Treatment De-Escalation for HPV+ Oropharynx Cancer (OPX)

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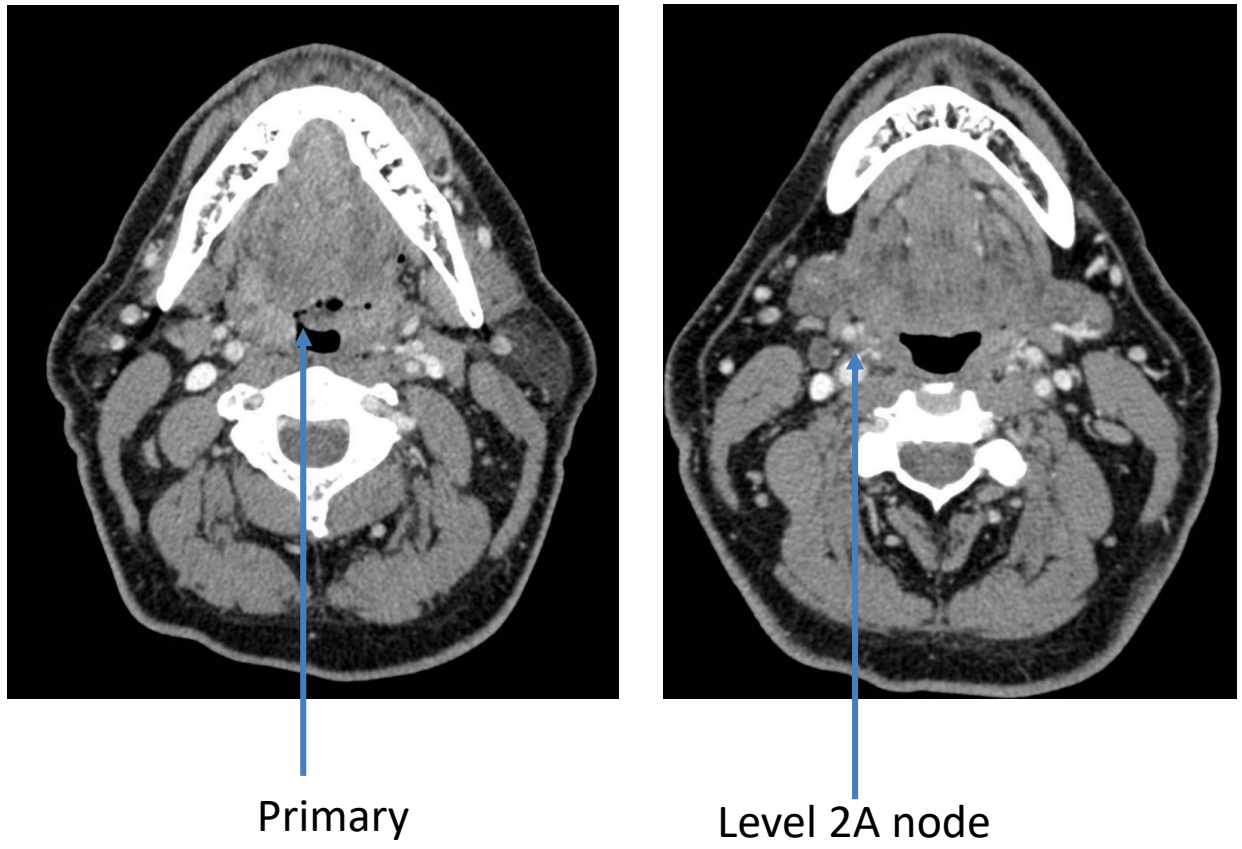
Case

- 58 yo male with dysphagia who noticed a right tonsillar mass
- Referred to ENT
  - Right tonsillar mass confined to the tonsillar fossa
  - Biopsy of mass = +p16 squamous cell carcinoma
- CT Larynx with contrast
  - 2.5 x 1.3 cm right tonsillar soft tissue mass
  - Subcentimeter hypodense/necrotic lymph node level 2A concerning for metastasis
- PET-CT positive tonsil and right 2a node, negative for metastatic disease

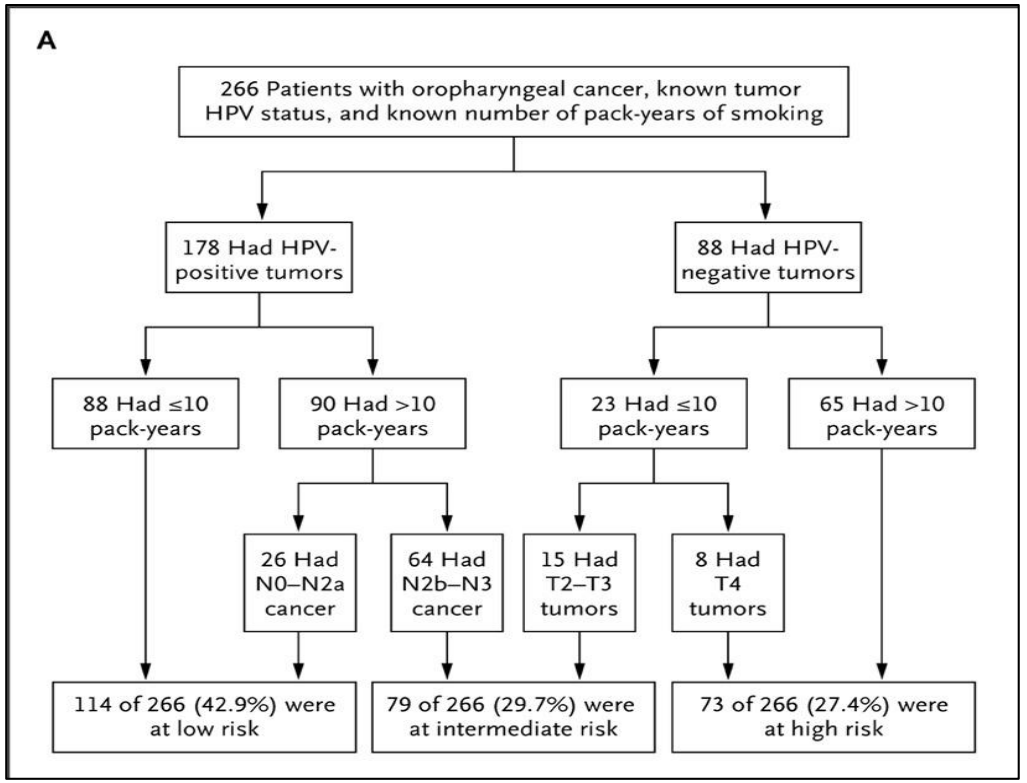


Case

- Standard treatment options for locoregionally advanced OPX include
  - Surgery + adjuvant RT (60 Gy) +/- concurrent cisplatin
  - Chemoradiation (70 Gy + cisplatin)
- For more details on work-up and standard of care treatment, refer to Oropharynx ARRO Case by Drs. Thaker, Haque, and Garden
- Our patient enrolled in ECOG 3311:
  - Transoral Surgery (TORS) for HPV+ OPX followed by risk-stratified adjuvant therapy (more to follow)
- Several methods to treatment de-escalation have been proposed since the release of the sub-analysis of OPX patients from RTOG 0129 (next slide)

Rationale for HPV+ OPX Treatment De-Escalation

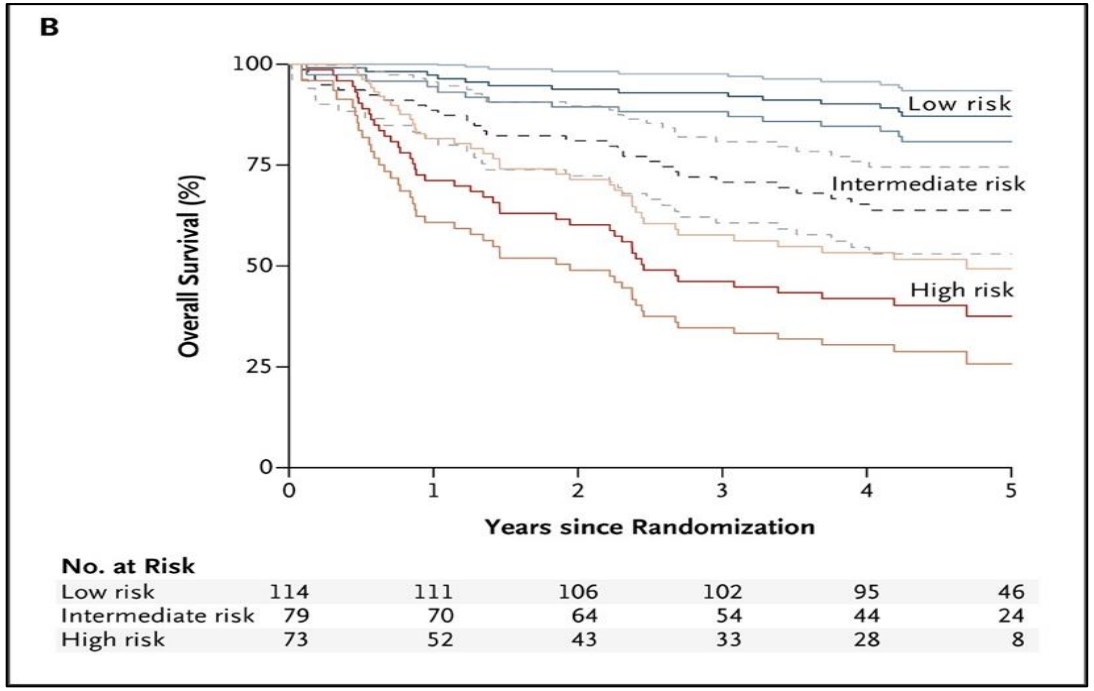
- Analysis of OPX patients on RTOG 0129 noted differences in outcomes comparing patients with HPV+ vs HPV- tumors
- Low, intermediate, and high risk stratification created based on variables shown to determine overall survival on recursive-partitioning index analysis (figure on the right)
- All HPV+ OPX cancers are either low or intermediate risk



Ang et al NEJM 2010

Rationale for HPV+ OPX Treatment De-Escalation

- OS at 3 years:
  - Low-risk: 93%
  - Intermediate-risk: 70.8%
  - High risk: 46.2%
- HPV+ OPX patients demonstrated improved outcomes with radiation compared to HPV- population
- Hypothesis: De-escalating therapy to reduce side effects could be achieved without compromising control outcomes in HPV+ OPX
- Many methods to de-escalate treatment have been proposed



Ang et al NEJM 2010

Proposed Ways to De-Escalate Treatment

- 1) Induction chemotherapy (IC) and response dependent RT de-escalation
  - E1308
  - OPTIMA
  - UCLA/UC Davis
- 2) Concurrent chemoRT with reduced RT dose
- 3) Change Cisplatin to Cetuximab
- 4) Surgery + Adjuvant RT+/- Chemo

E1308: Phase II trial

- Pts: Stage III-IV (T1-3N0-N2b)
- Intervention
  - IC
    - Cisplatin 75 mg/m^2 day 1, paclitaxel 90 mg/m^2 days 1, 8 and 15, cetuximab 400 mg/m^2 day 1 followed by weekly 250 mg/m^2
    - Repeat every 21 days x 3
  - Assess clinical response within 2 weeks of completing induction chemotherapy
    - Complete response (CR) = no residual disease
    - Partial response (PR)= 30% or more reduction in the sum of the longest diameter
    - Progressivedisease (PD) = 20% or more increase in the sum of the longest diameter
    - Stable disease (SD) = between PR and PD

Marur et al JCO 2016

E1308: Phase II trial

- Radiation dose stratification to primary site and nodes determined by response
  - If cCR: 54 Gy/27 fx at primary site
  - If not cCR: 69.3 Gy/33 fx at primary
  - Uninvolved cervical nodes treated to 51.3 Gy in 27 fx
  - 1 cm margin was required for all involved lymph nodes
  - Both arms continued cetuximab until the end of radiotherapy
- Endpoints
  - Progression free survival (PFS) and OS @ 2-years, clinical and radiologic responses
  - Common Terminology Criteria for Adverse Events vs 4.0
  - Vanderbilt H&N Survey: 50-item survey

E1308

- Characteristics
  - 80 analysis-eligible patients with T1-3 (89%), N0-2b (69%), non-current smokers (84%)
  - 96.2% completed IC
    - 56 pts (70%) with primary CR
      - 51/56 completed 54 Gy (other 5 underwent 69.3 Gy, protocol deviation)
    - 8 of 18 pts with less than CR received only 54 Gy (protocol deviation)
    - 46 pts (58%) with nodal CR

Marur et al JCO 2016

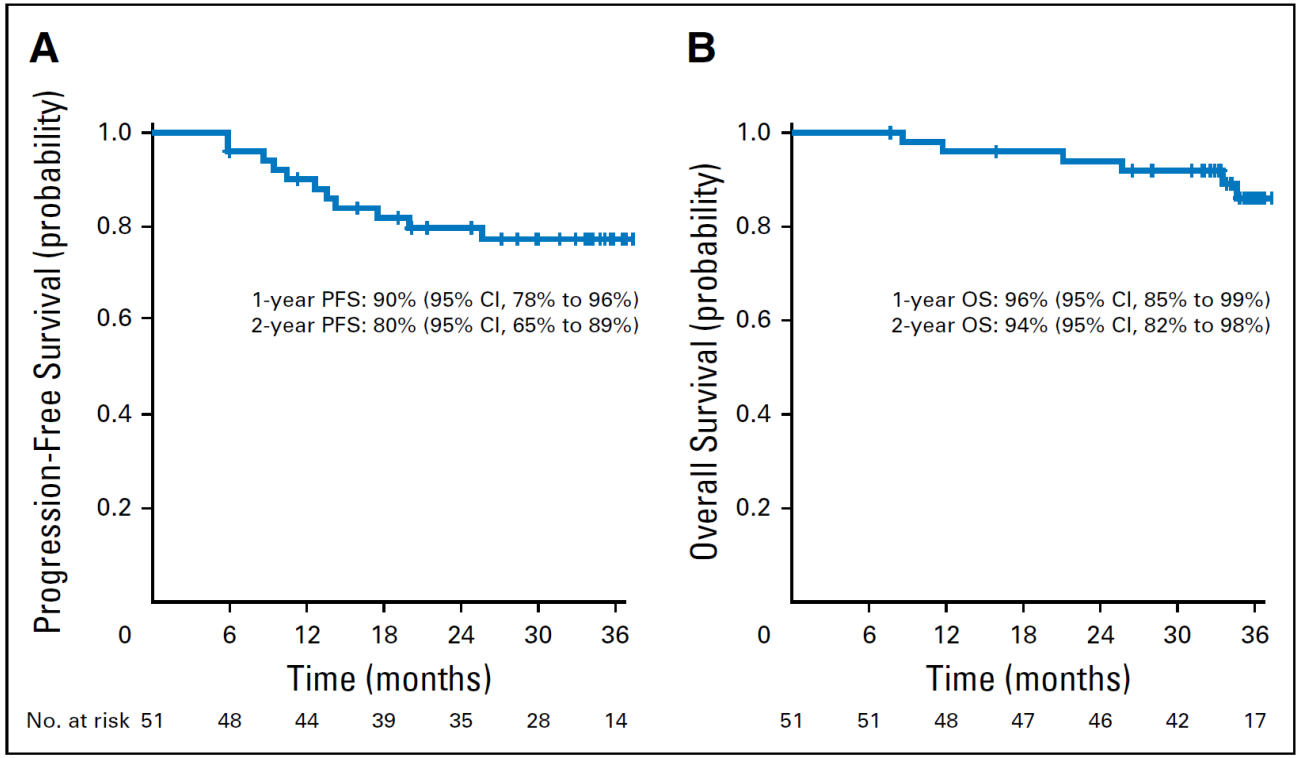
E1308

- Toxicity
  - CTCAE Grade 3/4 toxicity during
    - IC: acneiform rash (28%), lymphopenia (6%), neutropenia (12%)
    - 54 Gy: mucositis (30%), dysphagia (15%), acneiform rash (12%), RT dermatitis (7%)
    - 69.3 Gy: mucositis (47%), dysphagia (29%) acneiform rash (24%), RT dermatitis (12%)
  - Vanderbilt H&N Score @ 12 months
    - Less difficulty swallowing solids in 54 Gy arm (40% vs 89%, p = 0.011)
    - Less impaired nutrition (10% vs 44%. P = 0.025)

Marur et al JCO 2016

E1308

- Patients treated to 54 Gy to the primary site
  - 2-yr PFS: 80%
  - 2-yrs OS: 94%
  - Subgroup analysis
    - T1-3, N1-2b disease < 10 pack-year history (PYH) of smoking: 2-yr PFS and OFS 96%
  - Pattern failures
    - 4 at primary site
    - 2 at nodal site
    - 2 at nodal and primary site
    - 1 distant failure



Marur et al JCO 2016

E1308

- With short follow-up, dose de-escalation appears to be safe especially in low-volume, low-risk patients (T1-3, N1-2b disease < 10 PYH)
  - Less dysphagia, mucositis, and dermatitis compared to traditional 69.3
- Interestingly: Small number of patients with < CR at primary site (n = 11) also received 54 Gy (off protocol) had similar disease control to those with cCR

Marur et al JCO 2016

OPTIMA Trial: Phase II

- Stratified patients:
  - Low risk: T1-3, N0-2b (except nodal disease ≥ 6 cm), ≤ 10 PYH
  - High risk: T4, N2c and bulky N2b, > 10 PYH
- Treatment:
  - 3 cycles of carboplatin (AUC = 1) and nab-paclitaxel (100 mg/m^2 days 1, 8 , and 15) – every 21 days
  - RT (VMAT or IMRT) dose stratified by primary and nodal response using RECIST v1.1 criteria
    - Low risk patients with ≥ 50% response : 50 Gy RT alone in 25 fractions
    - Low risk patients with 30-50% or high-risk with ≥ 50% response: 45 Gy (1.5 Gy BID) + TFHX (below)
    - Low risk < 30% response, high risk < 50% response: 75 Gy (1.5 Gy BID) + TFHX x 5 (14-day cycles)
  - TFHX: 5-FU 600 mg/m^2 infusion days 0-5, paclitaxel 100 mg/m^2 day 1, hydroxyurea 500 mg PO BID (11 doses /cycle)

Seiwert et al Annals of Oncology 2018

OPTIMA

- Treatment ctd
  - Unique RT volumes
    - PTV1 = pre-induction chemotherapy gross disease + 1.5 cm expansion
    - PTV2 = next echelon of uninvolved at-risk lymph nodes
- Patients underwent surgical evaluation 4-8 weeks after radiation
- Endpoints:
  - Toxicity scored with CTCAE vs 4.0
  - 2-yr PFS, locoregional control, distant control, OS

OPTIMA

- Characteristics
  - 62 patients
    - Low risk: 82% T1-2, 89% N2b
    - High risk: 56% T1-2, 53% N2b
  - More than 50% with any tumor size reduction
    - Low risk (all completed): 71%
    - High risk (33/34 completed): 71%
  - 82% of patients received some form of de-escalated treatment

Seiwert et al Annals of Oncology 2018

OPTIMA

	Patients with pCR
50 Gy arm	18/19
45 Gy + TFHX	25/27 (6/6 low risk; 19/22 high risk)
75 Gy + TFHX	4/5

2-yr	**Low Risk**	**High Risk**
PFS	95%	94%
OS	100%	97%
LC	100%	97%
DC	100%	100%

No statistical differences between two groups

Seiwert et al Annals of Oncology 2018

OPTIMA

	RT50	CRT45	CRT75
Acute G3+ mucositis	30%	63%	90%
Acute G3+ dermatitis	0%	20%	45%
% requiring a PEG tube	0%	31%	82%

De-escalation arms with less mucositis, dermatitis, and needing a PEG tube (all statistically significant)

Conclusion: Radiation alone after induction chemotherapy could be an option for low-risk patients with complete response after IC. Radiation dose reduction even with chemotherapy reduces toxicity

Seiwert et al Annals of Oncology 2018

UCLA/UC Davis study: Phase II

- Pts: Stage III/IV (T1-4, N0-3)
- Treatment
  - IC: 175 mg/m^2 paclitaxel and carboplatin AUC 6 for 2 cycles 21 days
  - IMRT/VMAT dose stratified by response on CT using RECIST:
    - If CR or PR
      - 54 Gy in 27 fx with 30 mg/m^2 paclitaxel
      - 43 Gy to uninvolved areas
    - If SD*
      - 60 Gy in 30 fx with 30 mg/m^2 paclitaxel
      - 48 Gy to uninvolved areas
- Endpoints: 2-yr PFS, OS, toxicity assessed with CTCAE (early = within 90 days, late)

*patients with PD required surgical salvage

Chen et al Lancet Oncol 2017

UCLA/UC Davis study

- Characteristics
  - 44 analyzable patients with T1-2 (77%), N2 (83%)
  - All but 1 completed IC (allergic reaction)
  - Response after IC at all sites
    - 54% with PR or CR received 54 Gy
  - Median f/u 30 months

Chen et al Lancet Oncol 2017

UCLA/UC Davis study

- CTCAE Grade 3 events during (two most common)
  - IC: leukopenia (39%), Neutropenia (11%)
  - ChemoRT: dysphagia (9%), mucositis (9%)
    - No differences in grade 3+ muco-esophageal toxicity between 54 vs 60 Gy @ 2 years ~ 15%
- 2-yr PFS: 92%
  - 1 patient with distant failure, 3 with locoregional failure
- 2-yr OS: 95%
- Conclusion: RT reduction for higher risk (T3-4, bulky T2b, > 10 year PYH) HPV+ OPX produces high rates of control at 2 years but differences in toxicity benefit of 54 Gy is unclear

Chen et al Lancet Oncol 2017

Proposed Ways to De-Escalate Treatment

- 1) Induction chemotherapy (IC) and response dependent RT de-escalation
- 2) Reduce RT Dose
  - UNC/Florida
- 3) Change Cisplatin to Cetuximab
- 4) Surgery + Adjuvant RT+/- Chemo

UNC/Florida Phase II

- Pts: T0-T3, N1-2 < 10 PYH or > 10 PYH with 5 years cessation
- Intervention
  - RT to 60 Gy with cisplatin (above)
    - Subclinical disease treated to 54 Gy
  - Chemo
    - Cisplatin (30 mg/m2) weekly (cetuximab, carboplatin, or carboplatin/paclitaxel not allowed)
  - Surgery
    - If CR on CT at the primary, direct visualization and biopsies performed. If PR, then minimal surgery (i.e. TORS)
    - Patients with N+ disease underwent removal of initially involved nodes only (limited dissection)

Chera et al Cancer 2018

UNC/Florida

- Endpoints
  - pCR (primary), LC, regional control, LRC, DMFS, OS
  - Toxicity including CTCAE, patient reported (PRO)-CTCAE and EORTC-Quality of Life Questionnaire (QLQ)

UNC/Florida

- Characteristics
  - 45 patients with T1-2 (80%), N+ (91%) disease
  - 70% completed all six doses of cisplatin
  - Median f/u 36 months
    - 3-yr LC, RC, LRC, CSS and DMFS: all 100%
    - 3-yr OS: 95% (1 stroke, 1 GBM)
    - pCR at primary: 98% (per discussion)
    - pCR at nodes: 84% (per discussion)

Chera et al Cancer 2018

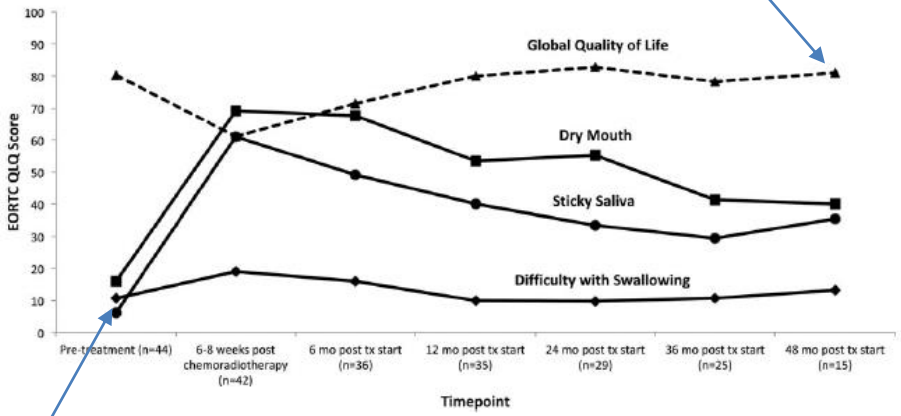
UNC/Florida Phase II

- CTCAE Acute Grade 3+ Toxicity
  - 39% dysphagia, 35% mucositis, 2% xerostomia
  - Chemo related: 11% hematologic, 18% nausea, 5% vomiting
- PRO-CTCAE Grade 3+
  - 75% xerostomia, 55% dysphagia, 45% mucositis
  - Increased dry mouth and xerostomia compared to baseline

EORTC-QLQ (below)

- Improved quality of life but residual dry mouth and sticky saliva
- No major changes in swallowing

Higher = improved quality of life



Lower the number means improved symptoms

Chera et al Cancer 2018

UNC/Florida

- De-escalated chemoRT for favorable risk HPV+ OPSCC is feasible
  - Both RT and chemo de-escalated
- Limitations
  - Unclear how much “non-definitive” neck dissection affects control rates
  - No comparison for toxicity data

Chera et al Cancer 2018

Proposed Ways to De-Escalate Treatment

- 1) Add Induction chemotherapy and de-escalate well for responding patients
- 2) Reduce RT Dose
- 3) Change Cisplatin to Cetuximab
  - De-ESCALaTE
  - RTOG 1016
- 4) Surgery + Adjuvant RT+/- Chemo

De-ESCALaTE trial: Phase III

- Pts: T3N0-T4N0, T1N1-T4N3, non-smokers or less than 10 PYH
- Intervention: RT in both 70 Gy in 35 fx
  - Arm 1: Cisplatin 100 mg/m^2 (days 1, 22, and 43)
  - Arm 2: Cetuximab 450 mg/m^2 at week 1, 250 mg/m^2 weekly after
- Endpoints
  - Acute and late CTCAE
  - OS, recurrences
  - QoL and swallowing

Mehanna et al Lancet 2019

De-ESCALaTE trial

- Characteristics
  - 334 patients (166 in cis arm, 168 in cetux arm)
  - Median follow-up 25.9 months
  - T1-2 (65%) N2-3 (76%)
  - 38% complete all 3 cycles of cis (51% completed 2 cycles)
  - 79% received all 8 cycles of cetux

Mehanna et al Lancet 2019

De-ESCALaTE trial

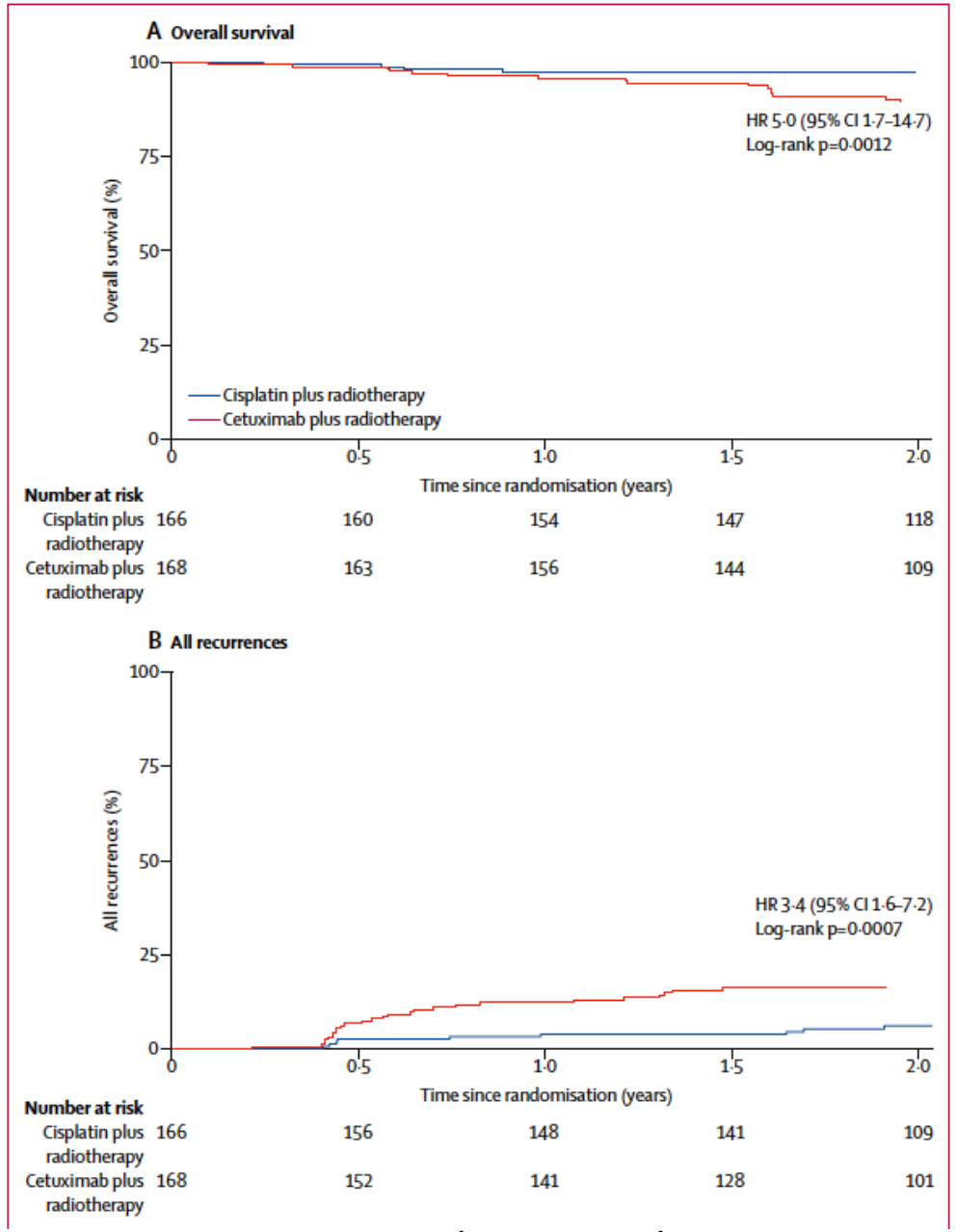
2-yr	Cis Arm	Cetux
CTCAE G3-5 events per patient	29.2	30.1
Acute CTCAE per patient	20.0	20.4
Late CTCAE per patient	0.5	0.4

- No differences in EORTC QLQ-30
- No differences in swallowing (per MDA dysphagia index)

Mehanna et al Lancet 2019

De-ESCALaTE trial

- 2-yr OS (all significant)
  - 97.5% cisplatin vs 89.4% cetuximab
    - Subgroup analysis
      - Stage I/II: 98.4% cisplatin vs 93.2% cetuximab
      - Stage III/IV: 93.3% cisplatin vs 67.1% cetuximab
- Recurrences: 6% cisplatin vs 18% cetuximab (all significant)
  - LRC: 3 vs 12%
  - Distant: 3 vs 9%



Mehanna et al Lancet 2019

RTOG 1016: Phase III

- Pts: All patients with +HPV OPSCC except T1-2N1
- Intervention: Accelerated RT in both, 70 Gy in 35 fx (BID once per week)
  - Arm 1: Cisplatin 100 mg/m^2 (days 1, 22)
  - Arm 2: Cetuximab 450 mg/m^2 at week 1, 250 mg/m^2 weekly after
- Endpoints
  - OS (primary), LRC, DM
  - CTCAE

Gillison et al Lancet 2019

RTOG 1016: Results

- Characteristics
  - 805 patients (399 cetuximab, 406 cisplatin)
  - Median f/u 4.5 years
  - T2-3 (66%), N2 disease (86%)
  - 85% completed 7 doses of cetuximab
  - 88% completed 2 cycles of cisplatin

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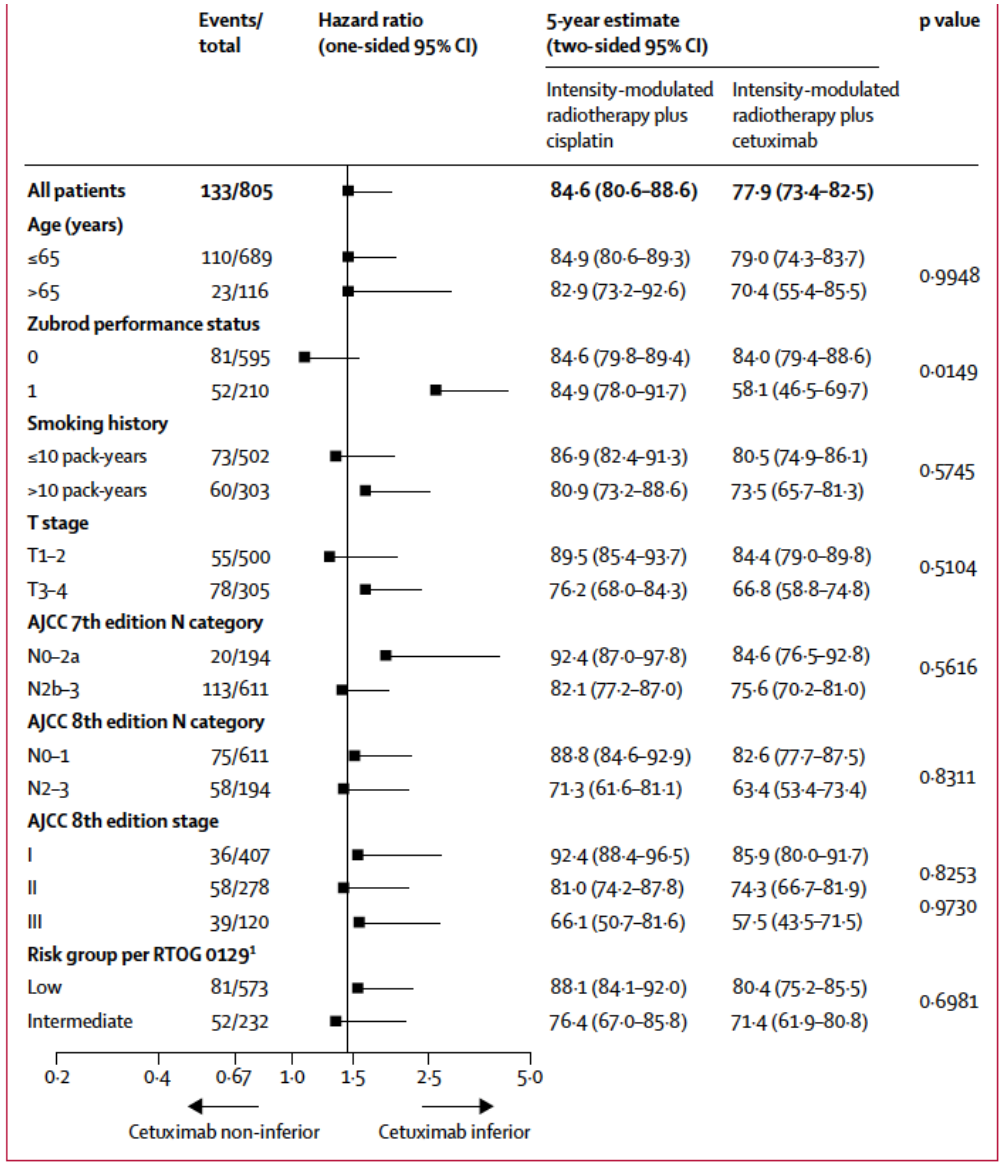
RTOG 1016: Res

- OS inferior with cetuximab (HR 1.03-2.05, p = 0.016)
  - 5 yr: 77.9% (cetux) vs 84.6% (cisplatin)
- PFS was inferior in cetux group (67.3% vs 78.4% @ 5-years)
  - LR failure 39% in cetuximab vs 30% in cisplatin arm
- LRC was inferior in cetux group (9.9% vs 17.3% @ 5-years)
- No differences in DM



	Events/ total	Hazard ratio (one-sided 95% CI)	5-year estimate (two-sided 95% CI)		p value
			Intensity-modulated radiotherapy plus cisplatin	Intensity-modulated radiotherapy plus cetuximab	
All patients	**133/805**		**84·6 (80·6–88·6)**	**77·9 (73·4–82·5)**	
Age (years)					
≤65	110/689		84·9 (80·6–89·3)	79·0 (74·3–83·7)	0·9948
>65	23/116		82·9 (73·2–92·6)	70·4 (55·4–85·5)	
Zubrod performance status					
0	81/595		84·6 (79·8–89·4)	84·0 (79·4–88·6)	0·0149
1	52/210		84·9 (78·0–91·7)	58·1 (46·5–69·7)	
Smoking history					
≤10 pack-years	73/502		86·9 (82·4–91·3)	80·5 (74·9–86·1)	0·5745
>10 pack-years	60/303		80·9 (73·2–88·6)	73·5 (65·7–81·3)	
T stage					
T1–2	55/500		89·5 (85·4–93·7)	84·4 (79·0–89·8)	0·5104
T3–4	78/305		76·2 (68·0–84·3)	66·8 (58·8–74·8)	
AJCC 7th edition N category					
N0–2a	20/194		92·4 (87·0–97·8)	84·6 (76·5–92·8)	0·5616
N2b–3	113/611		82·1 (77·2–87·0)	75·6 (70·2–81·0)	
AJCC 8th edition N category					
N0–1	75/611		88·8 (84·6–92·9)	82·6 (77·7–87·5)	0·8311
N2–3	58/194		71·3 (61·6–81·1)	63·4 (53·4–73·4)	
AJCC 8th edition stage					
I	36/407		92·4 (88·4–96·5)	85·9 (80·0–91·7)	0·8253
II	58/278		81·0 (74·2–87·8)	74·3 (66·7–81·9)	0·9730
III	39/120		66·1 (50·7–81·6)	57·5 (43·5–71·5)	
Risk group per RTOG 0129[1]					
Low	81/573		88·1 (84·1–92·0)	80·4 (75·2–85·5)	0·6981
Intermediate	52/232		76·4 (67·0–85·8)	71·4 (61·9–80·8)	

Gillison et al Lancet 2019

RTOG 1016: Results

- Proportion of patients with 1 or more Grade 3-4 acute AE:
  - 77.4% cetuximab vs 81.7% cisplatin (not significant)
- More hearing impairment in cisplatin arm
- EORTC QLQ H&N scores higher in cetuximab arm @ 1 year but differences not clinically meaningful (7.6 vs 2.5 p = 0.0382)

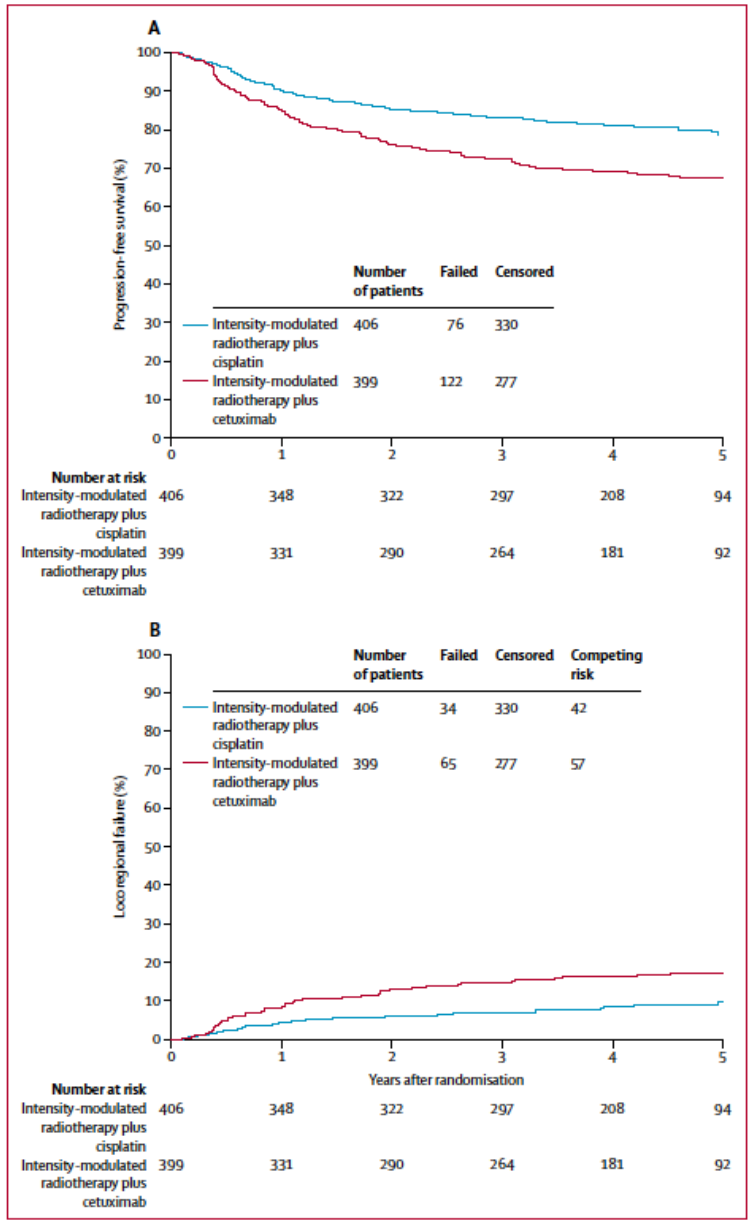


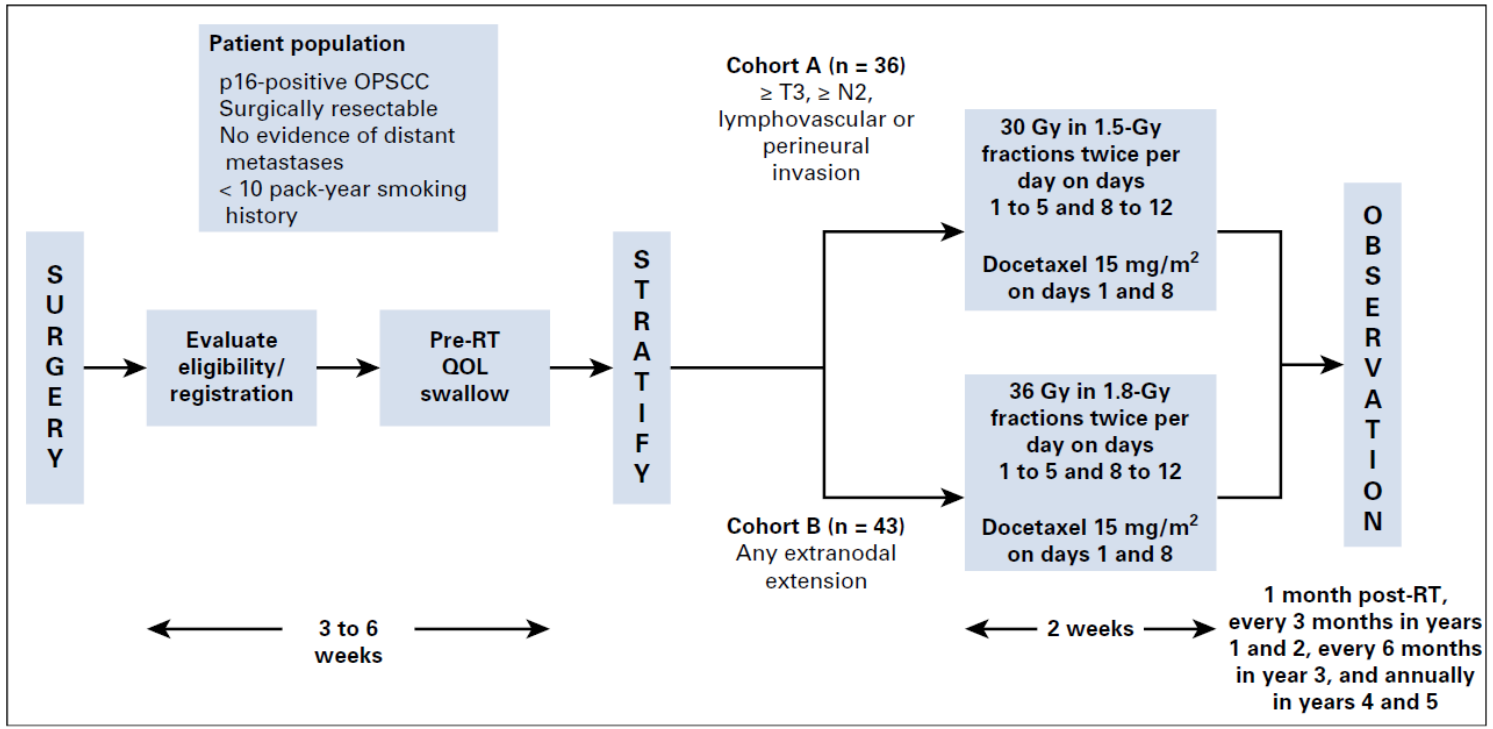
Figure 3: **Progression-free survival and locoregional failure**
(A) Kaplan-Meier estimates of progression-free survival are shown according to assigned treatment. (B) Cumulative incidence estimates of locoregional failure are shown according to assigned treatment.

Proposed Ways to De-Escalate Treatment

- 1) Add Induction chemotherapy and de-escalate well for responding patients
- 2) Reduce RT Dose
- 3) Change Cisplatin to Cetuximab
- 4) Surgery + Adjuvant RT+/- Chemo
  - MC1273
  - ECOG 3311 (data pending)

MC1273: Phase II

- 80 pts with T104, N0-3
- Eligibility: ENE or intermediate risk factor (LVI, PNI, 2 or more involved lymph nodes, any lymph node greater than 3 cm, ≥ T3 disease), < 10 PYH
- Treatment:
  - Margin-clearing surgery
  - RT dose stratified by pathology
    - Cohort A: 30 Gy in 1.5 Gy fxs BID on days 1-5, 8-12 with docetaxel
    - Cohort B (with ENE): 36 Gy in 1.8 Gy fxs BID on same days as Cohort A
  - Docetaxel 15 mg/m^2 on days 1 and 8 in both arms



Ma et al JCO 2019

MC1273

- RT Design
  - 30 Gy target volumes
    - Ipsilateral dissected nodal volumes (II-IV, +/- IB, V, and retropharyngeal)
    - If base of tongue (BoT) primary OR tonsillar primary with either > 1 cm BoT or soft palate involvement
      - Included contralateral level II-IV
  - 36 Gy target volumes
    - Simultaneous integrated boost
    - Included nodal volumes with ENE only
- Endpoints
  - Locoregional control, PFS, OS
  - Toxicity: swallowing function, CTCAE vs 4.0, EORTC-QLQ
  - Financial analysis

MC1273

- Patient Characteristics
  - Cohort A = 37 pts, Cohort B = 43 patients
  - Median f/u 35.7 months (all patients had 2-yr follow-up)
  - T1-2 (81%), N1-2 (87.3%)
- Any CTCAE Toxicity: pre-RT, 1 yr and 2 yrs
  - Grade 2: 11.4%, 2.5%, 1.4%
  - Grade 3 or worse: 0.0%, 6.7%, 0.0%
  - Most common grade 2 events were oral mucositis, dysphagia, xerostomia
- No patients required a PEG tube by 1 month after treatment

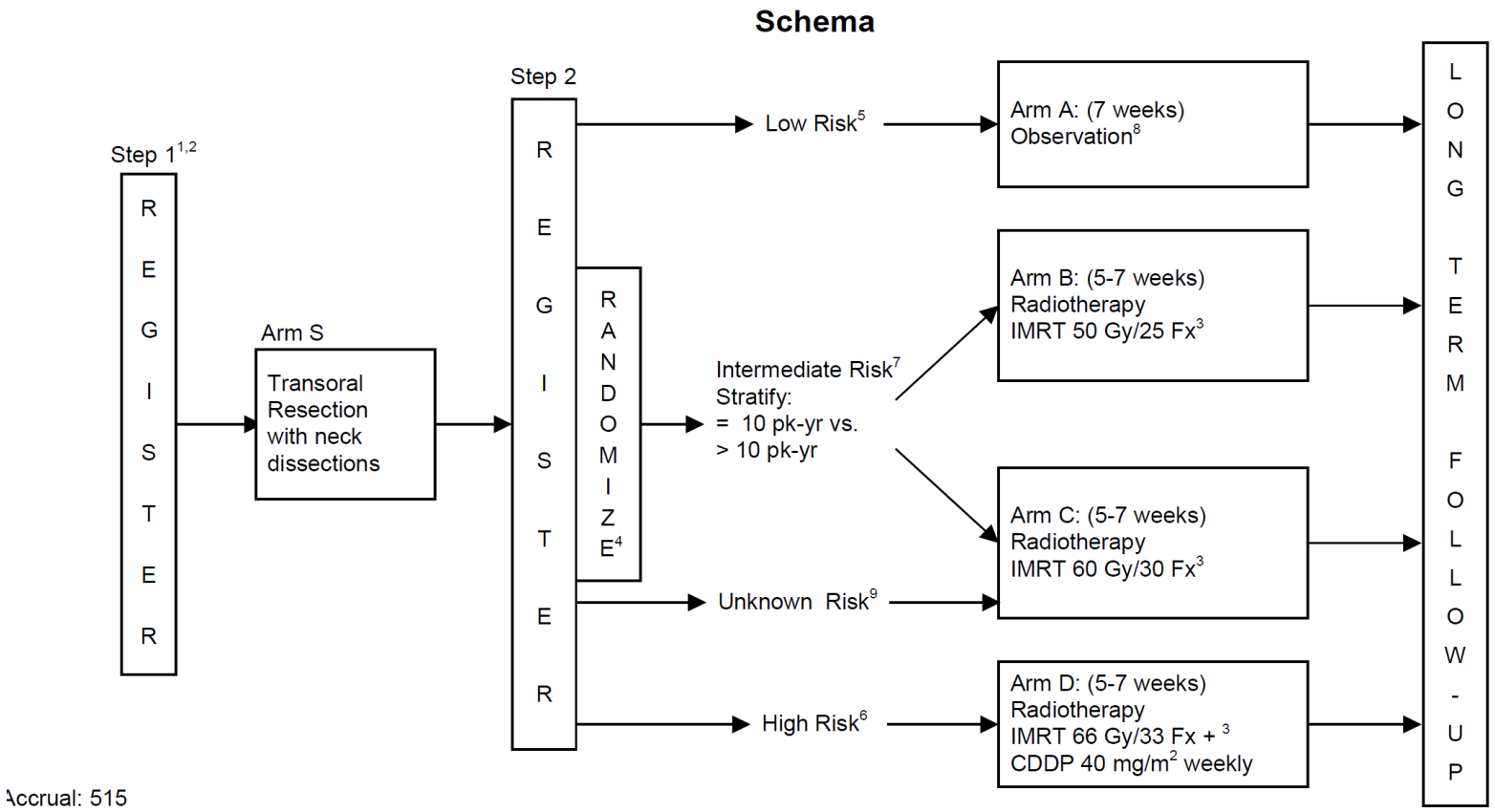
2-years	Cohort A	Cohort B
Locoregional control	100%	96.2%
Distant mets free survival	94.9%	91.9%

MC1273

- Quality of Life (@ 1 year compared to baseline)
  - Improved EORTC-QLQ H&N Score
  - Improved swallowing function on barium swallow
- Financial Analysis
  - Average cost of treatment = $45,884 = $17,791 (chemotherapy) + $28,093 (radiation)
  - Average cost of standard adjuvant treatment = = $57,845 = $26,603 (chemotherapy) + $31,242 (radiation)
- Conclusion: Aggressive adjuvant radiation dose de-escalation appears to provide comparable locoregional control to historical controls and results in significant improvements in toxicity. It is unclear if this treatment can be applied to heavy smokers as they were excluded

ECOG-ACRIN 3311: Phase II

- Results not released but our patient enrolled in this trial
- Patients with cT1-2, cN1-N2b undergo TORS + neck dissection
- Risk determination based on pathology
  - Low: T1-2, N0-1 with clear (≥ 3mm margins) without ECE or PNI/LVI
  - High: Positive margins OR extensive ECE (> 1 mm) OR ≥ 5 positive LNs
  - Intermediate: Close margins OR minimal ECE OR N2a, N2b (≤ 6 cm) OR +PNI or +LVI



ECOG-ACRIN 3311

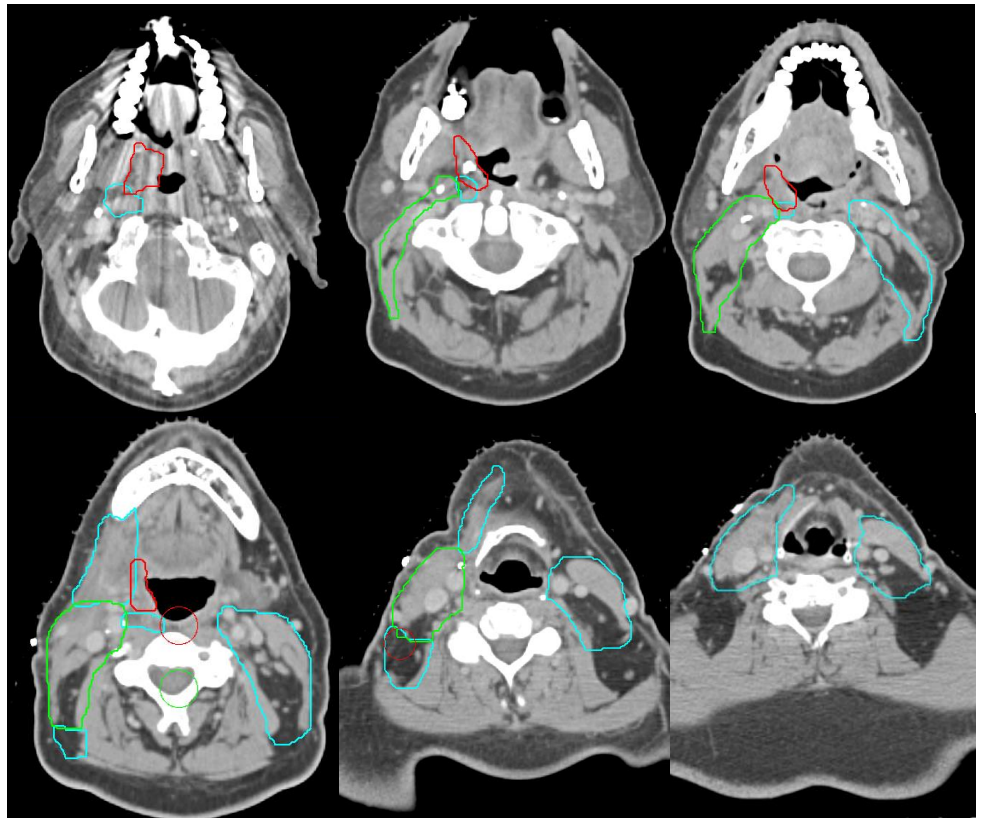
- Guidelines for Target Volume Delineation
  - CTV-P60: post-operative bed influenced by intra-operative assessment of the invasive base of the tumor
  - CTV-N60: dissected nodal volumes with metastasis
  - CTV-N50: either dissected nodal volumes that were negative or undissected volumes
    - Ipsilateral involved nodal volumes adjacent to disease
    - Lateral retropharyngeal nodes if ipsilateral level II or primary extends to posterior pharyngeal mucosa
    - Contralateral retropharyngeal nodes covered if ipsilateral retropharyngeal nodes involved
    - Contralateral undissected neck levels II-IV
      - Can be omitted if
        - » Tumor is > 1 cm from midline
        - » BoT tumors without medial margin involvement
      - Required if
        - » N2c disease
        - » Ipsilateral retropharyngeal involvement
- Note: If randomized to the 50 Gy arm, CTV-P60 and CTV-N60 are treated to 50 Gy

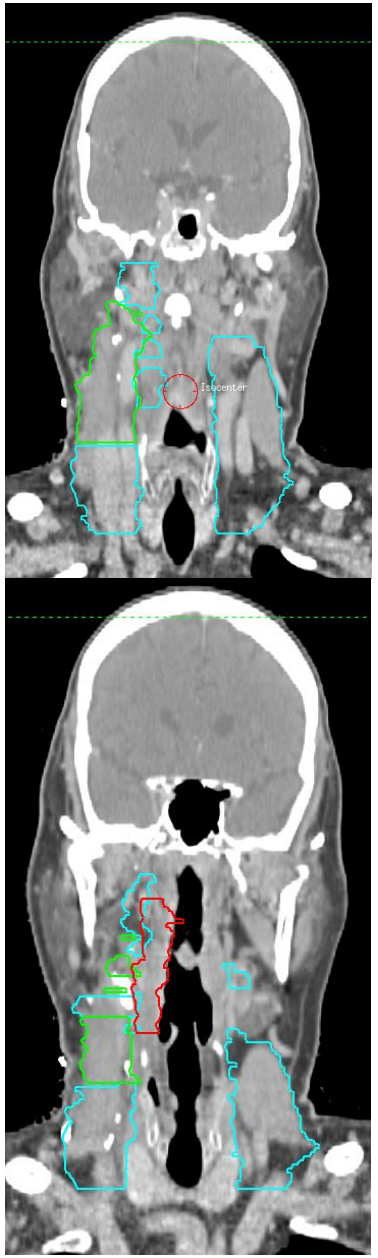
Case: Surgical Pathology

- Right neck dissection
  - Levels 1B, 2B, 3, and 4 all negative
  - Level 2A: 2 of 3 nodes positive measuring 0.8 and 0.3 cm without ENE
- TORS performed 2 weeks later
  - 3.1 cm squamous cell carcinoma without LVI but with PNI
  - Initial deep margin was positive but final margins were negative
- TNM Stage:
  - AJCC 7th: pT2N2b – Stage IVA
  - AJCC 8th: pT1N1 – Stage I
- All trials mentioned used prior AJCC 6th and 7th edition staging. Stage III-IV accrued in trials is most likely early stage disease by AJCC 8th standards

Case: Radiation Planning

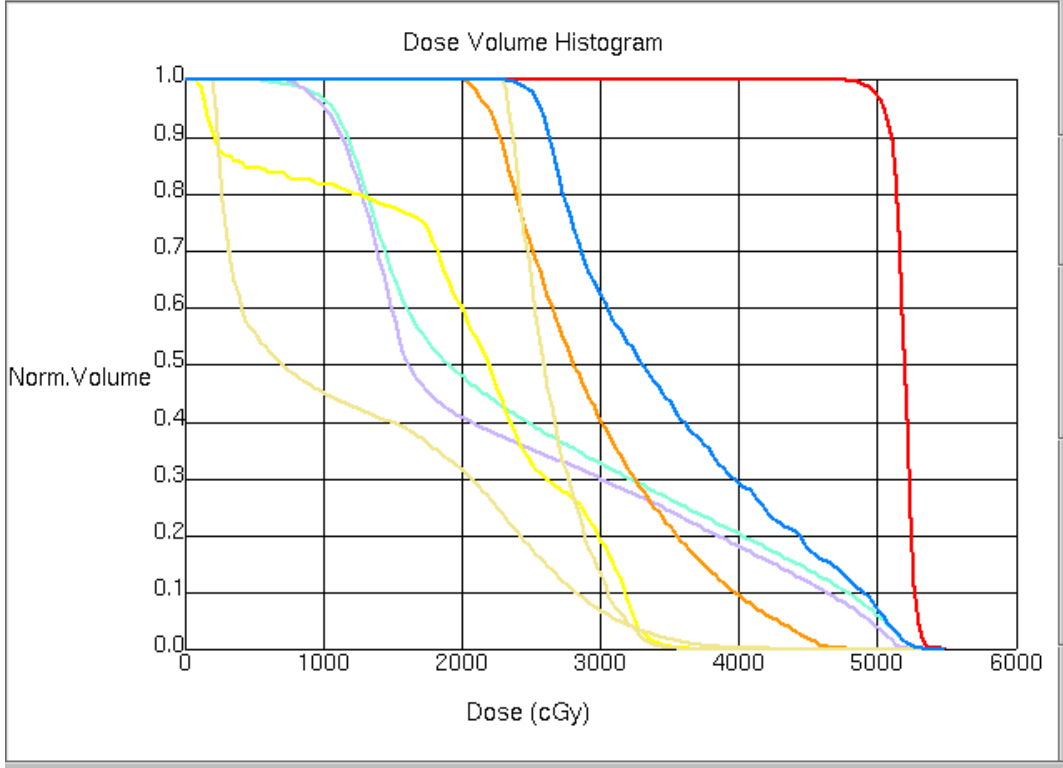
- The patient was randomized to 50 Gy arm of intermediate risk disease group
- CTV-P60 – post-op cavity
- CTV-N60 – right level 2A
- CTV-N50 – R level IB and V, bilateral II-IV (minus right 2A)
- PTV = CTV + 3 mm
- All volumes treated to 50 Gy





Case: Radiation Planning

- Ensure PTV50 receives 95% of the prescribed dose
- Spinal Cord: 1 cc < 45 Gy
- R or L parotid: V20 < 50% (Mean < 26 Gy for both which was met for this case)
- Brainstem: 1 cc < 54 Gy
- Endolarynx: 1 cc < 50 Gy (V30 < 50%)
- Cricopharyngeus: 1 cc < 50 Gy (V30 < 50%)
- Submandibular gland: V35 < 50%



ROI Statistics

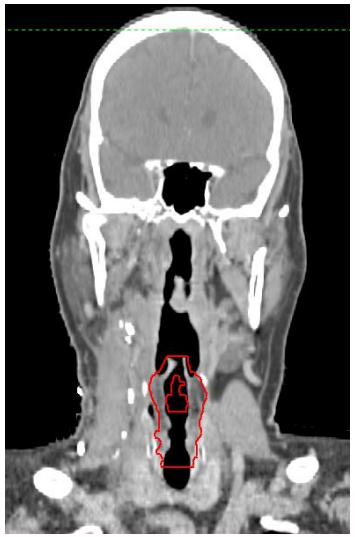
Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	PTV50	Head and Neck	3826.9	5462.3	5184.0	80.5
	Parotid R	Head and Neck	476.7	5340.4	2487.6	1355.2
	Parotid L	Head and Neck	619.4	5220.9	2337.3	1327.3
	Spinal Cord	Head and Neck	103.9	3649.5	2022.9	981.1
	Brain Stem	Head and Neck	192.6	4223.0	1251.5	1070.9
	Mod Endolarynx	Head and Neck	1961.1	4770.8	2967.8	643.3
	Mod Cricopharyngues Mu	Head and Neck	2265.1	3581.3	2654.9	264.8
	Submandibular L	Head and Neck	2253.0	5331.9	3523.2	831.5

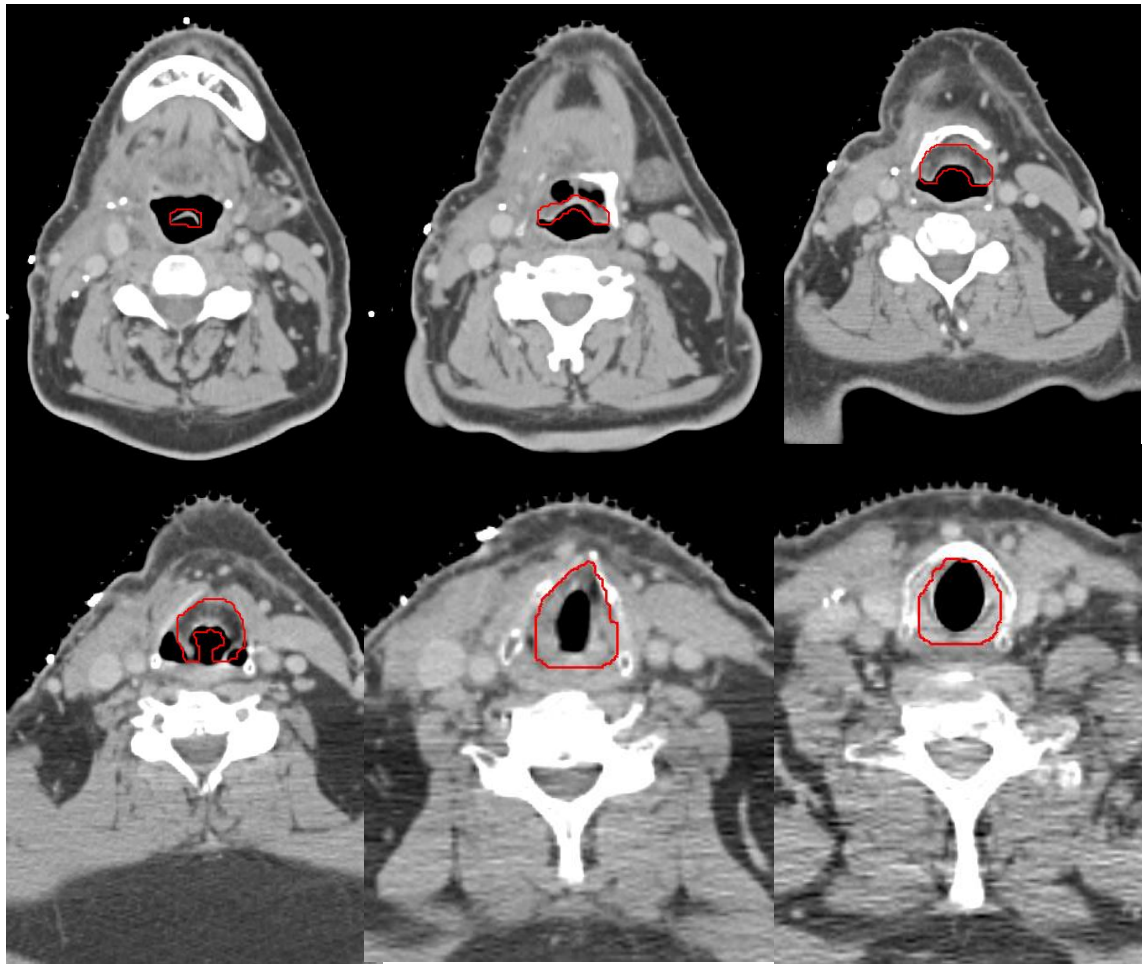
Case: Follow-up

- Adverse events during and at the end of treatment:
  - Notable mucositis and ulcer at the surgical site around 32 Gy
  - Decreased oral intake secondary to pain and lack of taste
  - Required multiple infusions of fluids because of dehydration
  - Moist desquamation of the neck
- 1-month follow-up
  - Pain resolved along with mucositis and ulceration
  - Improved fatigue and taste
  - Cleared to return to work
- 21-month follow-up:
  - Mentions minor xerostomia that does not bother him
  - CT larynx and indirect laryngoscopy negative for recurrent disease

Case Radiation Planning

- Endolarynx description per ECOG311
  - “This volume will consist of the tissues medial and contained within the laryngeal cartilage and will include the endolaryngeal structures from the level of the tip of the suprahyoid epiglottis to the inferior extent of the cricoid cartilage that does not overlap with any adjacent PTV”





General Conclusions

- Treatment de-intensification using induction chemotherapy, definitive chemoradiation, and adjuvant radiation approaches appears to be promising producing control rates comparable to historical data with significant reductions in toxicity
  - Await Phase III data
- Cetuximab is not a substitute for cisplatin therapy in the definitive setting in HPV+ low risk cancers
  - Inferior outcomes even when only 2 cycles of cisplatin are given
- Choice of de-escalation method should be tailored towards patient risk factors
  - Smoking history (> 10 years vs ≤ 10 years)
  - Extent of disease (i.e. induction chemo to reduce burden followed by smaller RT volumes/dose)
  - Surgical pathology (ENE, + margins)
  - Performance status (surgical candidate?)