

De-Intensification of Treatment for p16 Positive Oropharynx Ca



Robert Amdur, MD
Radiation Oncology, U. of Florida

Goal of De-Intensification:

Decrease toxicity (without decreasing cure rate)

Quality of Life



Risk of De-Intensification: Cancer Recurrence



SAM Question

The primary goal of treatment
De-Intensification is to:

Decrease Toxicity

U. North Carolina-U. Florida De-Intensification Studies: To decrease toxicity in p16 pos Orophx Ca.



Chera

Prospective Single-Arm Phase II

Trial #1 started 2012, Trial #3 will close soon

No Trans Oral Surgery

No Neoadj chemo

60 Gy RT

No chemo in early stage

Otherwise, Weekly Platinum 30mg/m²

10 peer-reviewed publications: JCO, JNCI, etc

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Outline



Historic standard

Summary of “D-I” efforts

Our Studies

Standard Tx for Orophx Ca



Primary RT:

70 Gy @ 2 (T1: 66 Gy)

UF: 74 Gy @ 1.2 BID

Chemo (most stg 2-4):

CisPlat 100 mg/m² q3 wks

Stage 4: Neoadj TPF

Neck dissection:

Only scan pos at 12 wks

SAM Question

During most of the past few decades, standard treatment for oropharynx cancer has been:

Radiation Therapy, with or without, chemotherapy

Weekly platinum 30-40 mg/m²

**Good results from UF:
and about 5 other single
institution series**

Original Article

U Florida: Cancer 2010

Concomitant Weekly Cisplatin and Altered Fractionation Radiotherapy in Locally Advanced Head and Neck Cancer

Heather E. Newlin, MD¹; Robert J. Amdur, MD¹; Charles E. Riggs, MD²; Christopher G. Morris, MS¹; Jessica M. Kirwan, MA¹; and William H. Mendenhall, MD³

2 RCT conclude Q3 wk 100 mg/m² BETTER

2012: Chang Gung, Taiwan



RESEARCH

Open Access

The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity

Din Li Tsai¹, Chien-Hu Lin¹, Chung-Jan Keng², Shang-Fu Huang², Kang-Hsing Fim^{1A}, Chun-Tzu Liao², Hsiao-Chen¹

Q3weeks:

Less toxicity (same LRC)

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

2018: Tata, India

Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial

Vanita Noronha, Amit Joshi, Vijay Manuti Patil, Jaiprakash Agarwal, Sarbani Ghosh-Laskar, Ashwini Budrukkar,

Q3weeks:

Better LRC but more toxicity

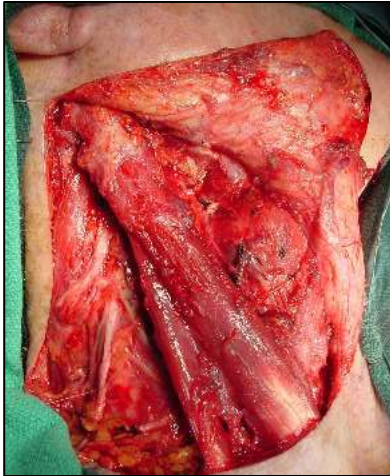
Plat 100 mg/m² q 3 wk is U.S. standard and control arm in most NCI trials of HPV+ Orophx Ca

SAM Question

Results from Randomized Controlled Trials (RCTs) of Weekly versus Q-3 week Cisplatin during radiotherapy for head and neck cancer support this conclusion:

Q-3 week Cisplatin is better than Weekly

Now Everything is called “De-Intensification”



**Many “D-I” programs do NOT
meaningfully decrease overall toxicity**

**They just offset a decrease in one toxicity
with an increase in another**

Some “D-I” programs INTENSIFY Toxicity

Survey of “De-Intensification” Programs

Oropharynx Ca (usually p16 positive)

Add Surgery to decrease RT/Chemo

ECOG 3311 (Holsinger *JCO* 2015): TOS+ 0,50,60Gy, 66+wkly Plat

Mayo 1273 (Ma *JCO* 2019): TOS + 30Gy 1.5BID + wkly Taxol



Tougher Chemo to decrease RT

ECOG 1308 (Marur *JCO* 2016): Tax-Plat-Cetux x 3, 54Gy 1.8 + Cetux

UCLA (Chen, *Lancet Oncol* 2017): Taxol-Carbo x 2, 54Gy 1.8 + wkly Plat

Gentler Chemo = Cetuximab + ~Standard RT

~~NRG 1016 (Gillison, *Lancet* 2019): 70Gy/6wks + Plat 100mg vs Cetux~~

~~De-ESCALaTE (Mehanna, *Lancet* 2019): 70Gy/7wks + Plat 100mg vs Cetux~~

NRG 005 (Yom): 70 or 60Gy/6wks + Plat 100mg vs 60Gy/5wks + Nivolumab

Gentler Chemo and Gentler RT

NRG 002 (Yom): 60Gy/6wks + weekly Platinum vs ~~60Gy/5wks no chemo~~

UNC-UF (Chera): 60Gy/6wks no chemo or weekly Platinum

SAM Question

A major finding from NRG 1016 that randomized Cisplatin versus Cetuximab concurrent with 70 Gy RT was:

Cisplatin should remain the standard because survival was lower with Cetuximab

RT Technique

“De-Intensification” Programs

Oropharynx Ca (usually p16 positive)

Decreasing dose to Elective Targets

Lower dose intensity: 40 at 2Gy, 50 at 1.7Gy

MSK: Tsai-NLee (*PRO* 2019): 30 Gy at 2Gy



Decrease the Low Dose Bath

MDAH (Frank): RCT NCT01893307

70 at 2Gy + standard chemo

Proton vs Photon Beams



Eliminating PTV

Stuart/Eisbruch, U. Michigan IJROBP 2016





A Shifting Paradigm for Patients with Head and Neck Cancer: Transoral Robotic Surgery (TORS)

ONCOLOGY, Oct 2010

MIHIR K. BHAYANI, MD

Department of Head
and Neck Surgery

The University of Texas

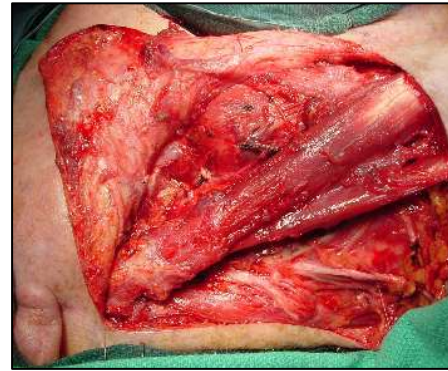
M.D. Anderson Cancer Center

TORS paradigm of De-Intensification for Oropharynx Ca

TORS



Neck dissection(s)



+

Observe: Margin > 1-3 mm, N0 or 1node, no ENE

RT: Margin < 1-3mm, ≥ 2nodes, or ENE

60 Gy @ 2 (10 Gy less than 70 Gy)

Chemo (Plat 100 mg/m²): pos margin or ENE

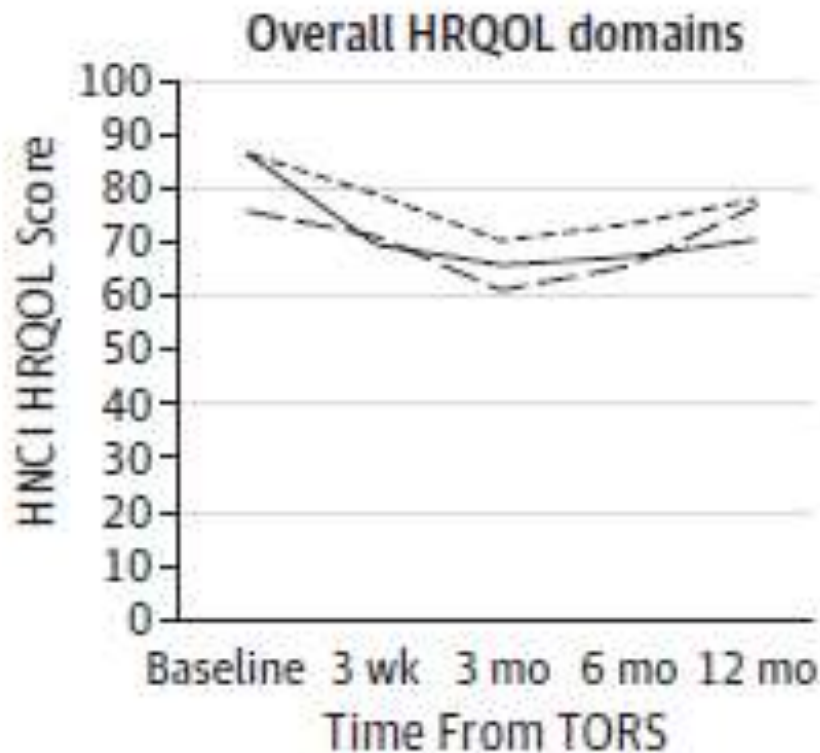
QoL surveys show great results

Ohio State U: 2013: JAMA Oto

Transoral Robotic Surgery for Oropharyngeal Cancer
Long-term Quality of Life and Functional Outcomes

≥ 60 Gy in 87% plus
chemo in 62%

Peter T. Dziegielewski, MD, FRCSC; Theodoros N. Teknos, MD; Kasim Durmus, MD; Matthew Old, MD;
Amit Agrawal, MD; Kiran Kakarala, MD; Anna Marcinow, MD; Enver Ozer, MD



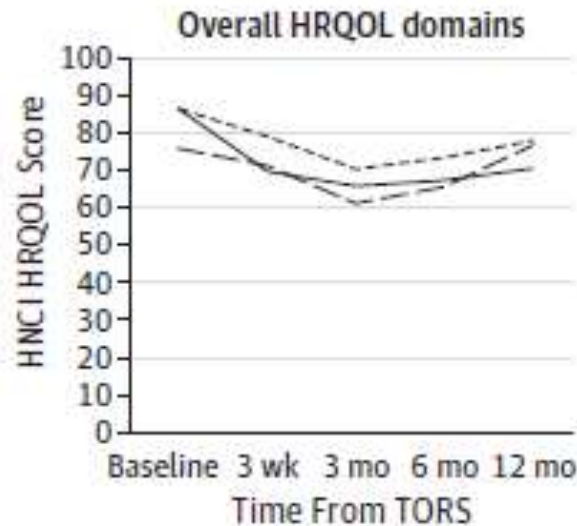
Conclusion: U-Shaped Curve means great QOL results

Ohio State U: 2013: JAMA Oto)

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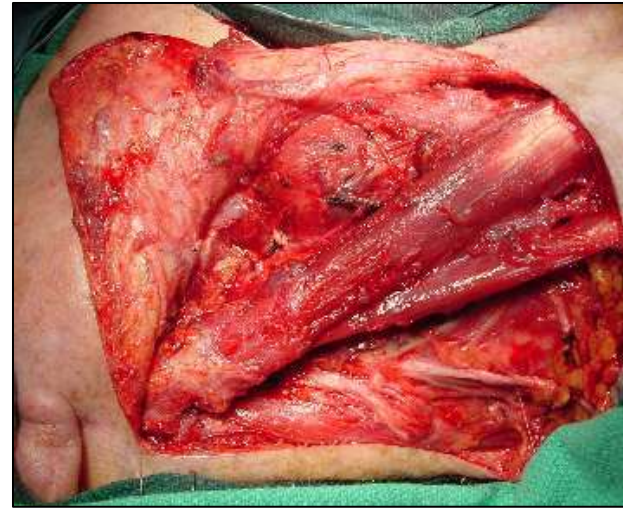
12 months post TORS, overall QOL returns to baseline values. Although these data are still preliminary, TORS is showing promise as an optimal treatment strategy in early-stage disease.

SAM Question

The main goal of using Trans Oral Surgery instead of 70 Gy Radiotherapy as primary treatment for oropharynx cancer is to:

Improve long term quality of life

Concern about the TORS paradigm



**Functional morbidity of
(Surgery + 60 Gy) is usually \geq (70Gy + Chemo)**

Smart, well meaning doctors and accurate data

**But,
we now know that QoL scores are misleading**

Concern #1 about TORS conclusion

U-Shaped QoL Curve does NOT mean good function

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

2015 Princess Margaret Hospital

Survivorship and Quality of Life in Head and Neck Cancer

Jolie Ringold

Misuse of Quality of Life Evaluation in
Oncology Studies: Reification, Adaptation,
and the U-shaped Curve **PRO 2019**

Robert J. Amdur MD^{a,*}, Bhishamjit S. Chera MD^b

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^bDepartment of Radiation Oncology, University of North Carolina Hospitals, Chapel Hill, North Carolina

Everyone lives with problems based on Symptom Specific studies but Global QoL scores look good after 1-year

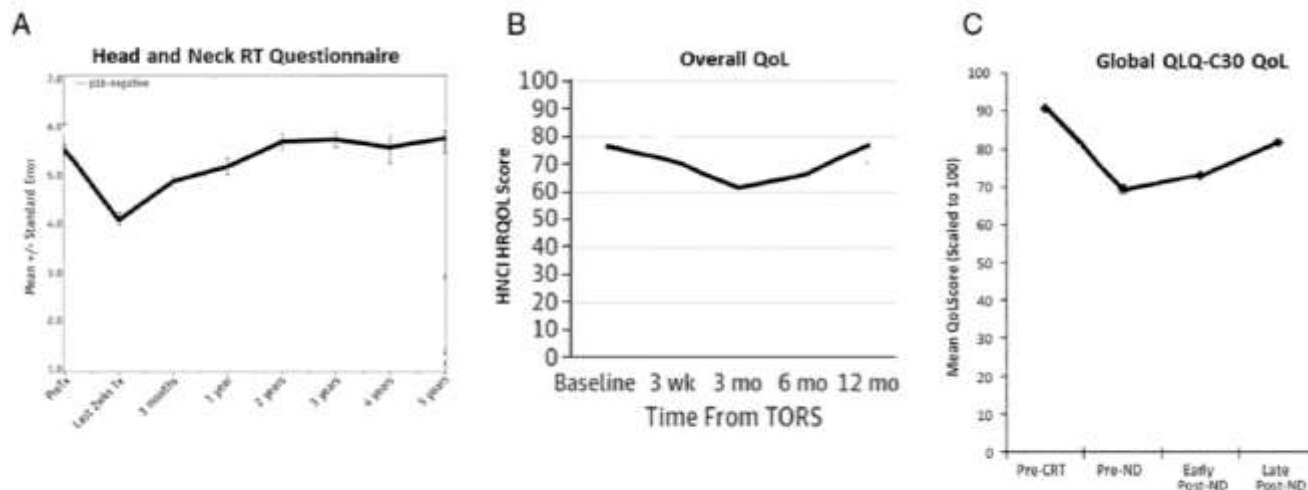


Fig. 1 Global quality-of-life assessment from 3 studies after multimodality treatment of head and neck cancer with plots modified clarity of presentation. (A) Xiao et al.⁴ (B) Dziegielewski et al.⁹ (C) Wang et al.¹²

Global QoL Following Cure of Rectal Ca: No Difference with or without Colostomy



Cochrane Database of Systematic Reviews

2012 Data from Many Trails

Quality of life after rectal resection for cancer, with or without permanent colostomy. (Review)

Pachler J, Wille-Jørgensen P



Conclusion:

“No apparent differences in quality of life are found in rectal cancer patients with a permanent stoma when compared to nonstoma pts”

Objective measures of morbidity

Chronic G-tube rate is the most definitive marker of serious swallowing problems-- and TORS doesn't look good

Cancer 2014: 2315 pts

A Multi-Institution Pooled Analysis of Gastrostomy Tube Dependence in Patients With Oropharyngeal Cancer Treated With Definitive Intensity-Modulated Radiotherapy

Jeremy Setton, MD¹; Nancy Y. Lee, MD¹; Nadeem Riaz, MD¹; Shao-Hui Huang, MSc²; John Waldron, MD²; Brian O'Sullivan, MD²; Zhigang Zhang, PhD³; Weij Shi, MS³; David I. Rosenthal, MD⁴; Katherine A. Hutcheson, PhD⁵; and Adam S. Garden, MD⁴

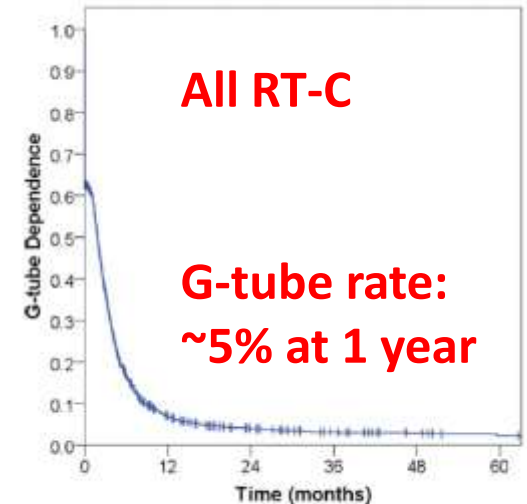


Figure 1. Gastrostomy tube (G-tube) dependence is illustrated among patients with stage III and IV disease who received concurrent chemotherapy.

OSU: JAMA Oto 2013

Transoral Robotic Surgery for Oropharyngeal Cancer
Long-term Quality of Life and Functional Outcomes

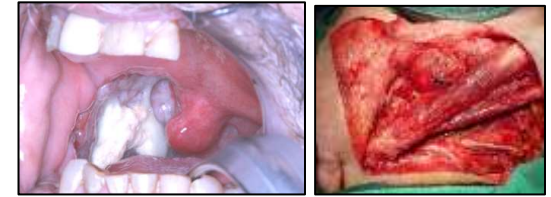
Peter T. Dziegielewski, MD, FRCSC; Theodoros N. Teknos, MD; Kasim Durmus, MD; Matthew Old, MD; Amit Agrawal, MD; Kiran Kakarala, MD; Anna Marcinow, MD; Enver Ozer, MD

	1-yr G-tube
Dz TORS	9%
Setton RT-C	5%

Changing the role of TORS?

NCI Canada, *Lancet Oncol* 2019

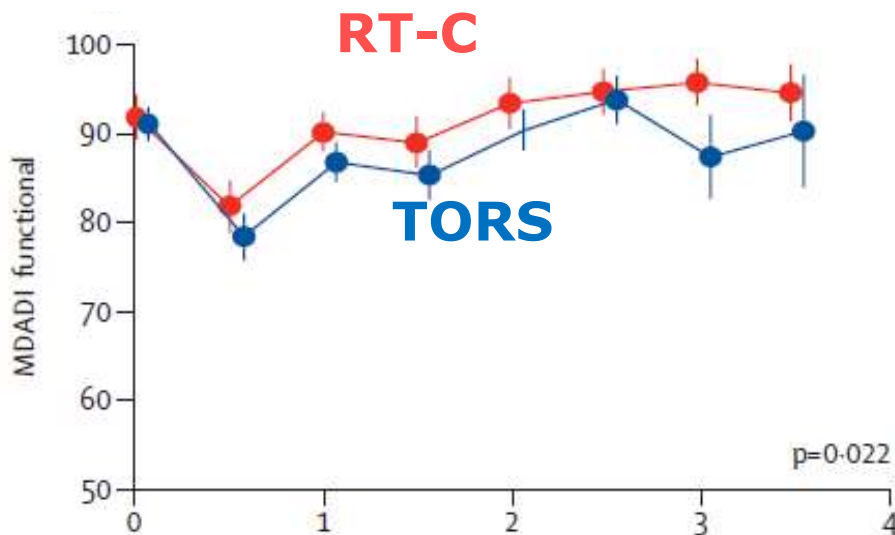
Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial



Anthony C Nichols, Julie Theurer, Eitan Prisman, Nancy Read, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley,

RCT:

TORS paradigm versus (70 Gy + Plat 100 mg/m²)



For every functional endpoint, TORS was **WORSE or no better than full dose RT-C**





UNC-UF Phase II Studies: To decrease toxicity in favorable Orophx Scca

p16 pos Orophx or unknown, T0-3 N0-2c

Studies #1-2: < 10 pk-yr smoking
Study #3: includes all smokers

60 Gy alone: T0-2, N0-1 (7th Edition)
T3 or N2: + Weekly Plat 30 mg/m²

D-I Study #2: 2014-2017

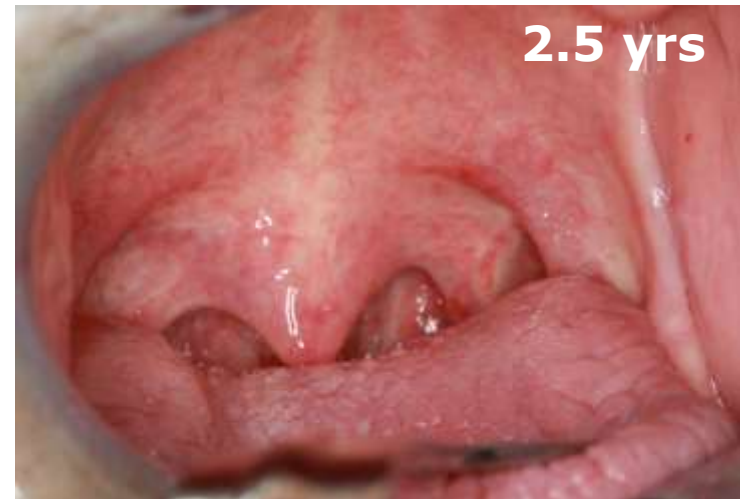


Primary Endpoint: 2-yr Progression Free Survival
Secondary Endpoints: QoL-many, Swallowing test
114 patients enrolled

JCO 2019

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

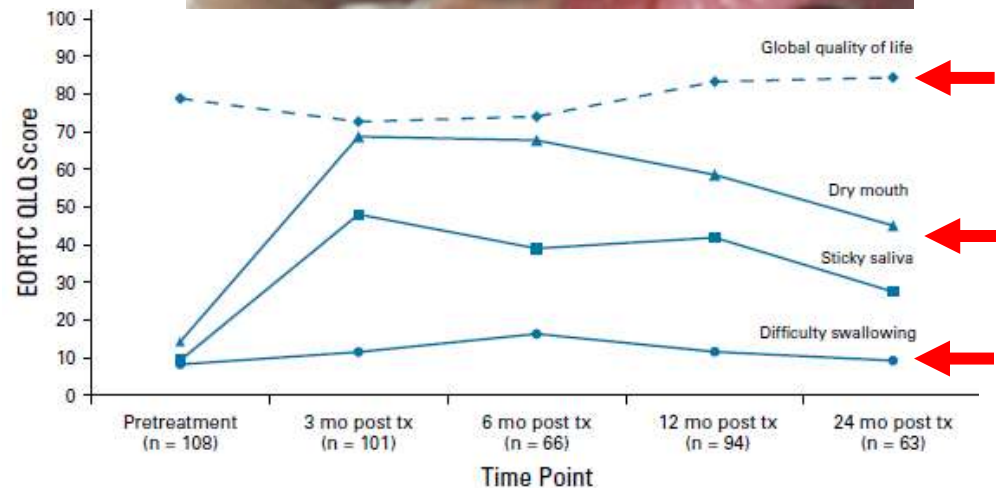
Shishamjit S. Chera, MD^{1,2}; Robert J. Amdur, MD³; Rebecca Green, MSW⁴; Colette Shen, MD, PhD^{1,2}; Gaorav Gupta, MD, PhD^{1,2}; Ganming Tan, PhD⁵; Mary Knowles, ANP¹; David Fried, PhD¹; Neil Hayes, MPH, MD⁶; Jared Weiss, MD^{1,2}; Juneko Grilley-Olson, MD^{1,2}; Iibetal Patel, MD, PhD^{1,2}; Adam Zanation, MD¹; Trevor Hackman, MD¹; Jose Zevallos, MPH, MD⁷; Jeffrey Blumberg, MD¹; Jampip Patel, MD¹; Mohit Kasibhatla, MD⁸; Nathan Sheets, MD⁷; Mark Weisser, MD¹; Wendell Yarbrough, MMHC, MD^{1,2}; and William Mendenhall, MD⁹



2 year results

L-R Control: 95%

Progression-Free: 91%



D-I Study #3: 2017-2019

p53 in Smokers

Same inclusion criteria: p16 pos, T0-3 N0-2c

But #3 includes ≥ 10 pk-year smokers



Deintensification RT still 60 Gy @ 2Gy to gross disease

#3 decreases elective dose to 50 Gy at 1.67 (was 54/1.8)

Deintensification RT (60/50 Gy) for all < 10 pk-yr smokers

AND > 10 pk-yr smokers that are p53 wild type

> 10 pk-yr smokers with p53 mutation get 70/56 Gy

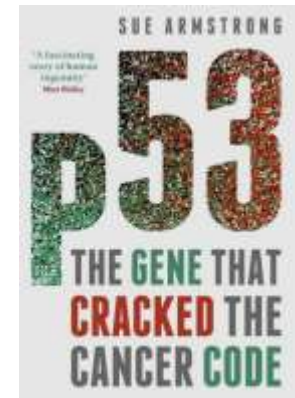
Same chemo program:

No chemo if < 10 pk-year smoker AND T0-2, N0-1

All others get Weekly Plat 30 mg/m²

Exploratory testing pre and post tx: plasma HPV DNA

~150 patients



Circulating Tumor HPV DNA (ctDNA)



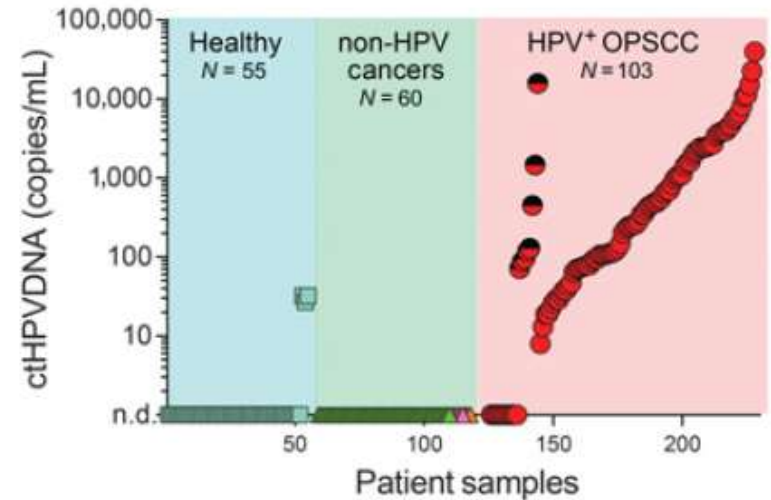
Precision Medicine and Imaging

Clinical
Cancer
Research

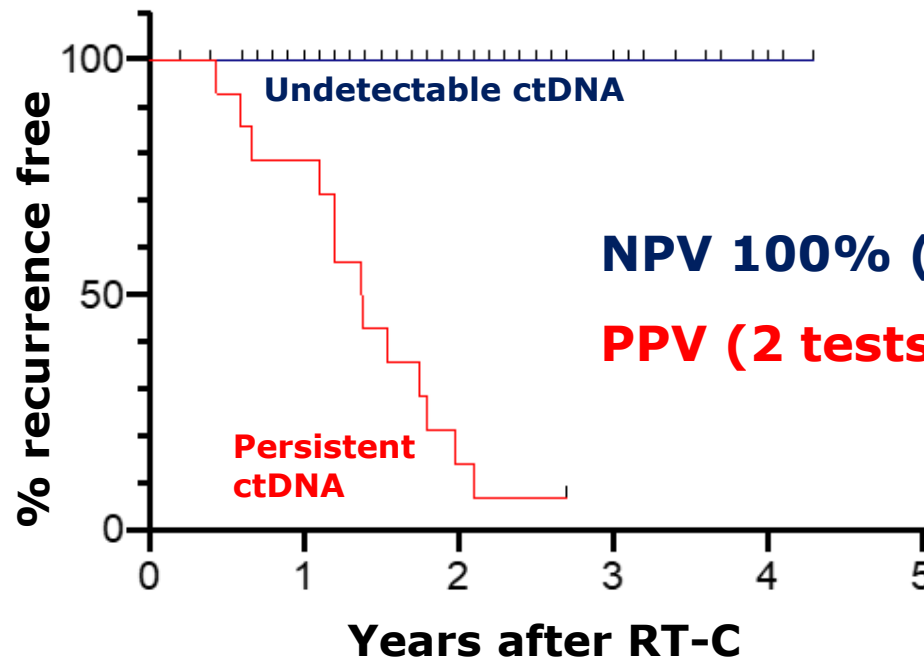
2019

Rapid Clearance Profile of Plasma Circulating Tumor HPV Type 16 DNA during Chemoradiotherapy Correlates with Disease Control in HPV-Associated Oropharyngeal Cancer

Bhishamjit S. Chera^{1,2}, Sunil Kumar^{1,2}, Brian T. Beaty¹, David Marron^{2,3}, Stuart Jefferys^{2,3}, Rebecca Green¹, Emily C. Goldman¹, Robert Amdur¹, Nathan Sheets⁵, Roi Dagan⁶, D. Neil Hayes⁷, Jared Weiss^{2,6}, Juneko E. Grilley-Olson^{2,8}, Adam Zanation⁹, Trevor Hackman⁹, Jeffrey M. Blumberg⁹, Samip Patel⁹, Mark Weissler⁹, Xianming M. Tan^{2,10}, Joel S. Parker^{2,3,11}, William Mendenhall⁴, and Gaorav P. Gupta^{1,2}



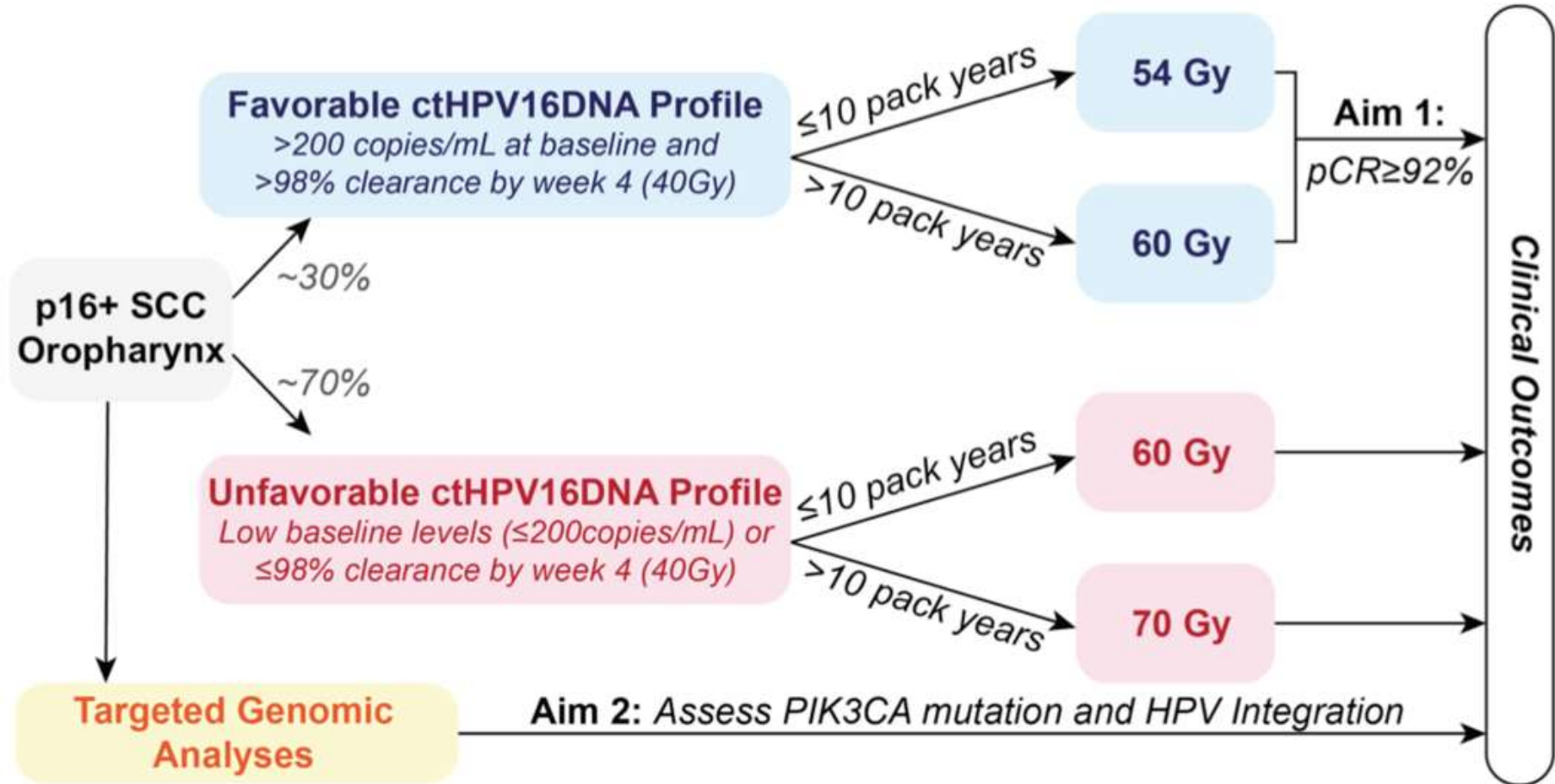
115 pts
HPV-pos Orophx ca
Txed with RT +/- C



NPV 100% (0/87)

PPV (2 tests) 94% (15/28)

D-I Study #4:



SAM Question

A serum marker that is showing promise in predicting cure following radiotherapy for HPV-Associated oropharynx cancer is:

Tumor HPV DNA

Questions?