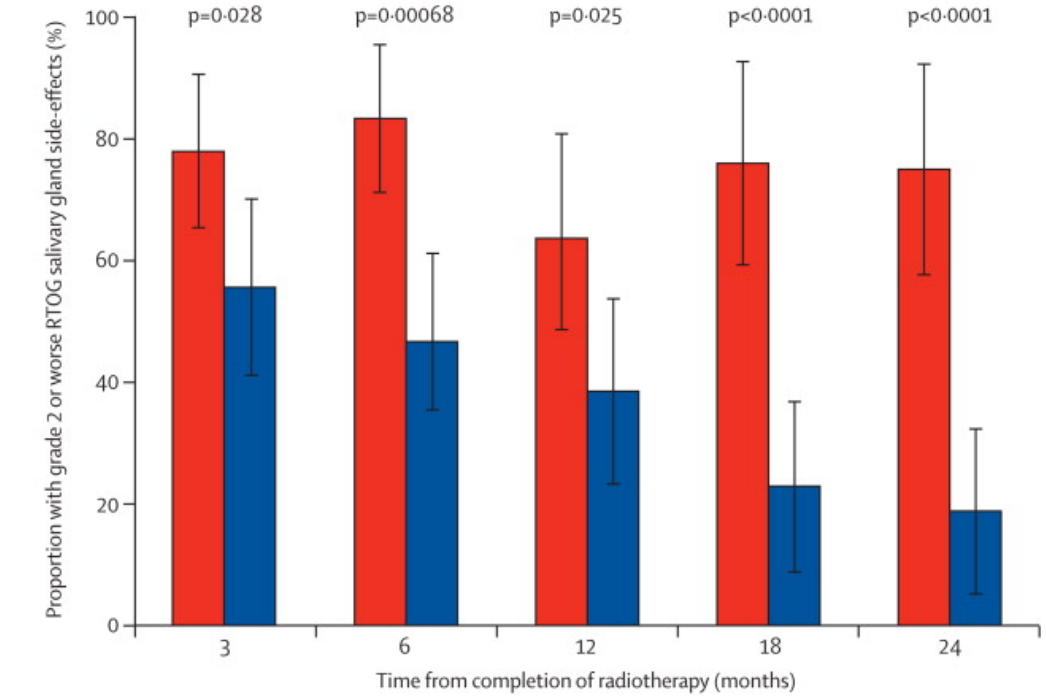


Fig. 2 Distribution of mean dose values per structure for each outcome. *T*-tests were performed to evaluate the association between each dose metric and each outcome. Multiple dose metrics were significantly (p-value < 0.05) associated with early dysphagia, but none were associated with late dysphagia



De-Escalation - Cetuximab

- 424 patients with locoregionally advanced (stage III/IV) head and neck cancer randomized to RT +/- weekly cetuximab
- Median OS 49 months RT + cetux vs 29.3 months RT alone (HR 0.74, p=0.03)
- No difference in distant metastasis

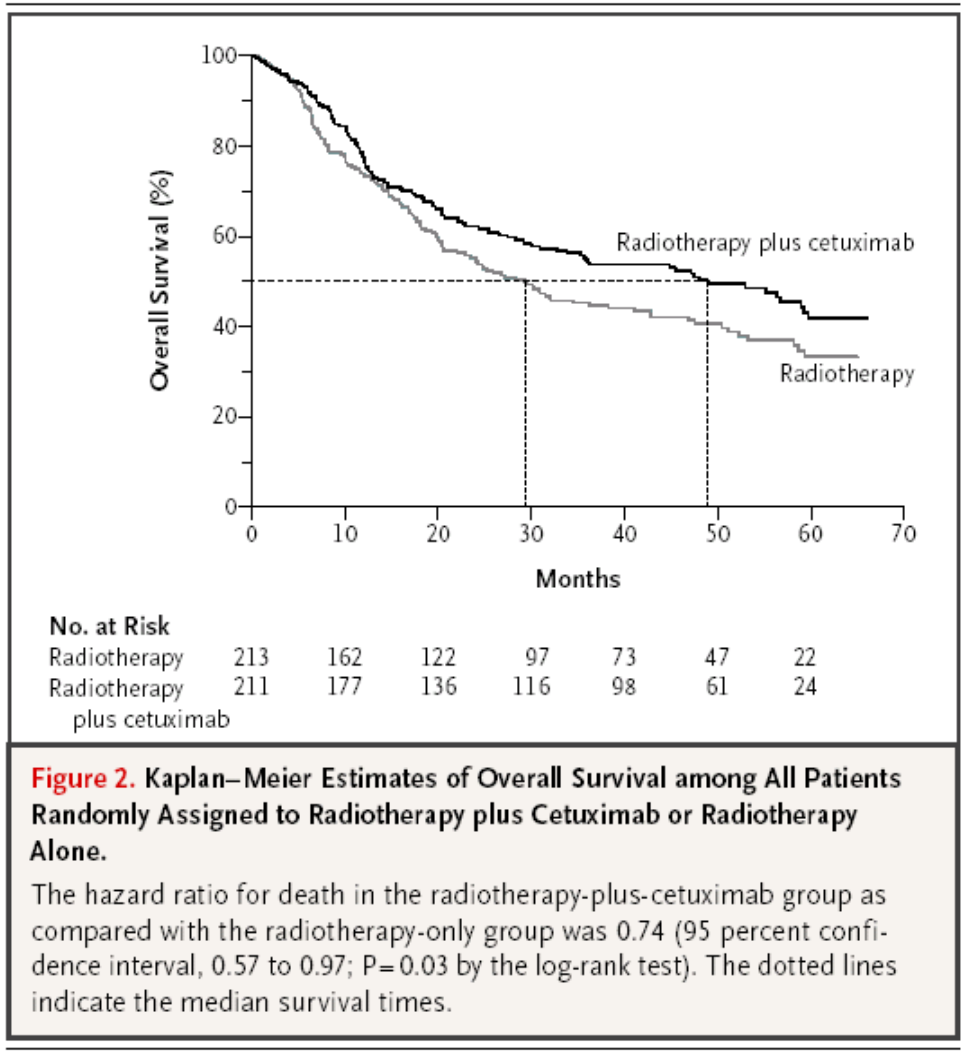
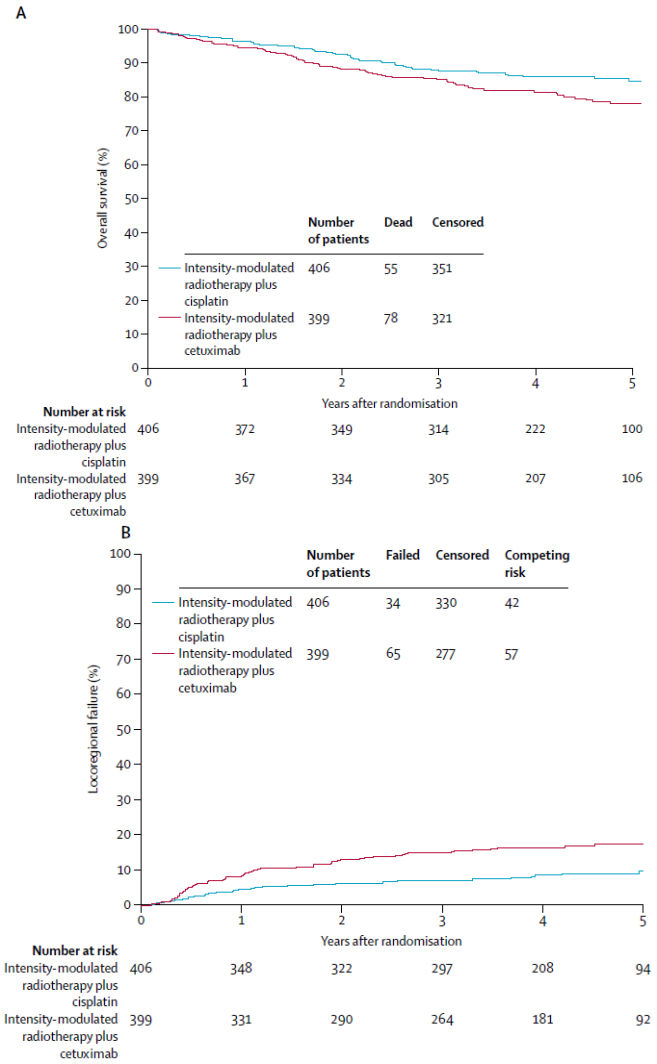


Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.

De-Escalation – Cetuximab vs Cisplatin

RTOG 1016



De-Escalation – Cetuximab vs Cisplatin

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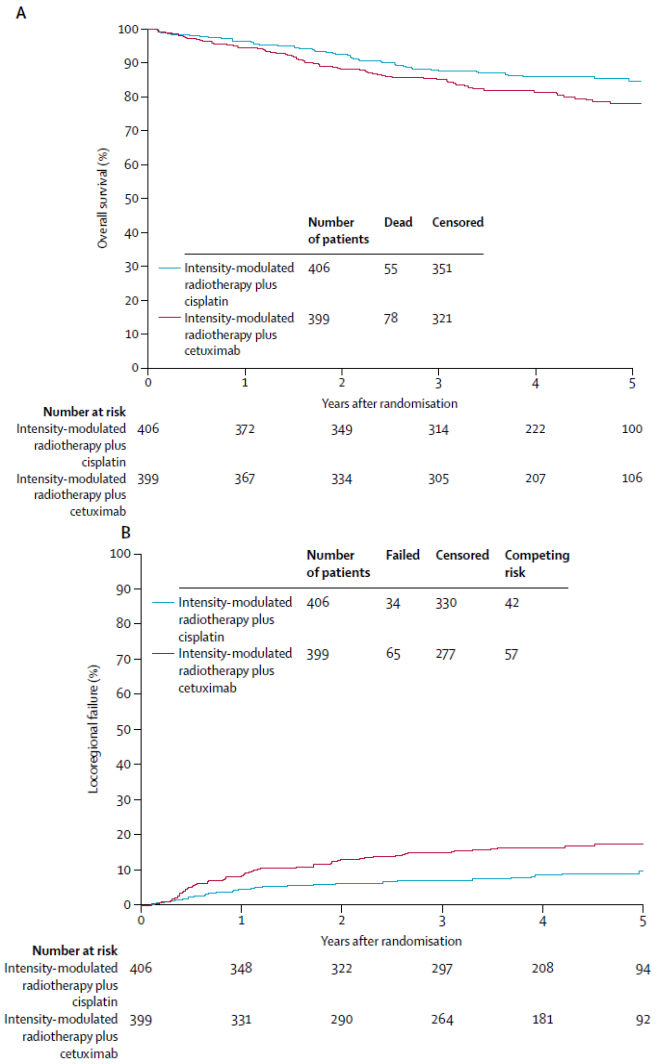
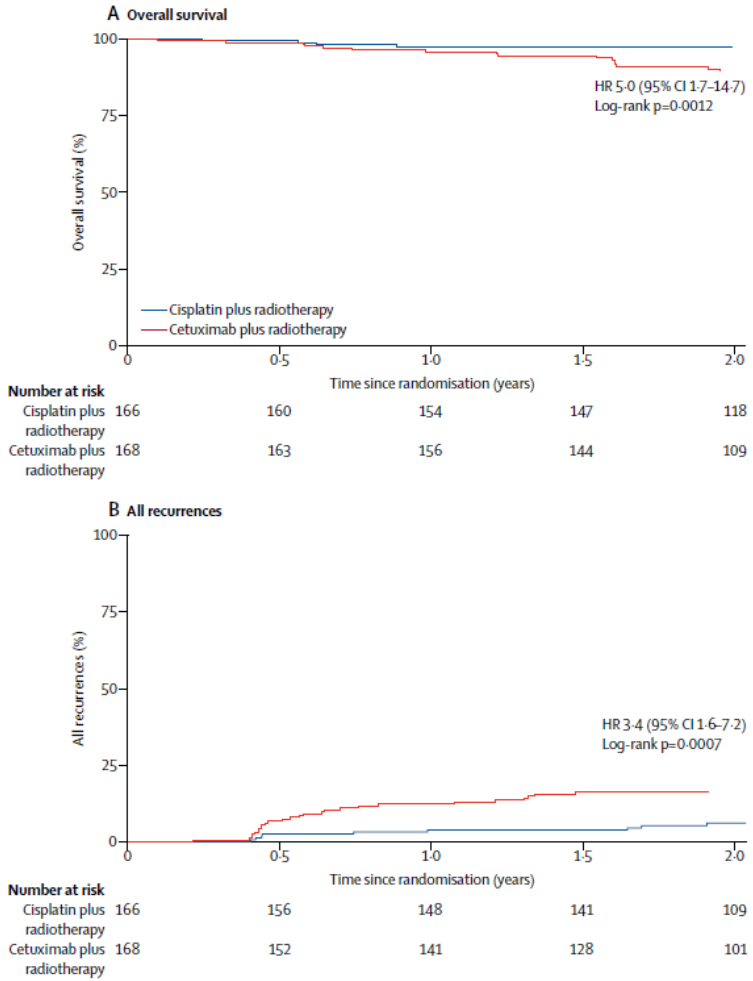


De-ESCALaTE



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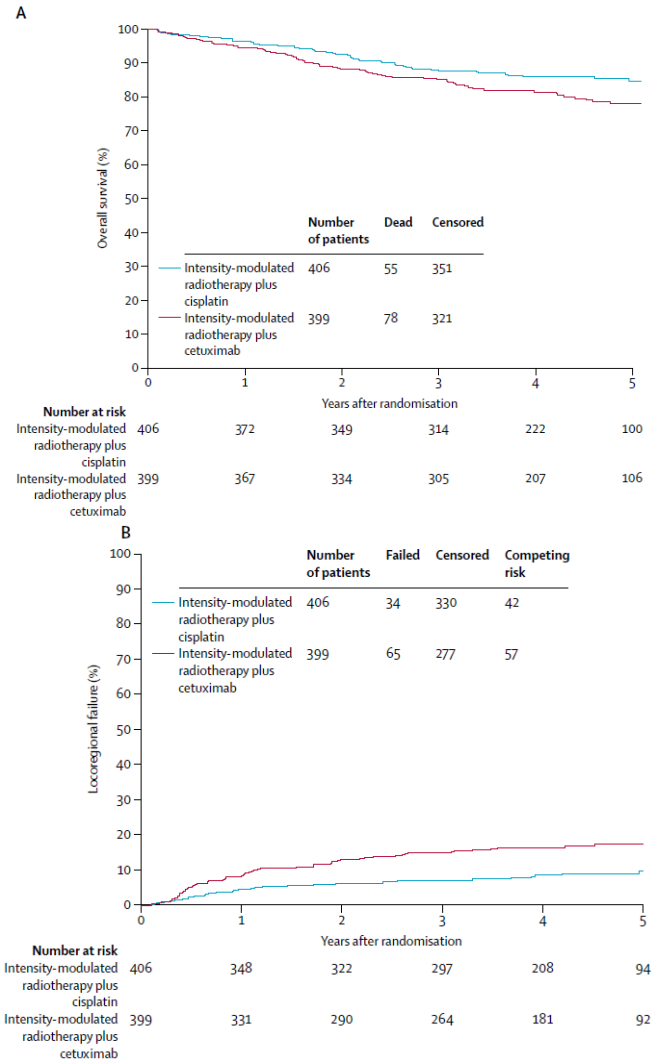

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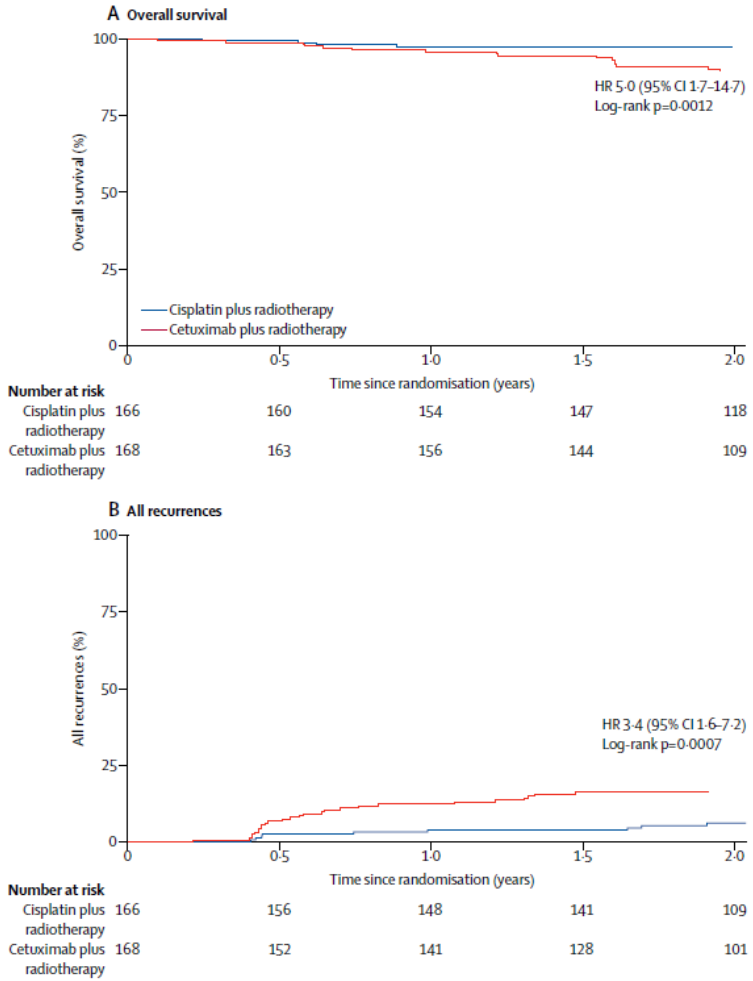
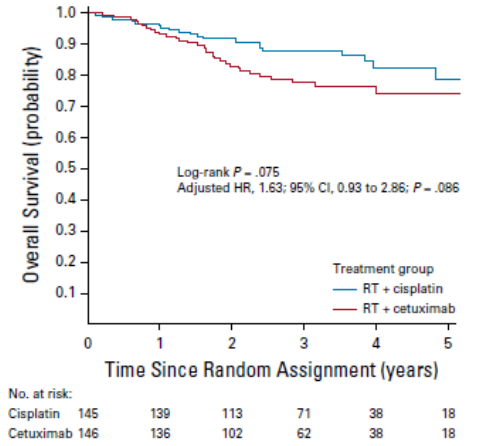
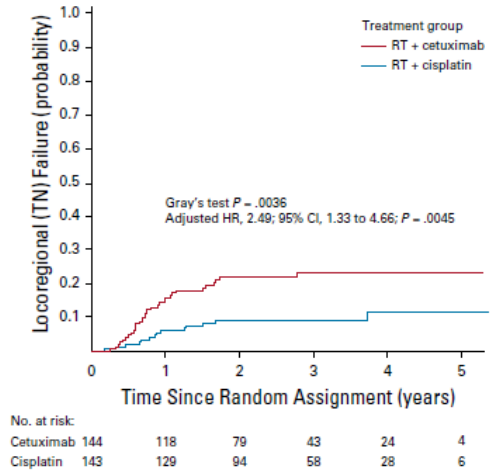


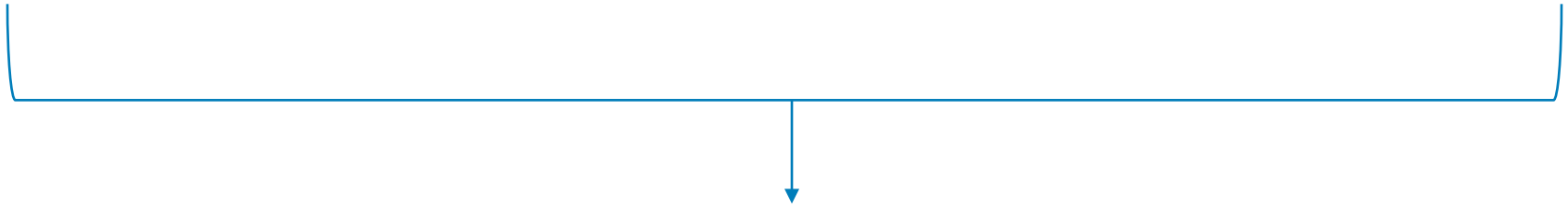
ARTSCAN III





De-Escalation - Cetuximab

RTOG 1016 | De-ESCALaTE | ARTSCAN III



Overall acute and late g3-4 toxicity rates not different

Cisplatin
- More n/v
- Hematologic
- Ototoxicity
- AKI

Cetuximab
- Cutaneous
- Other AEs still present

Gillison et al Lancet 2018, Mehanna et al Lancet 2018, Gabre-Medhin et al JCO 2021

De-Escalation - Cetuximab

RTOG 1016 | De-ESCALaTE | ARTSCAN III

Overall acute and late g3-4 toxicity rates not different

Cisplatin
- More n/v
- Hematologic
- Ototoxicity
- AKI

Cetuximab
- Cutaneous
- Other AEs still present

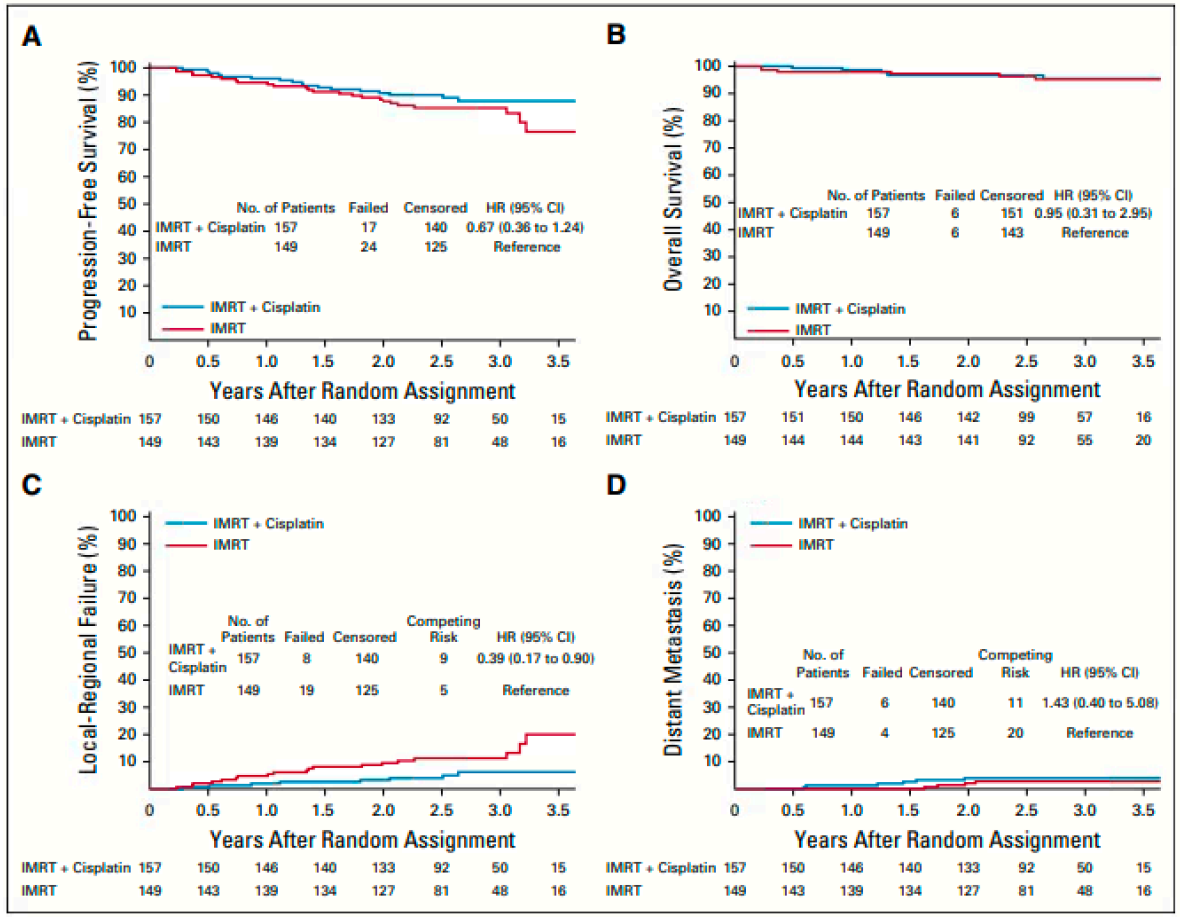
Late toxicities similar

De-Escalation – Dose Reduction

original reports

Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002)

Sue S. Yom, MD[1]; Pedro Torres-Saavedra, PhD[2]; Jimmy J. Caudell, MD[3]; John N. Waldron, MD[4]; Maura L. Gillison, MD[5]; Ping Xia, PhD[6]; Minh T. Truong, MD[7]; Christina Kong, MD[8]; Richard Jordan, PhD[1]; Rathan M. Subramaniam, MD[9]; Min Yao, MD[10]; Christine H. Chung, MD[3]; Jessica L. Geiger, MD[6]; Jason W. Chan, MD[1]; Brian O'Sullivan, MD[4]; Dukagjin M. Blakaj, MD[11]; Loren K. Mell, MD[12]; Wade L. Thorstad, MD[13]; Christopher U. Jones, MD[14]; Robyn N. Banerjee, MD[15]; Christopher Lominska, MD[16]; and Quynh-Thu Le, MD[17]



De-Escalation – Dose Reduction

- HN 005
  - Phase II/III trial
  - T1-2N1 or T3N0-1 p16+ oropharynx SCC

70 Gy + cisplatin

60 Gy + cisplatin

60 Gy + nivolumab

De-Escalation – Dose Reduction

- HN 005
  - Phase II/III trial
  - T1-2N1 or T3N0-1 p16+ oropharynx SCC

De-Escalation – Cisplatin Ineligible

- HN-004
- Multiple disease sites, p16+/p16-
  - ~45% p16+ oropharynx
  - SOC RT + cetuximab or durvalumab

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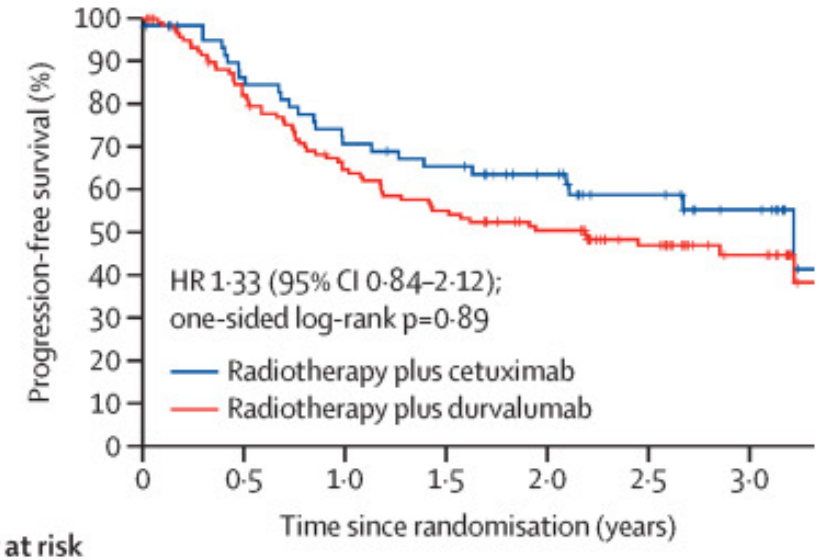
- HN-004
- Multiple disease sites, p16+/p16-
  - ~45% p16+ oropharynx
  - SOC RT + cetuximab or durvalumab
- No benefit with durvalumab over cetuximab
- Assessed as “inactive” in otherwise SOC therapy

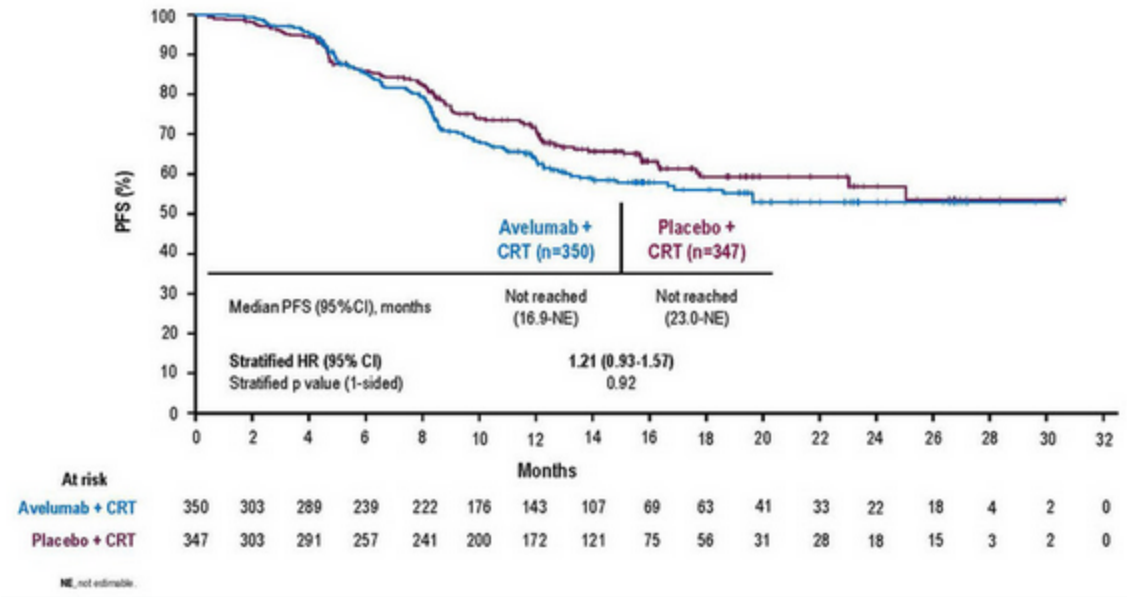
- *** best PFS in this group reported on any cetuximab trial



Number at risk (number censored)							
Radiotherapy plus cetuximab	63 (0)	50 (5)	41 (5)	37 (6)	29 (13)	19 (21)	11 (28)
Radiotherapy plus durvalumab	123 (0)	96 (6)	74 (8)	63 (8)	52 (14)	34 (29)	19 (43)

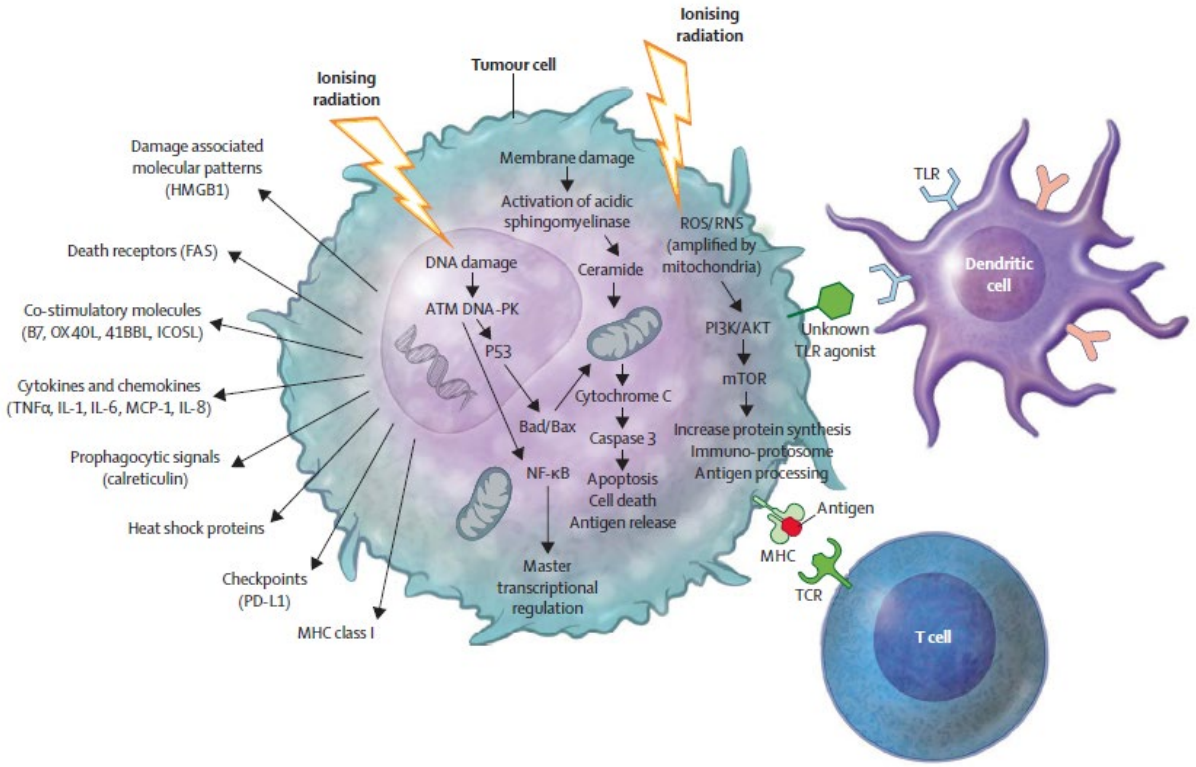
What about immunotherapy with SOC treatment?

- JAVELIN
  - chemoRT +/- avelumab
- No significant improvement with the addition of avelumab to chemoRT
- Grade ≥3 AEs more frequent with combined therapy

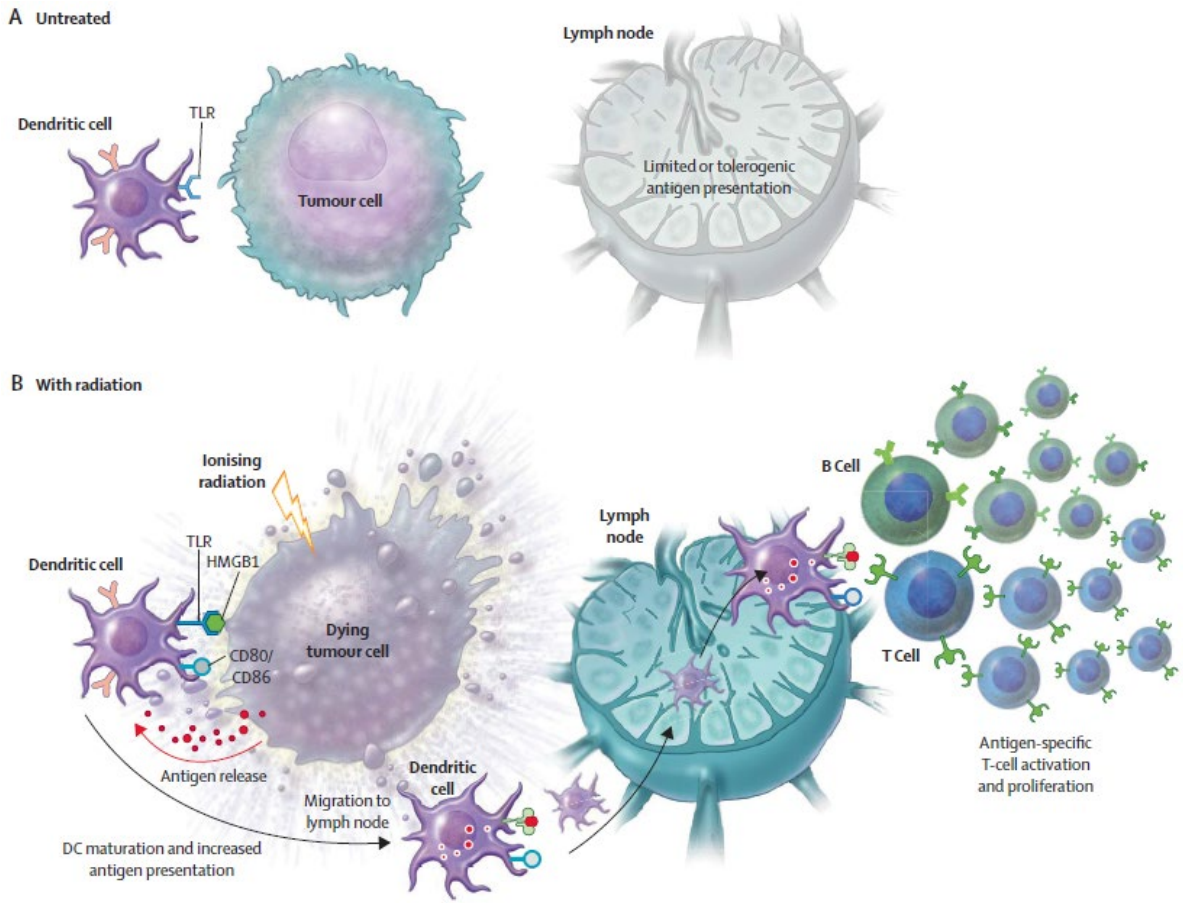


No improvement in PFS was observed with avelumab plus CRT followed by avelumab maintenance versus placebo plus CRT in patients with LA SCCHN.

Radiation & Immunotherapy

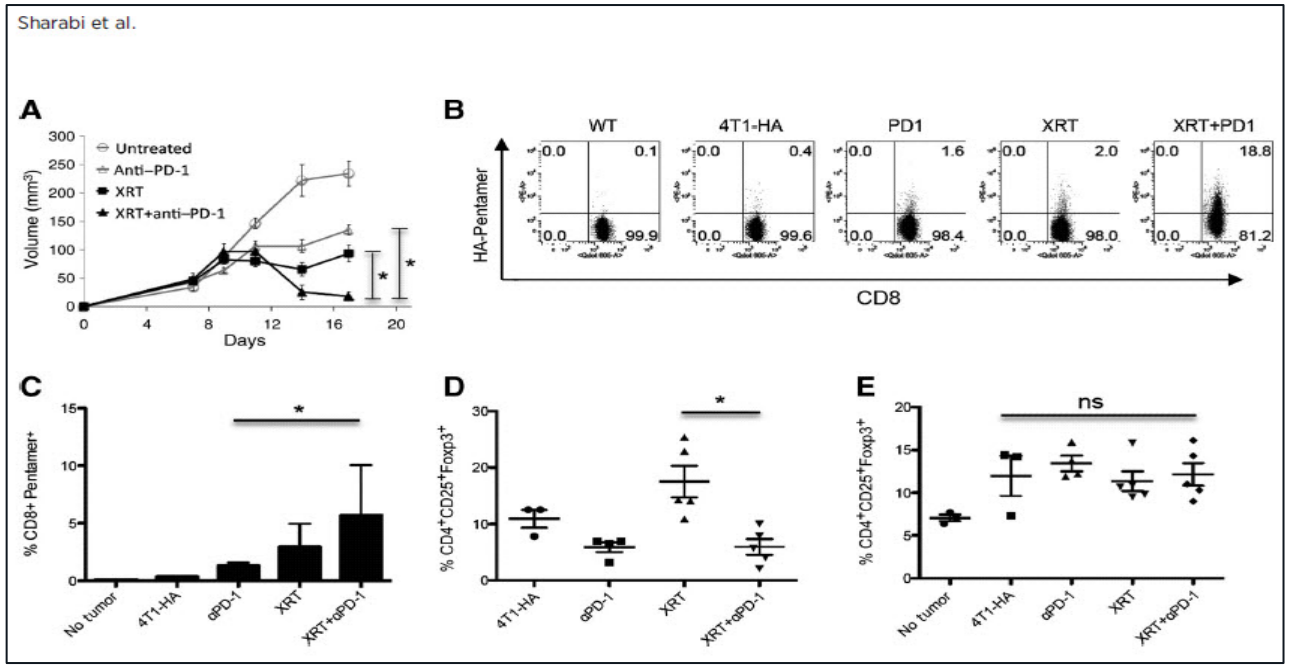


Radiation can induce modulation of immunophenotype and immunogenicity of tumor cells



Enhanced dendritic cell-mediated antigen presentation

Radiation & Immunotherapy

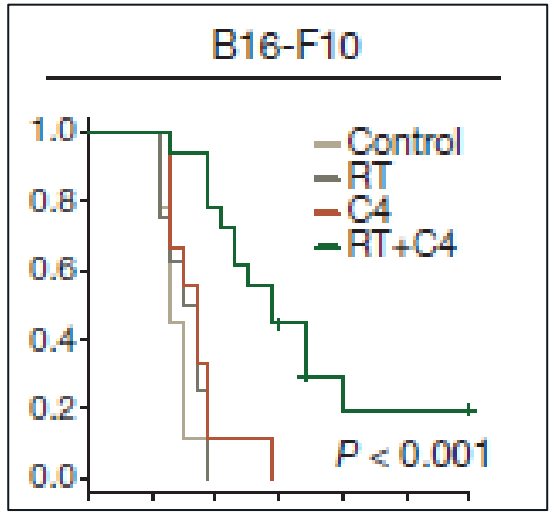


LETTER

doi:10.1038/nature14292

Radiation and dual checkpoint blockade activate non–redundant immune mechanisms in cancer

Christina Twyman–Saint Victor[1,2*], Andrew J. Rech[2*], Amit Maity[3,4], Ramesh Rengan[3,4†], Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4†], E. John Wherry[4,5,6§], Robert H. Vonderheide[1,2,4,6§] & Andy J. Minn[2,3,4,6§]



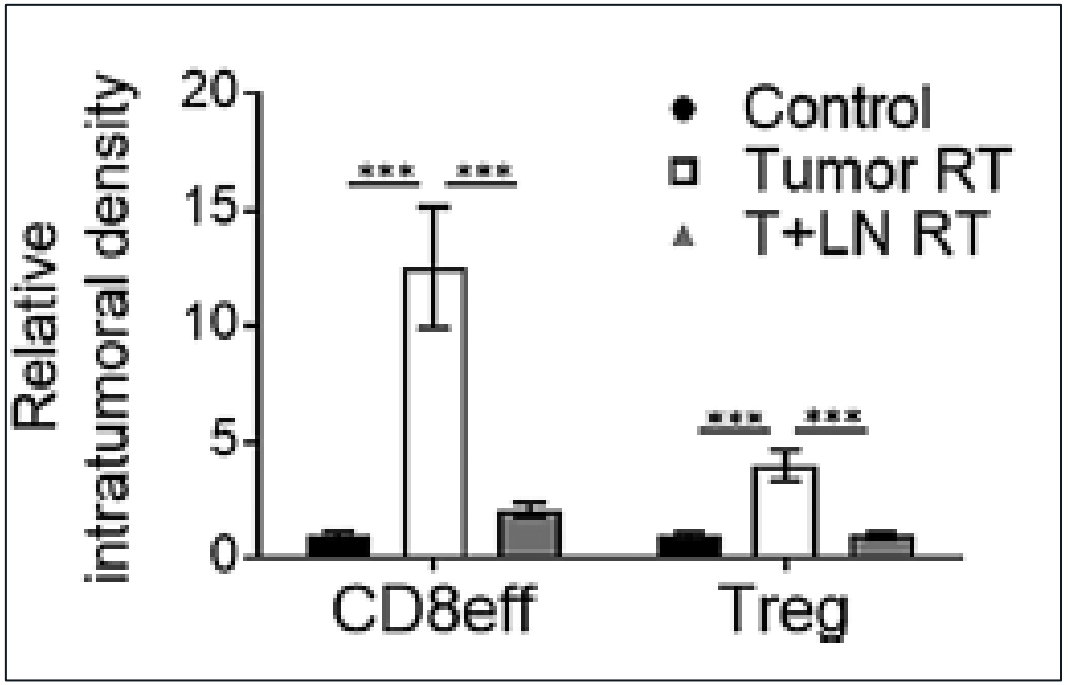
Elective Nodal Irradiation

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy

Ariel E. Marciscano[1], Ali Ghasemzadeh[2], Thomas R. Nirschl[2], Debebe Theodros[2], Christina M. Kochel[2], Brian J. Francica[2], Yuki Muroyama[2], Robert A. Anders[2,3], Andrew B. Sharabi[4], Esteban Velarde[1], Wendy Mao[2], Kunal R. Chaudhary[5], Matthew G. Chaimowitz[6], John Wong[1], Mark J. Selby[7], Kent B. Thudium[7], Alan J. Korman[7], David Ulmert[8], Daniel L.J. Thorek[2,9], Theodore L. DeWeese[1,2], and Charles G. Drake[2,6]

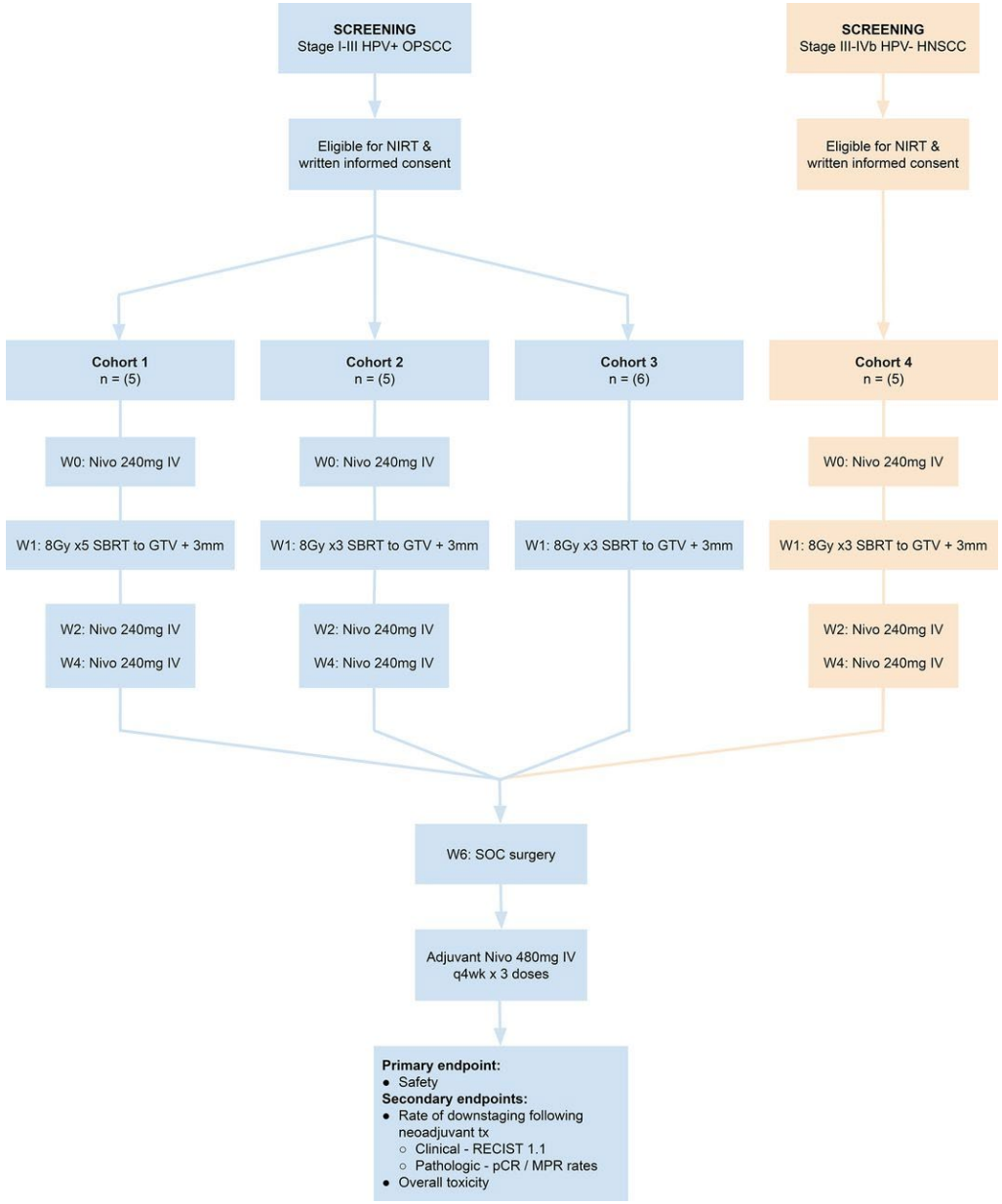


Neoadjuvant Immunoradiotherapy

- Neoadjuvant immunotherapy can result in meaningful pathologic responses and clinical down staging in multiple tumor types
  - Reponses are more limited in HNSCC
    - Melanoma mPR ~30%
    - HNSCC 7-14%

Neoadjuvant Immunoradiotherapy

- Neoadjuvant immunotherapy can result in meaningful pathologic responses and clinical down staging in multiple tumor types
  - Reponses are more limited in HNSCC
    - Melanoma mPR ~30%
    - HNSCC 7-14%
- Can neoadjuvant PD-1 blockade and SBRT improve outcomes?
  - Without delaying resection
  - Goal of mPR > 33%



Neoadjuvant Immunoradiotherapy

- 63 year old male
- R tonsil p16+ SCC, cT2N1M0
- Treated to primary & involved LNs
- Significant PR on post-treatment imaging

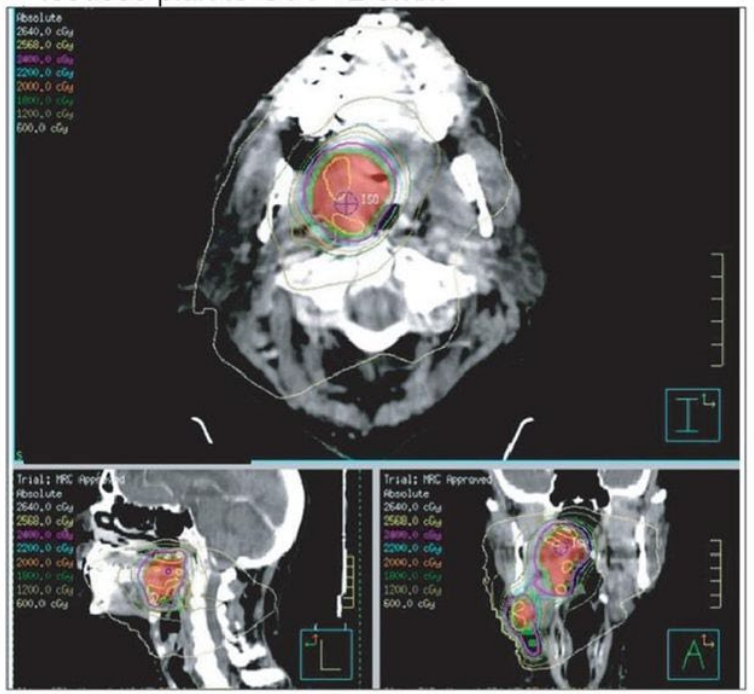
Pre-treatment

A 1° palatine tonsil

B Metastatic lymphadenopathy

Radiation treatment

C Isodose plan to GTV +2-3mm



Post-treatment

D 1° palatine tonsil

E Level II lymph nodes

Neoadjuvant Immunoradiotherapy

- 63 year old male
- R tonsil p16+ SCC, cT2N1M0
- Treated to primary & involved LNs
- Significant PR on post-treatment imaging
- At resection:
  - pCR in primary
  - mPR in LN (<10% viable cells)

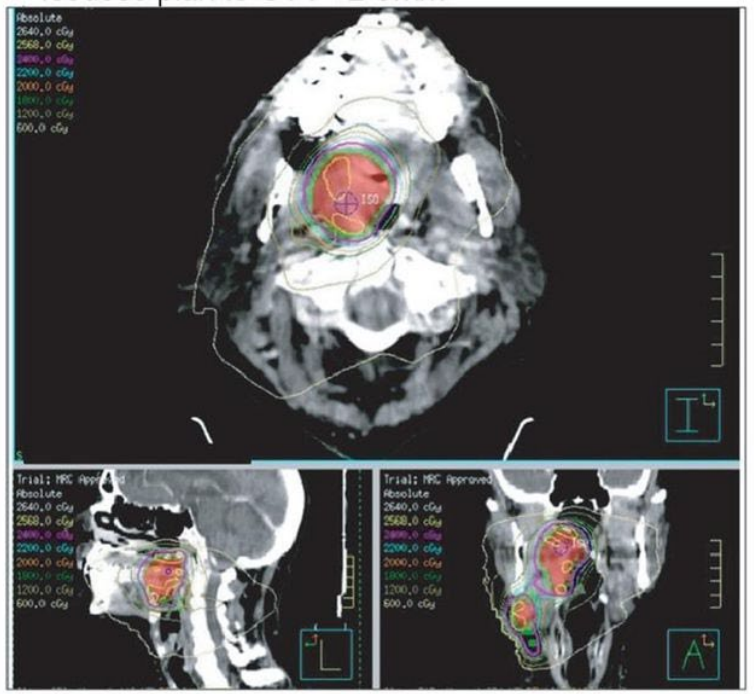
Pre-treatment

A 1° palatine tonsil

B Metastatic lymphadenopathy

Radiation treatment

C Isodose plan to GTV +2-3mm



Post-treatment

D 1° palatine tonsil

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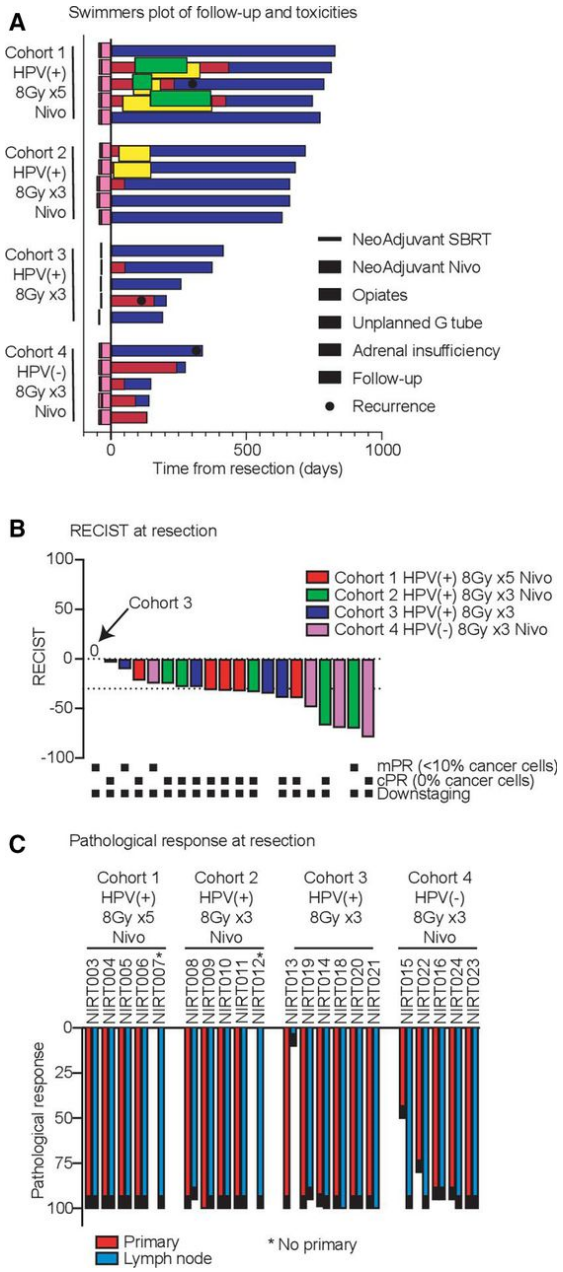
Neoadjuvant Immunoradiotherapy

- Summary
  - Pathologic down-staging in 90% of patients
    - mPR 86%
    - pCR 67%
  - HPV+
    - mPR 100%
    - pCR 90%
  - Only 1/21 patients required adjuvant therapy
  - SBRT alone
    - Lower mPR/pCR rates
  - Higher toxicity in 8 Gy x 5 arm



NIRT HPV+

A Phase II, Single Arm, Open Label, Multi-center Trial of Neoadjuvant Radiation and Evorpacept in Combination with Pembrolizumab in Patients with Previously Untreated Locally Advanced, Resectable, HPV Mediated Oropharynx Cancer

HCRN Protocol#: HN23-623
National Clinical Trial (NCT) Identified Number: 05787639
IND 166324

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HCRN Protocol#: HN23-623
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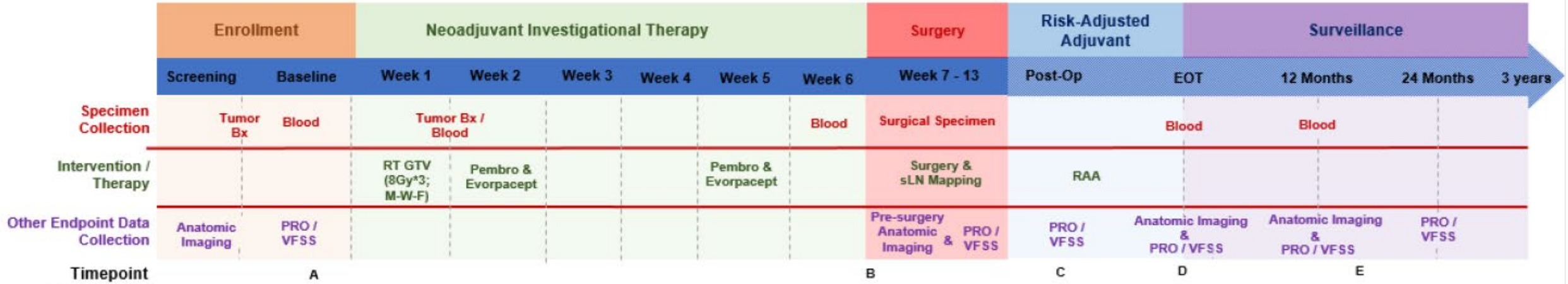
IND 166324

Study Population: Stage I HPV mediated oropharynx cancer amenable to surgical resection, including AJCC VIII T1-2N1M0 HPVOPC and excluding patients with solitary lymph nodes less than 3 cm.
Phase: 2
Description of Sites/Facilities Enrolling Participants: Multi-center (3 sites) - University of California, San Diego, Providence Health & Services, and Oregon Health Sciences University
Description of Study Intervention: Stereotactic radiation therapy (8Gy X 3 fractions) will be delivered to gross tumor volume +3mm on a Monday-Wednesday-Friday dose schedule on week 1, followed by Pembrolizumab 200 milligrams and Evorpacept 45 mg/kg administered by intravenous infusion every 3 weeks on Day 1 of each 21-day cycle x 2 cycles.
Study Duration: 5 years

By minimizing the radiation field and surgical resection, we hypothesize that the study therapy will be safe and well tolerated, quality of life will be improved, while supporting or enhancing locoregional control.

NIRT HPV+



Timeline for Individually Enrolled Patients: Biopsy (Bx); Pembrolizumab (Pembro); Gross Tumor Volume (GTV); Sentinal Lymph Node (sLN); Patient-Reported Outcome (PRO); Videofluoroscopic Swallow Study (VFSS); Risk-Adjusted Adjuvant (RAA), Neoadjuvant Immunoradiotherapy (NIRT)

Timepoint Designation		Estimated Time in Study	Specimen & Data Collection
A	Baseline	Week 1	Tumor Biopsy/Blood, Imaging, PRO/VFSS
B	Post-NIRT	Week 6-13	Surgical Specimen/Blood, sLN Mapping, Imaging, PRO/VFSS
C	Post-Surgery	Week 8	PRO/VFSS
D	EOT	Week 20	Blood, Imaging, PRO/VFSS
E	Long term follow-up	3 months - 3 years post surgery	Blood, Imaging, PRO/VFSS

Case

- 56 year old male
- Progressive L neck mass
- No visible primary

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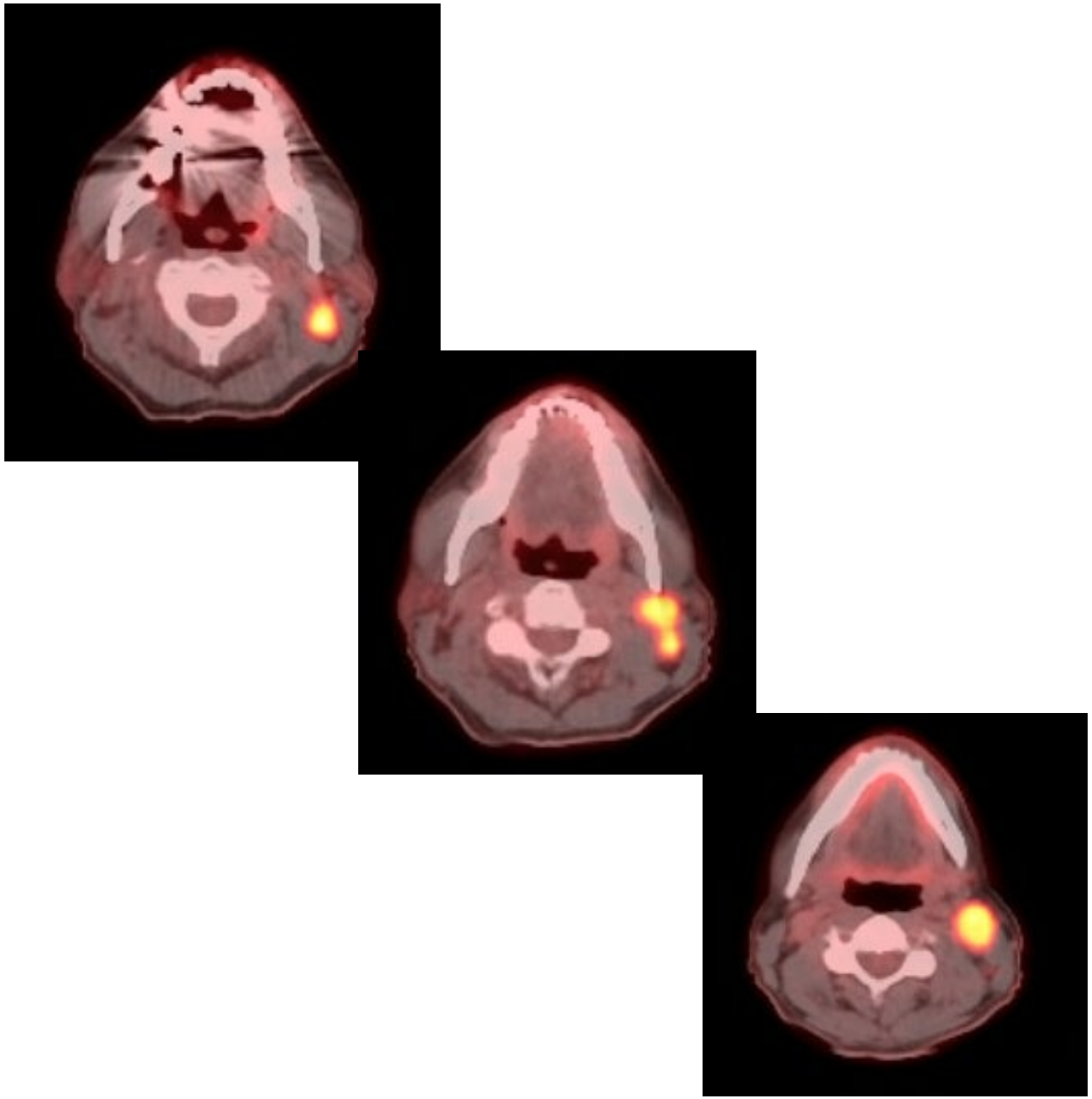
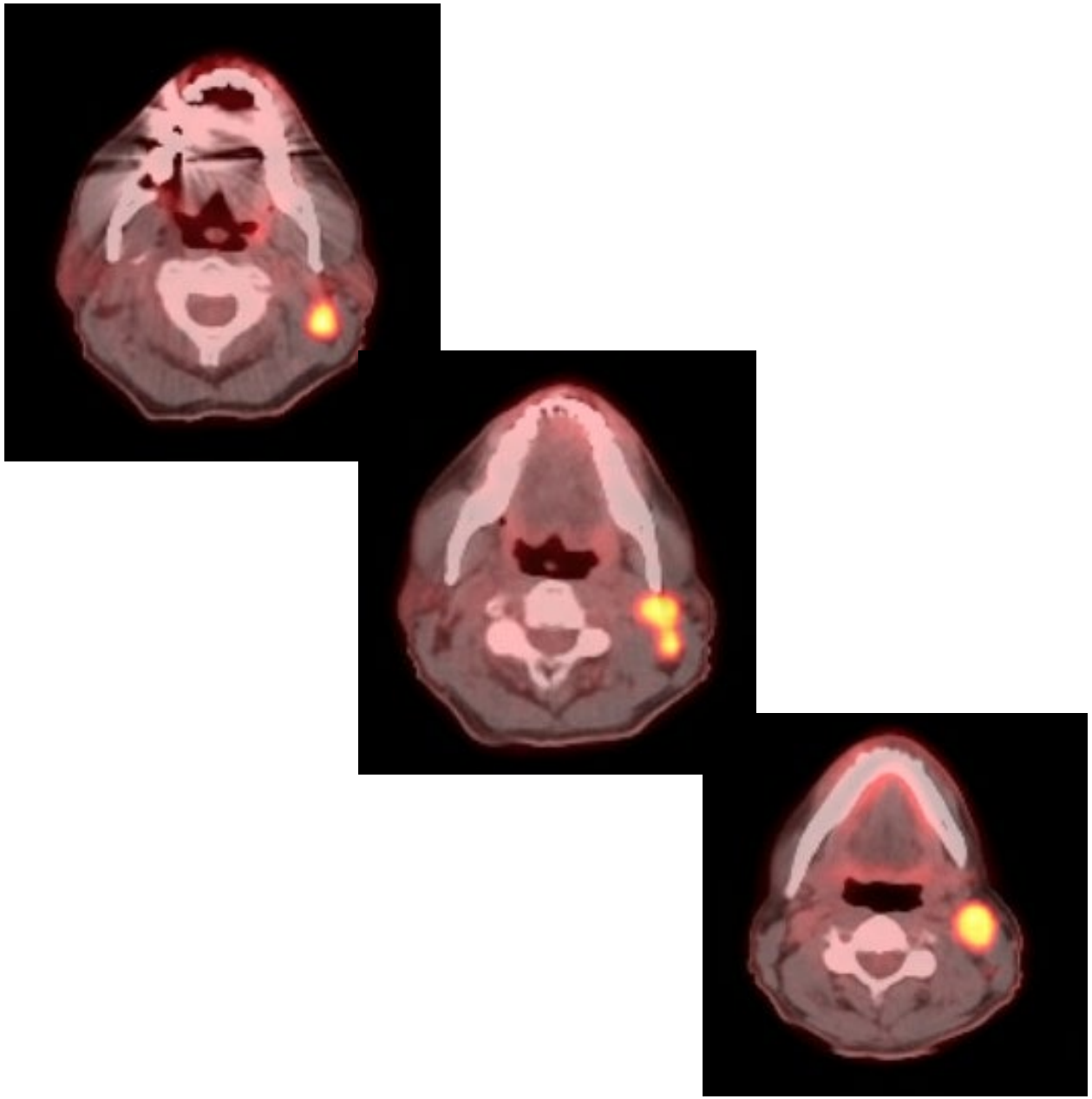


Case

- 56 year old male
- Progressive L neck mass
- No visible primary
- Biopsy: SCC, p16+
- L lingual tonsil –
- L palatine tonsil +



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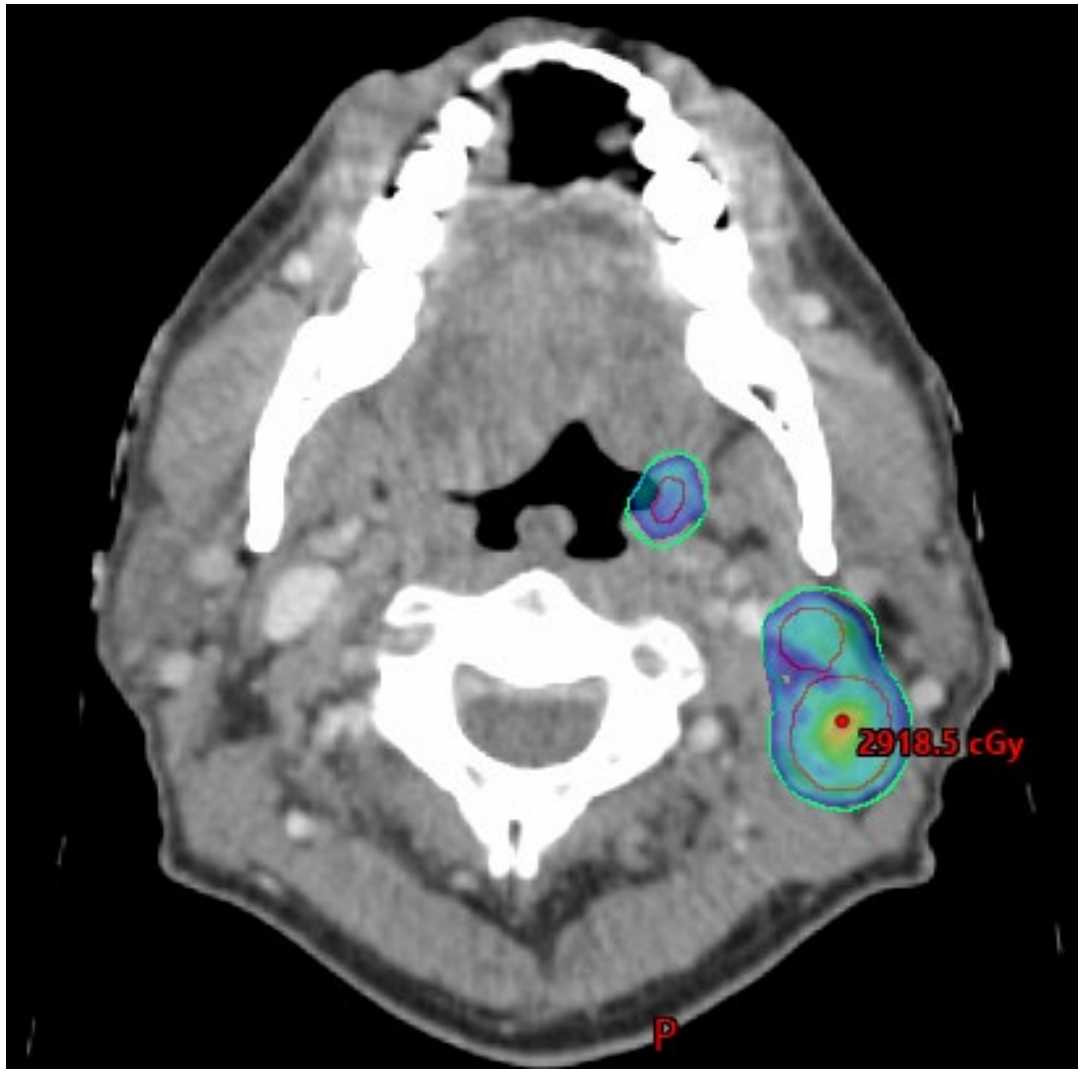

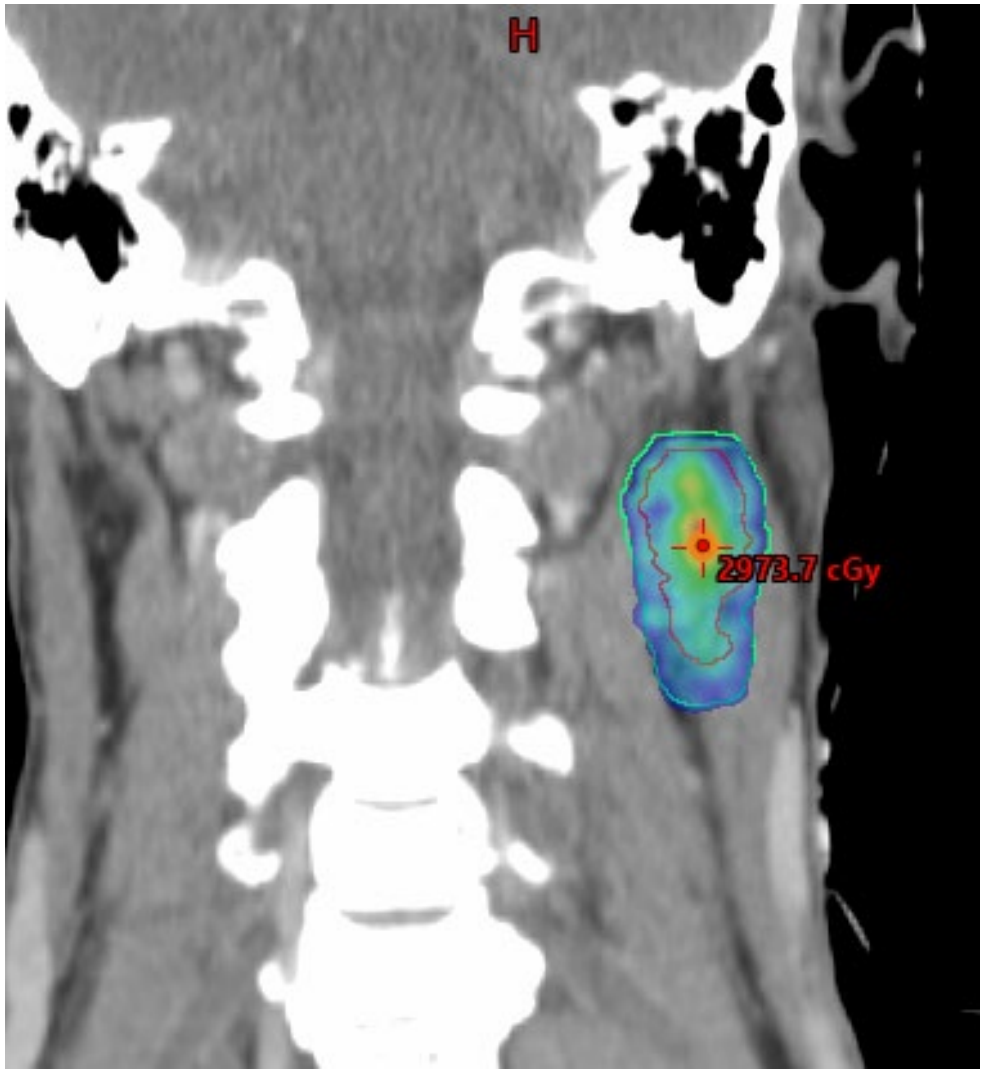

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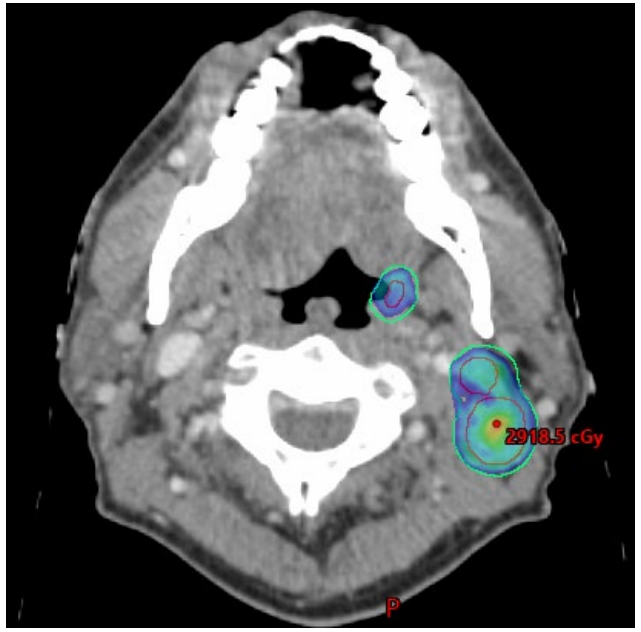
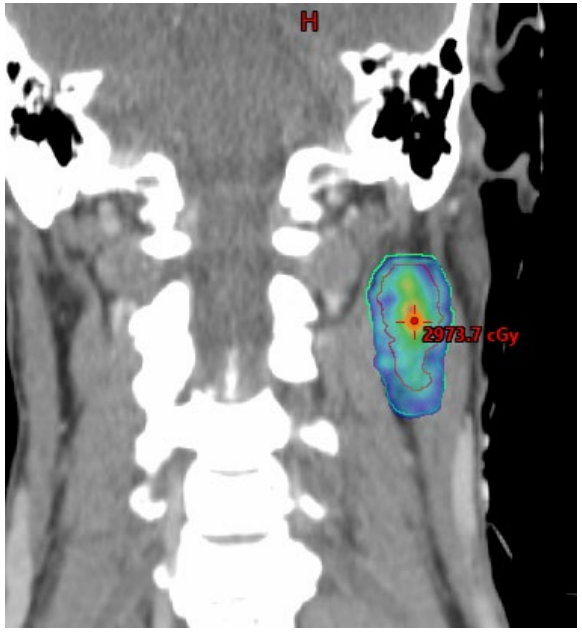
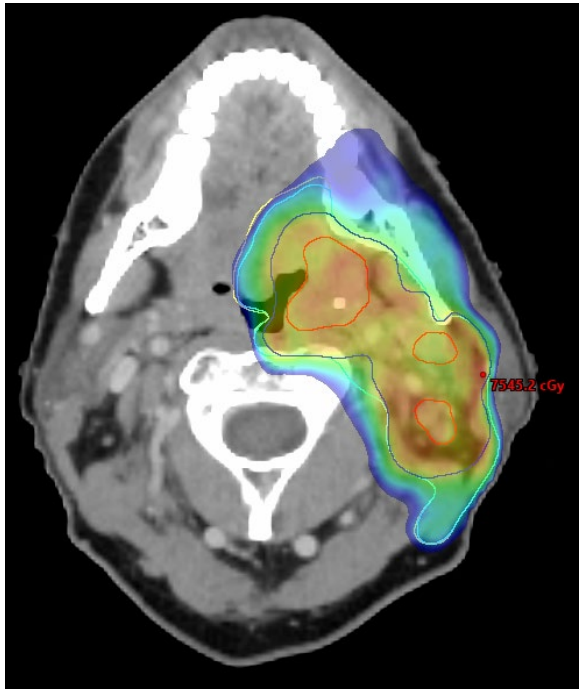
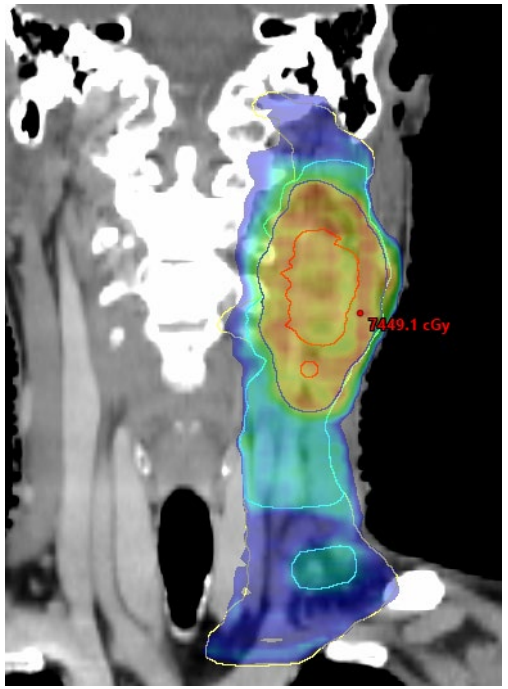


SBRT





IMRT



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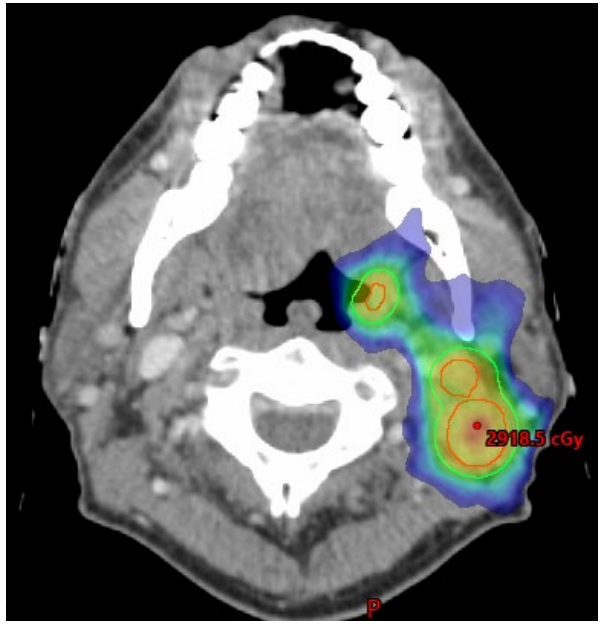

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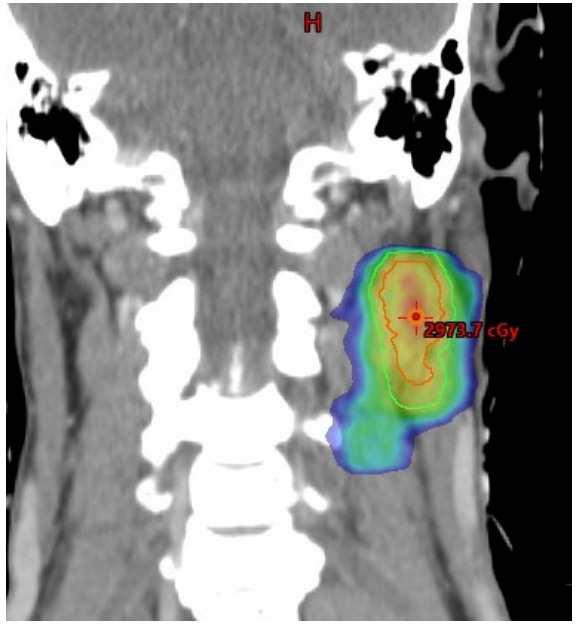
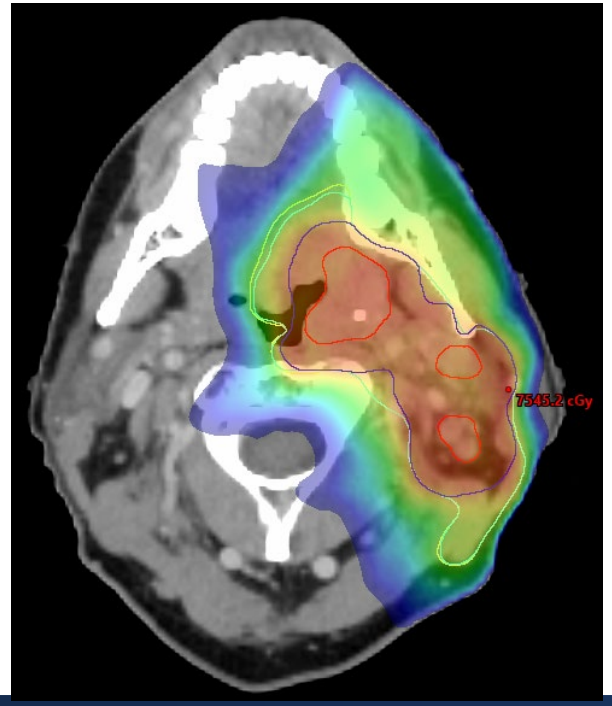
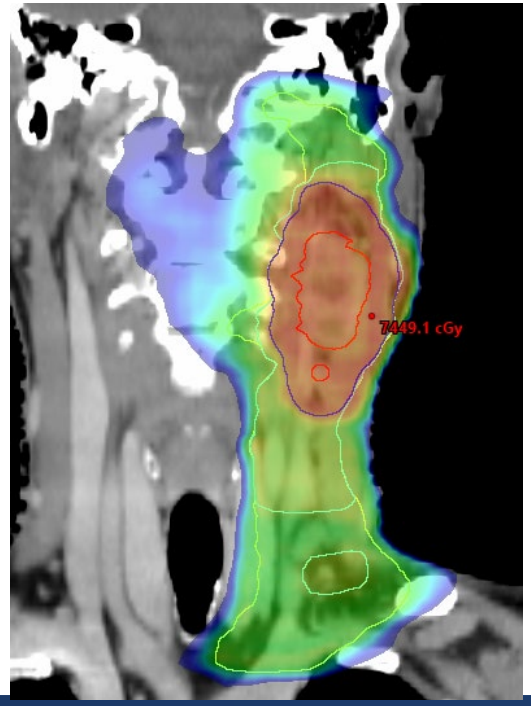


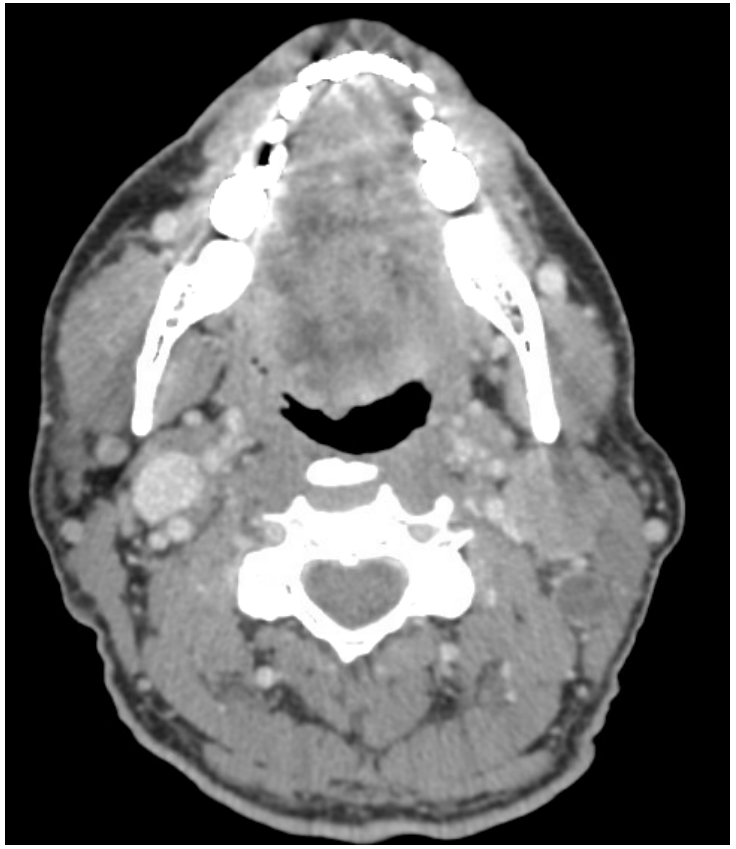


IMRT

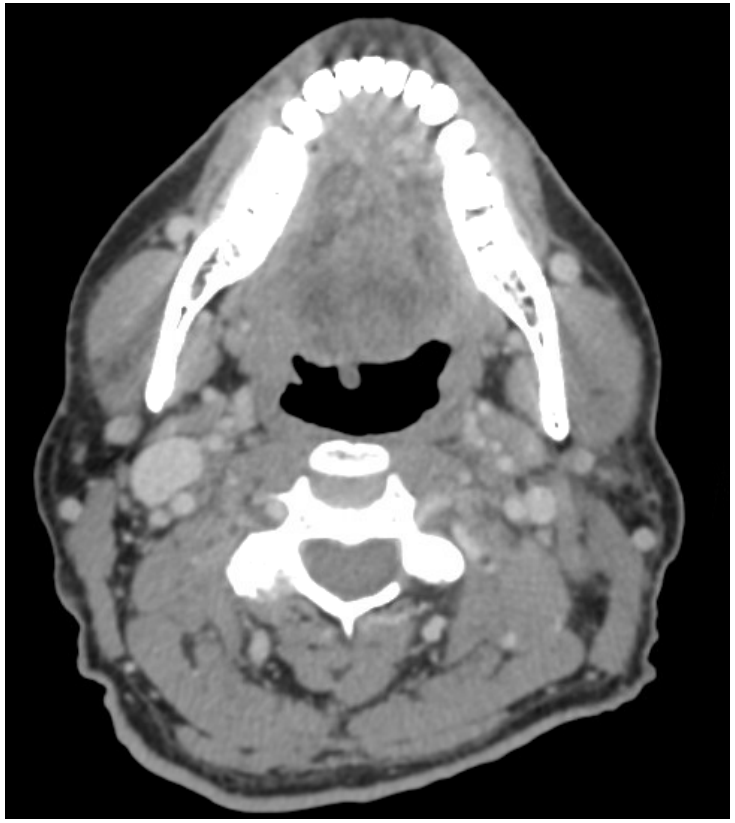


Case

- Completed SBRT
  - Mild mucositis, xerostomia, dysgeusia
- Systemic therapy
  - No issues



Pre-treatment



Post-SBRT/IO

Case

- Completed SBRT
  - Mild mucositis, xerostomia, dysgeusia
- Systemic therapy
  - No issues
- Resection
  - No residual carcinoma in tonsil
  - 0/37 LN, 3 with treatment effect
  - pCR in primary and LNs

Thank you!