De-escalation of Post-Operative Adjuvant Therapy for Patients with “High-Risk” Lymphatic Metastasis from p16+ Oropharyngeal Carcinoma

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Increase in Primary Surgical Treatment of T1 and T2 Oropharyngeal Squamous Cell Carcinoma and Rates of Adverse Pathologic Features: National Cancer Data Base

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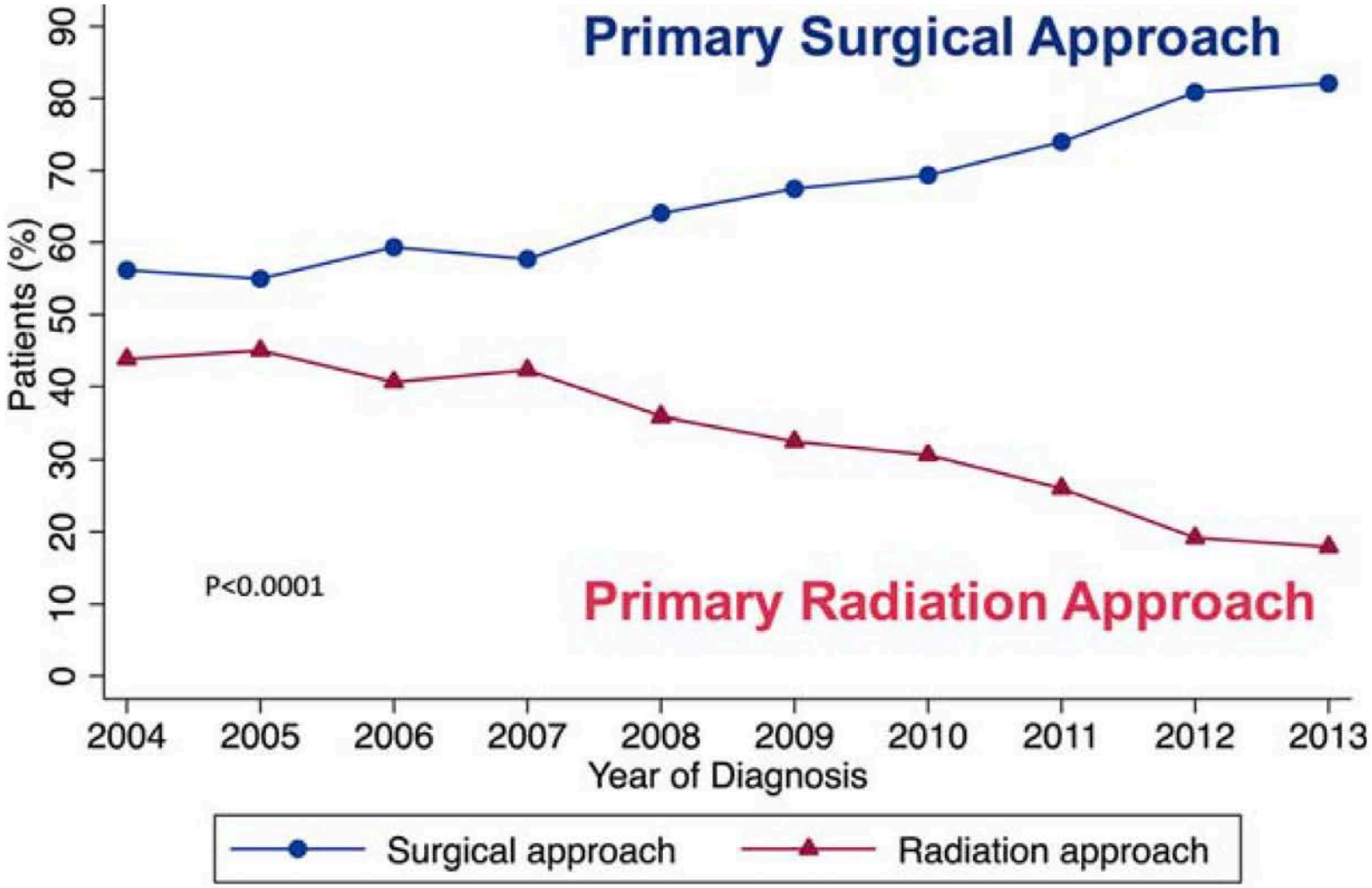

2004-2013

8768 patients (974 / yr)

68% of all T1-T2 patients were treated with surgery –significant rise *(especially)* since 2004

568 pts in 2004 *versus* 1021 pts in 2013 *(p<.0001)*

De-escalating Tx for p16+ OPC

- Two ongoing clinical trials (E3311 and NRG HN002) suggest consensus in the head and neck oncology community that treatment might be de-escalated for patients with HPV-associated p16+ SCC of the oropharynx.
- In E3311, patients with certain adverse biological features [(5 or more nodes, extracapsular spread (ECS) or extranodal extension =ENE)] receive post-operative chemoradiation, reflecting the current standard of care.
- **Retrospective literature suggests that these patients might have similar outcomes with post-operative radiation therapy alone. But there is no post-op trial.**

Original Article

Washington University School of Medicine in St.Louis

Extracapsular Spread and Adjuvant Therapy in Human Papillomavirus-Related, p16-Positive Oropharyngeal Carcinoma

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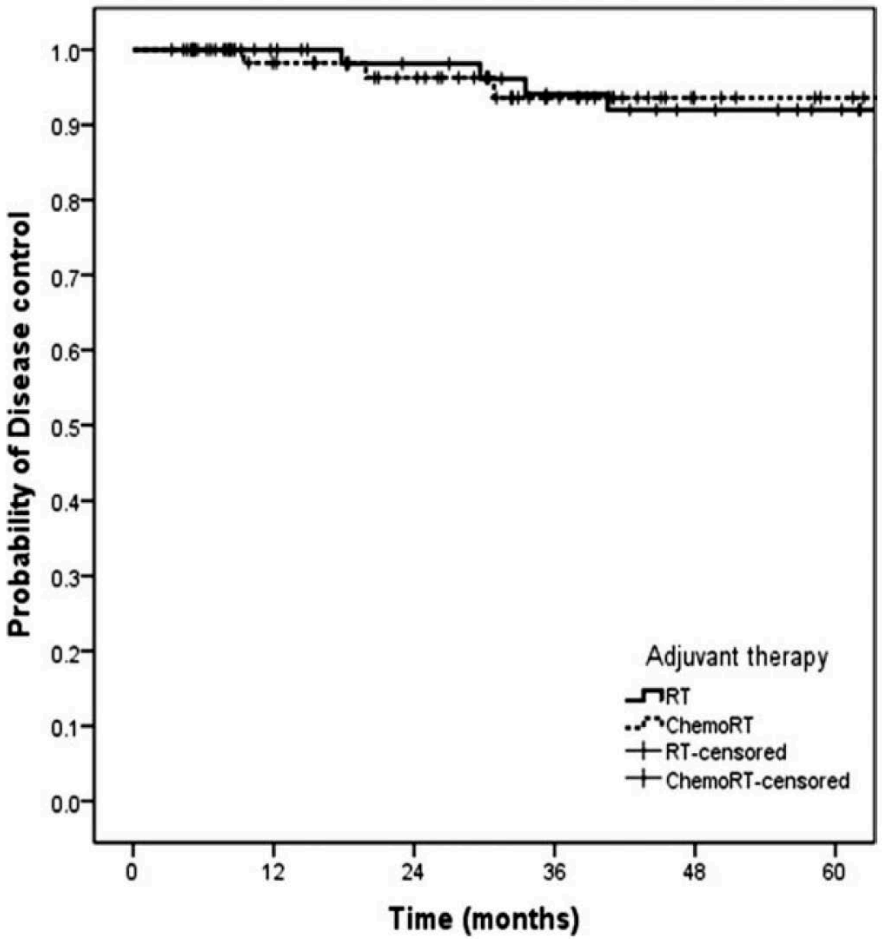

Retrospective review of 152 p16+ SCC OPC

Extracapsular spread: Novel histologic grading (ECS graded)

DFS did not differ significantly according to the presence versus the absence of ECS_{graded} (92% vs 97%, respectively; $P = .08$) or for ECS_{graded}-positive patients who received CRT versus RT alone (87.8% vs 89.4%; $P = .98$). However, patients with STM_{graded} had significantly reduced DFS compared with patients without STM_{graded} (80% vs 93%; $P = .02$). However, for patients with STM_{graded}, DFS was no better with CRT than with RT alone (80% vs 83%; $P = .32$).

Extracapsular Spread in Head and Neck Carcinoma: Impact of Site and Human Papillomavirus Status

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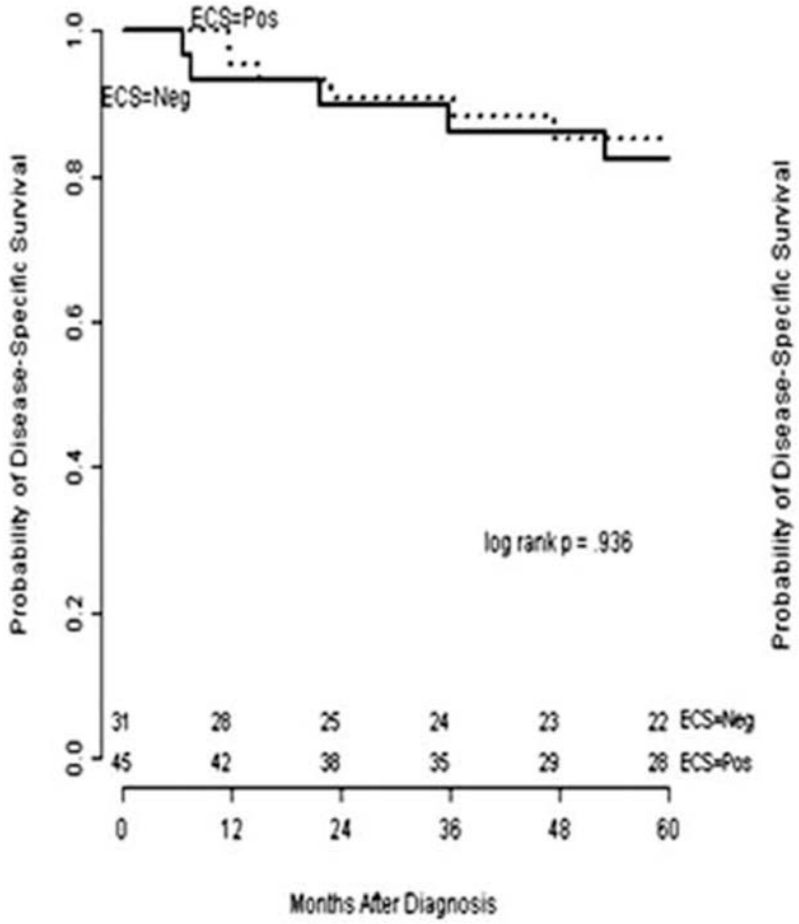

UPMC
University of Pittsburgh Medical Center

Retrospective review: 133 p16+ SCC OPC

TABLE 3. Demographics and Clinico-pathologic Data of Patients with Oropharyngeal Squamous Cell Carcinoma[a] by ECS status

Characteristic	ECS-Positive (n = 80)	ECS-Negative (n = 53)	*P*
No. of positive lymph nodes, mean (range)	4.2 (1-21)	2.3 (1-8)	.0008
AJCC stage[e]			.0018
III	9 (11.2)	18 (34.6)	
IV	71 (88.8)	34 (65.4)	
Radiation[f]			.0092
Yes	72 (94.7)	39 (78.0)	
No	4 (5.3)	11 (22.0)	
Chemotherapy[g]			.0058
Yes	31 (42.5)	9 (18.0)	
No	42 (57.5)	41 (82.0)	
Smoking status[b]			.101
Never-smoker	17 (27.9)	6 (14.0)	
Ever-smoker	44 (72.1)	37 (86.0)	
Tumor subsite			1.0
Tonsil	49 (61.2)	32 (60.4)	
Base of tongue	31 (38.8)	21 (39.6)	
p16			.8589
Positive	45 (56.2)	31 (58.4)	
Negative	35 (43.8)	22 (41.5)	

Proposal

- Therefore, we propose a Phase III prospective randomized clinical trial comparing a “de-escalated” regimen of post-operative IMRT + cetuximab *versus* our standard post-operative regimen of IMRT + cisplatin

- Selected patient with high-risk lymphatic metastasis (any ENE or >4 lymph nodes)

- p16+ oropharyngeal cancer (OPC)

- After open **OR** transoral endoscopic head and neck surgery

"High-Risk" Lymphatic Metastasis p16+ OPC PostOp Trial

Resection of Oropharyngeal Tumor (Standard of Care, Prior to Accural)
Surgery (Traditional Open or Transoral eHNS)
& neck dissection

Assess Eligibility

HPV (p16)$^{+}$ SCC oropharynx
(tonsil, tongue-base, GPC)

pT1-**3**, pN1-**3**
w/ high-risk metastasis=
ENE
>4 metastatic LN

Baseline Functional/ QOL Assessment

RANDOMIZE

1200pts

Radiation Therapy + Cetuximab
IMRT **60 Gy/30 Fx**
+ cetuximab
400mg/m^2 loading
250mg/m^2 weekly
(experimental arm)

Radiation Therapy + Cisplatin

IMRT 60 Gy/30 Fx +
CDDP 40 mg/m^2 weekly
(control arm)

Primary Endpoint:

2-year OS

Secondary Endpoints:
Local-Regional Recurrence, Functional Outcomes/QOL

Total Accrual = 1200

Study Period = **7½ yrs**

Eastern Cooperative Oncology Group

Eligibility Criteria

1. SCC
2. p16 IHC -- CLIA approved lab (no central review)
3. Staging: pT1-T3 or pN1-3, M0
4. Pathologically confirmed “high-risk” lymphatic metastatic adenopathy with **extranodal extension** (**ENE**) and/or **with >4 metastatic lymph nodes.**
5. **Negative or close surgical margins**
6. No post-operative adjuvant therapy for the index tumor.
7. No prior radiation to the head and neck region.
8. ECOG performance status 0-1.
9. Age ≥ 18 years.

   (No prior invasive malignancy (except non-melanoma skin cancer) unless disease-free for a minimum of 3 years.

Primary Objective

- **Primary objective:** overall survival, OS, as defined as the time between randomization to progression, or death from any cause.
- **Assumptions**: 3-year OS (standard arm – cisplatin chemoRT) = 80%.
- OS will be compared using a **log rank test**. The experimental arm will be considered as acceptable, **if the 3-year OS rate is no lower than 75%,** corresponding to a hazard ratio of **1.3**
- Test of non-inferiority here uses a null hypothesis of no difference, as when testing for superiority, but with a **larger type I error (one-sided 15%)** and **smaller type II error (6%) than usual**.
- The design assumes **1190 eligible patients** to be randomized over 7½ years

“High-Risk” HPV/p16+ Post-Op Trial
Stratification

- **Margin status:** clear (>3mm) versus close (<3mm)
- **Smoking status:** Never smoker vs. **<10 vs. >10 pack-years**
- **Extent of ENE: <2mm, >2mm;** soft-tissue extension with no recognizable lymphatic architecture in the dissected node (Lewis Level IV) vs. all other ENE
- **Type of surgery:** transoral endoscopic head and neck surgery (eHNS) *versus* open HNS
- ***Pre-op Imaging:*** *Matted nodes versus not?*

Summary

- Concept has been developed over the past year in the H&N Section of ECOG
- Preliminary review with PULA (October 12, 2016) and the ECOG Executive Committee (12/22/2016)
- Offers stepwise de-escalation from cisplatin chemoRT (avoids risks of simply moving to RT for potentially high-risk portion of ECS and highly metastatic post-op population.