

Should We Alter Therapy for HPV-Related Oropharynx Cancer?

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Current and New Concepts in the Biology and Treatment of
Head and Neck Cancer Review Course
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Overview

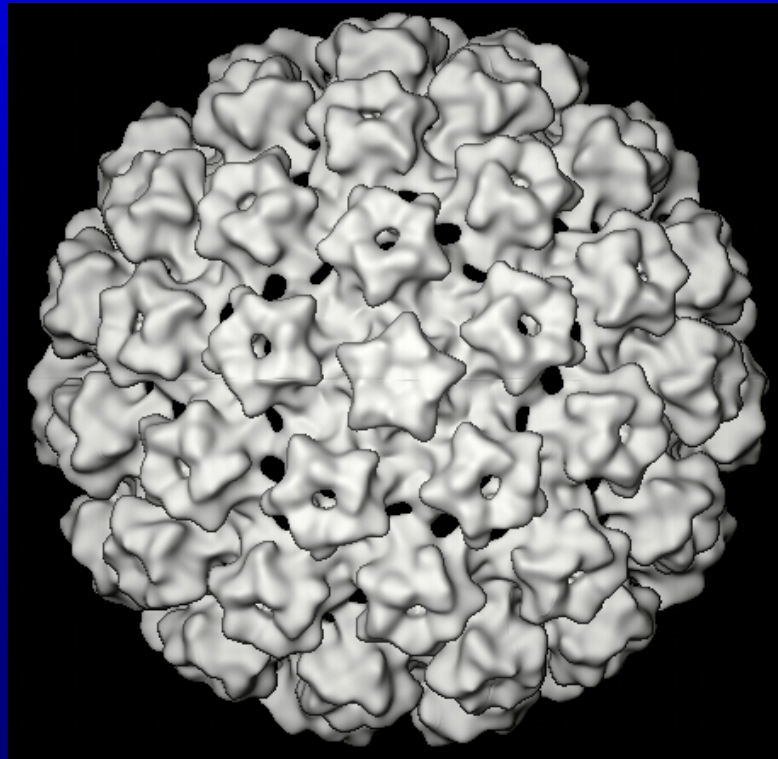
- Nature of the HPV Problem
- Response to Specific Standard Therapies Based on HPV Status
- What Are the Options for Altering Therapy?
- Do the Options Make Sense and How Should We Proceed?

Underlying Question

You Have a Patient in Your Office with a T3/4 N2b SCC of the Base of Tongue. How Would You Alter Treatment If This Were:

- A) 55 yo with a 60 py Smoking History, Drinks 2-3 Beers per Day and Has An HPV- Tumor
- B) 45 yo Non-Smoker, Drinks Rarely and An HPV+ Pathology Report

HPV Infection As a Causative Agent in Squamous Cell Cancer of the Head and Neck (SCCHN)



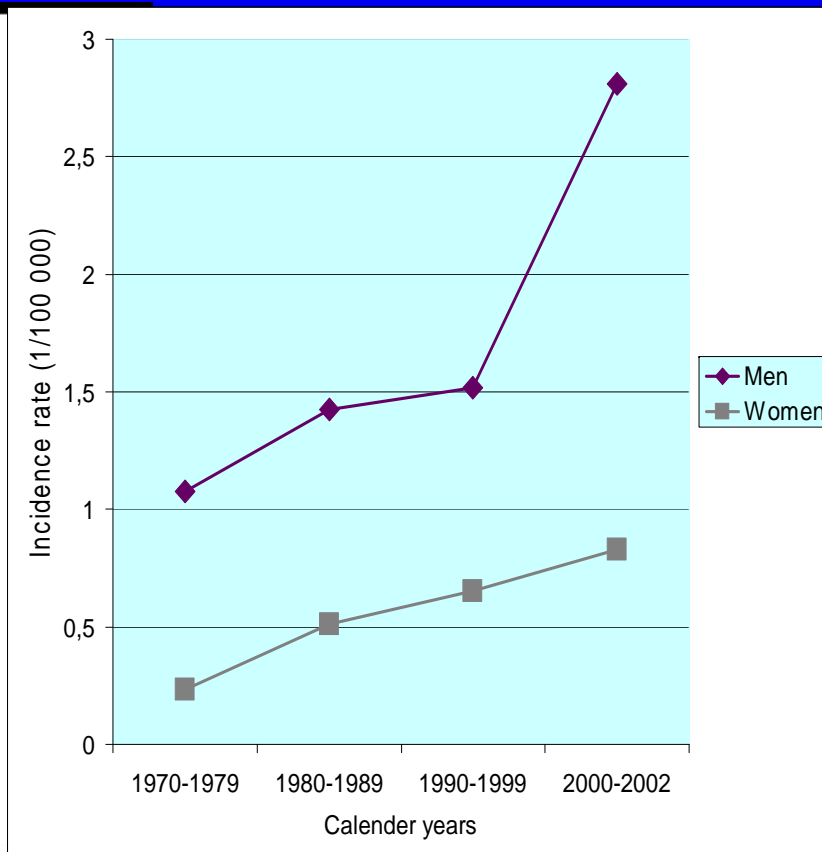
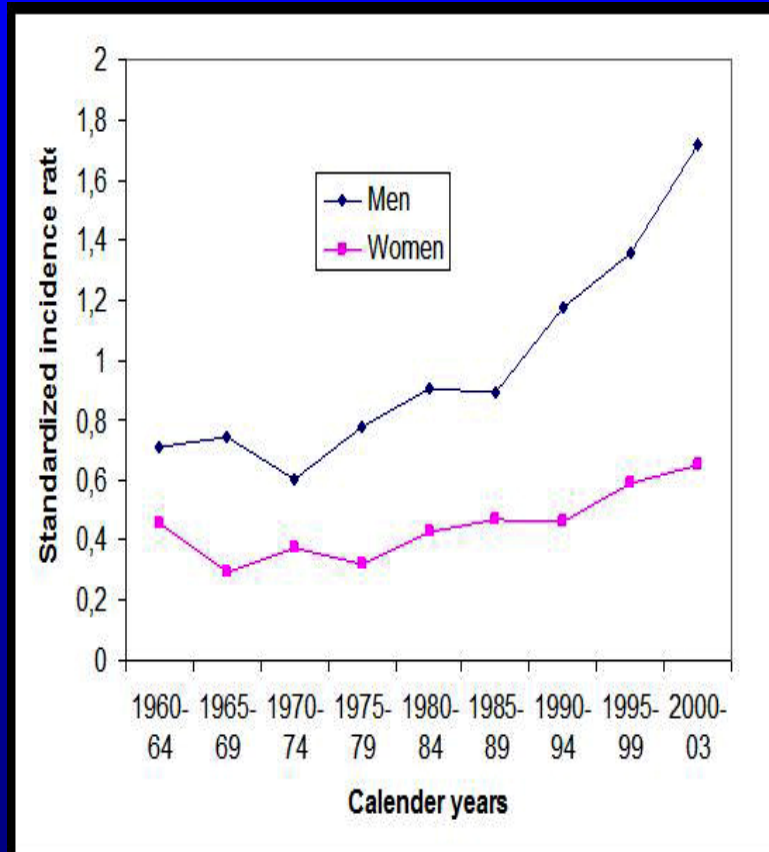
Epidemiology of HPV Infection in SCCHN

- Patient Population Tends to be Younger
- Tobacco, Alcohol Established Agents for SCCHN, But Are Not Correlated w/HPV Related Disease
- HPV- Cancers Associated with Measures of Tobacco, Alcohol Use and Oral Hygiene
- HPV Related Cancers Correlated with Measures of Sexual Behavior, Intensity of Use of Marijuana, **Not** w/Measures of Tobacco, Alcohol or Oral Hygiene

Epidemiology of HPV Infection in SCCHN

- Evidence of Increasing Prevalence of Oropharynx Cancers, As Incidence of Other SCCHN are Decreasing
- Proportion of HPV+ SCCHN Is Increasing
- Preferentially Identified in SCC of the Oropharynx—
Tonsil and Base of Tongue Primaries [Note: Has also
Been Identified in NPX]
- Preventative Vaccine Available—Role In Disease of
Adults, When Infection Is In Teens?

Epidemiology of HPV Infection in SCCHN—Tonsil Ca in Sweden



Epidemiology of HPV Infection in SCCHN—Tonsil Ca in Sweden

Years	HPV+/Total	P-Value
1970-79	7/30 (23%)	-
1980-89	12/42 (28%)	0.79
1990-99	48/84 (57%)	0.0025
2000-02	32/47 (68%)	<0.0001
Total	99/203 (49%)	

HPV Infection And Response to Therapy

- In 2010, We All “Know” HPV+ Patients w/SCCHN Fare Better Than HPV- Patients
- How Does This Improved Response Relate to the Type of Therapy Used?
- Is HPV+ SCCHN a Different Disease Compared with the Classic, HPV- Tobacco/Alcohol Related Entity? Yes, It is a Distinct Entity Based On Epidemiology and Response to Therapy

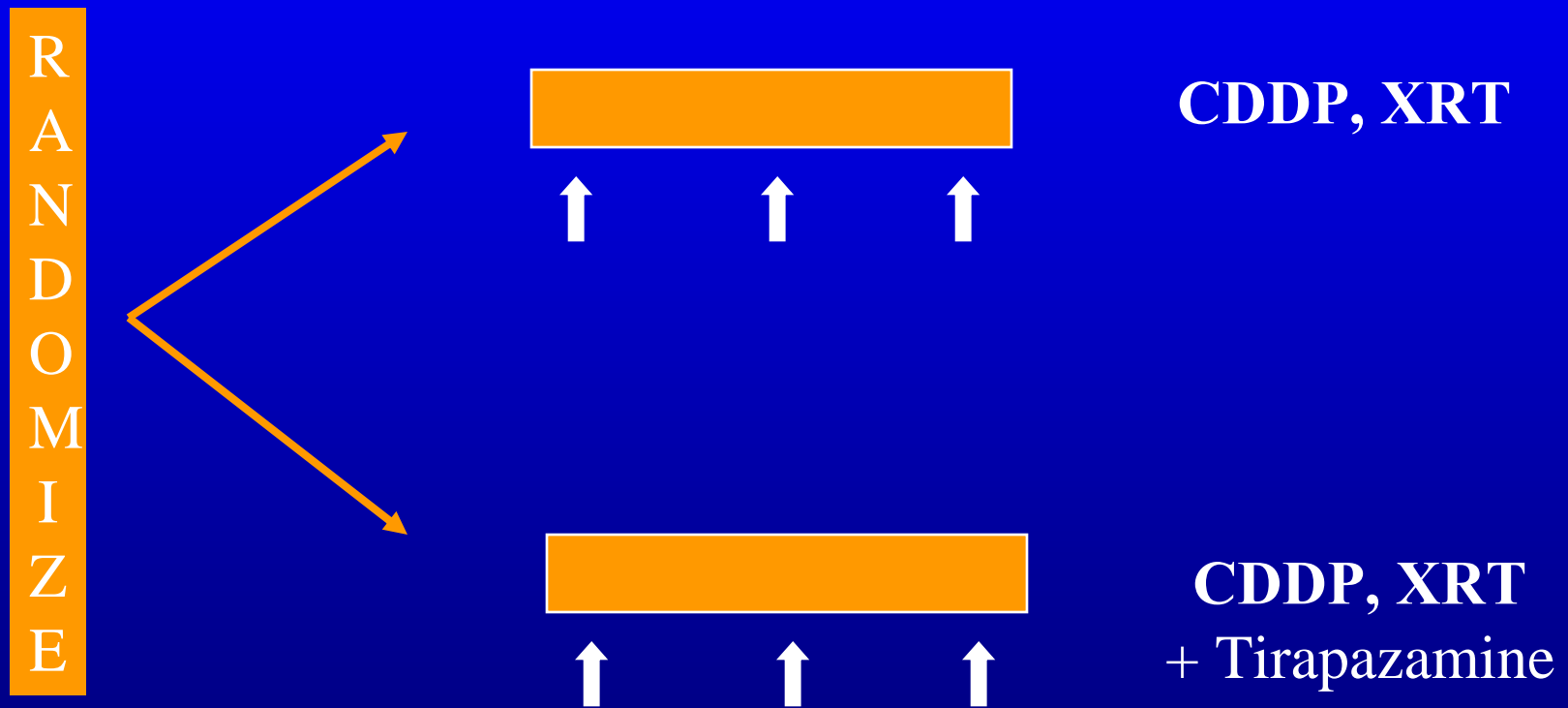
HPV Infection And Response to Therapy—Overall Survival

Modality	HR	Range	Reference
Radiation (DAHANCA)	0.44	0.28-0.68	Lassen, JCO 2009
ChemoRT (TROG)	0.29	NR	Rischin, ASCO 2009
ChemoRT (RTOG 0129)	0.44	0.29-0.69	Gillison, Submitted
Sequential (ECOG)	0.36	0.15-0.85	Fakhry, JNCI 2008
Sequential (TAX324)	0.20	0.10-0.38	Posner, Pers. Comm.

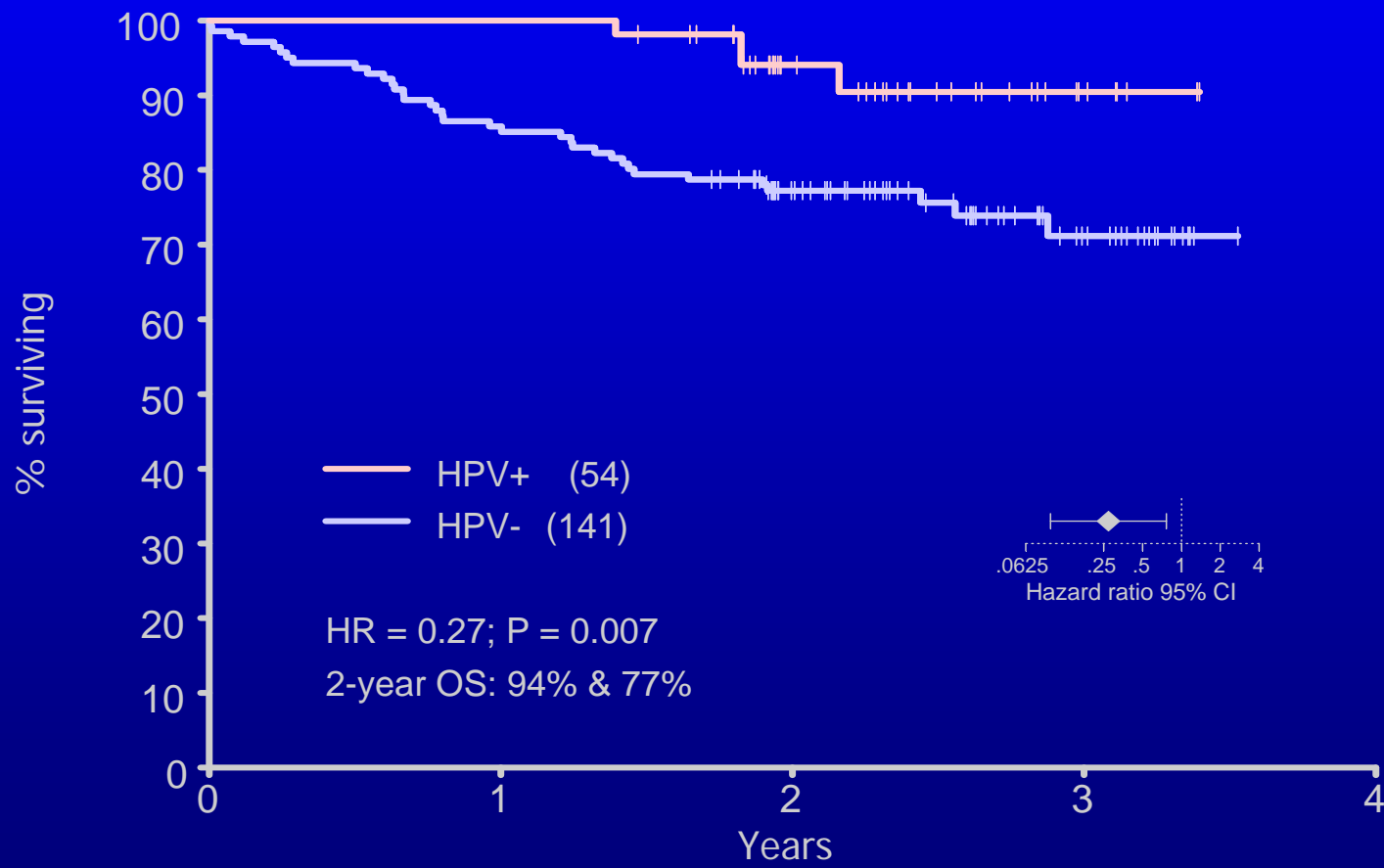
HPV Infection And Response to Therapy—Overall Survival

Modality	Time	HPV+	HPV-	p
Radiation (DAHANCA)	5 yrs	62%	26%	0.0003
ChemoRT (TROG)	2 yrs	94%	77%	0.007
ChemoRT (RTOG 0129)	3 yrs	79%	46%	0.002
Sequential (ECOG)	2 yrs	95%	62%	0.005
Sequential (TAX324)	5 yrs	83%	35%	<0.001

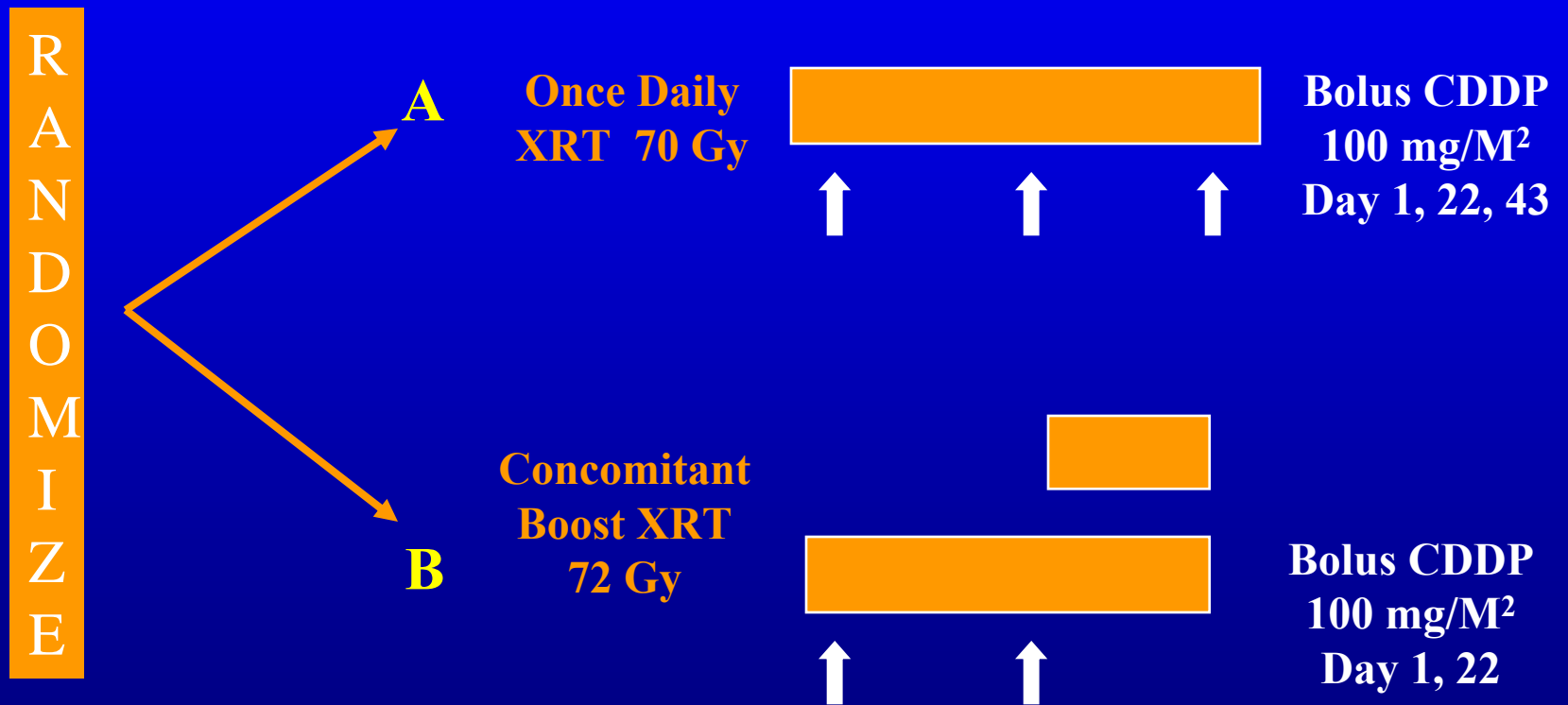
TROG 02.02: Bolus CDDP w/XRT \pm Tirapazamine



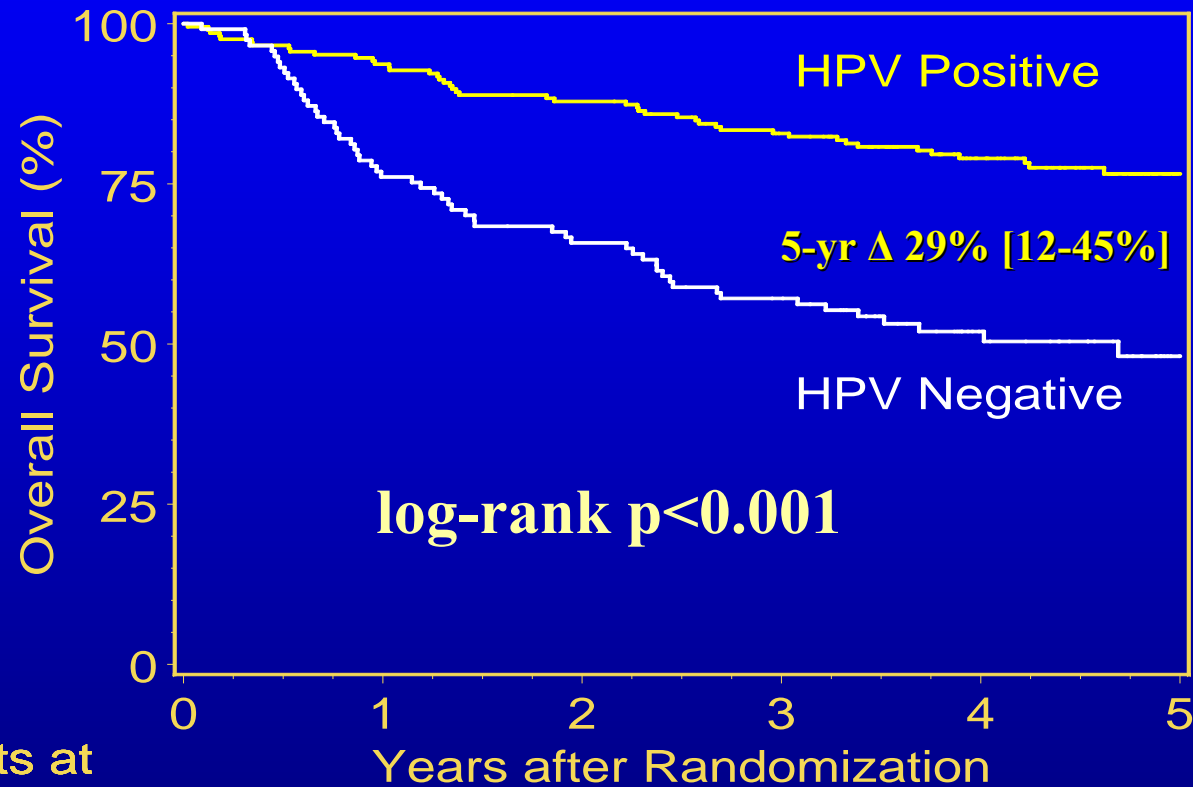
TROG 02.02: Bolus CDDP w/XRT + Tirapazamine



RTOG H0129: Bolus CDDP with SF vs. ACC-CB



RTOG H0129: Bolus CDDP with SF vs. ACC-CB—OS HPV



Patients at Risk

HPV Pos. 206
HPV Neg. 117

193
89

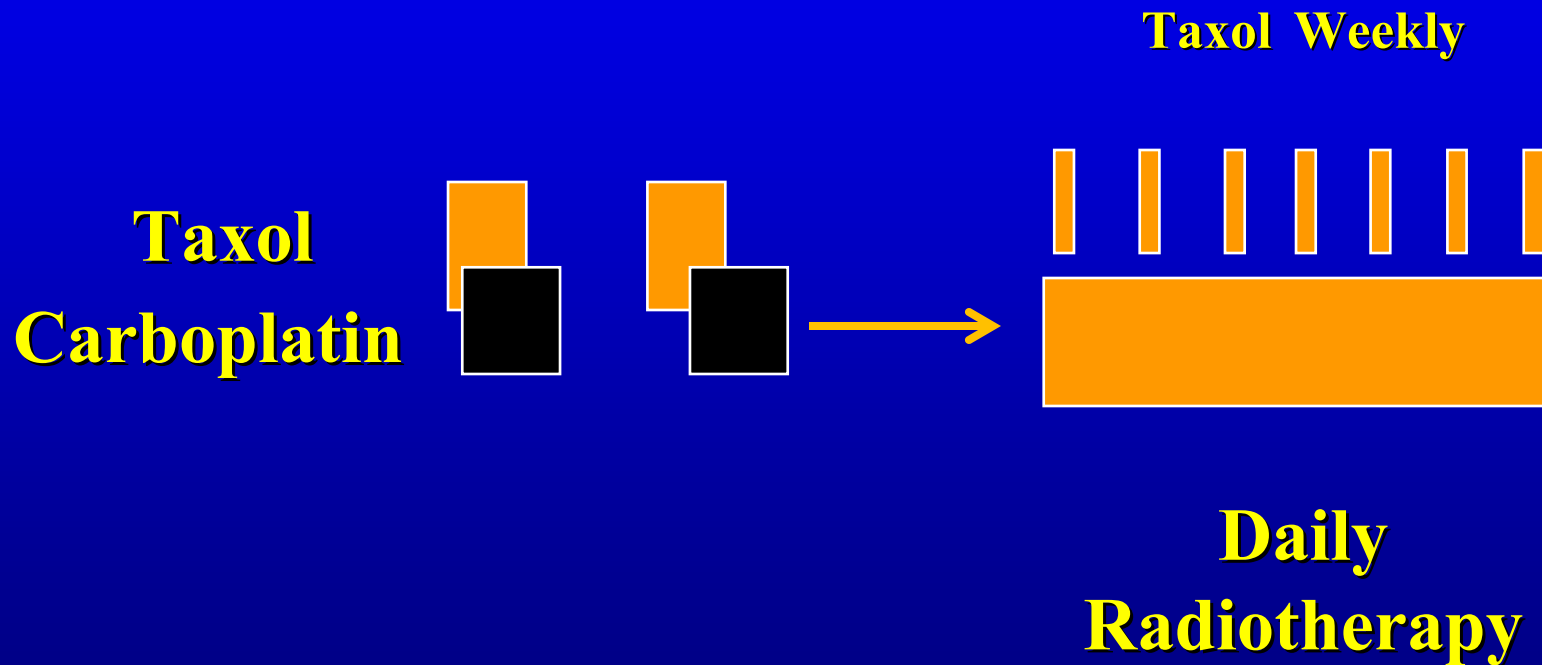
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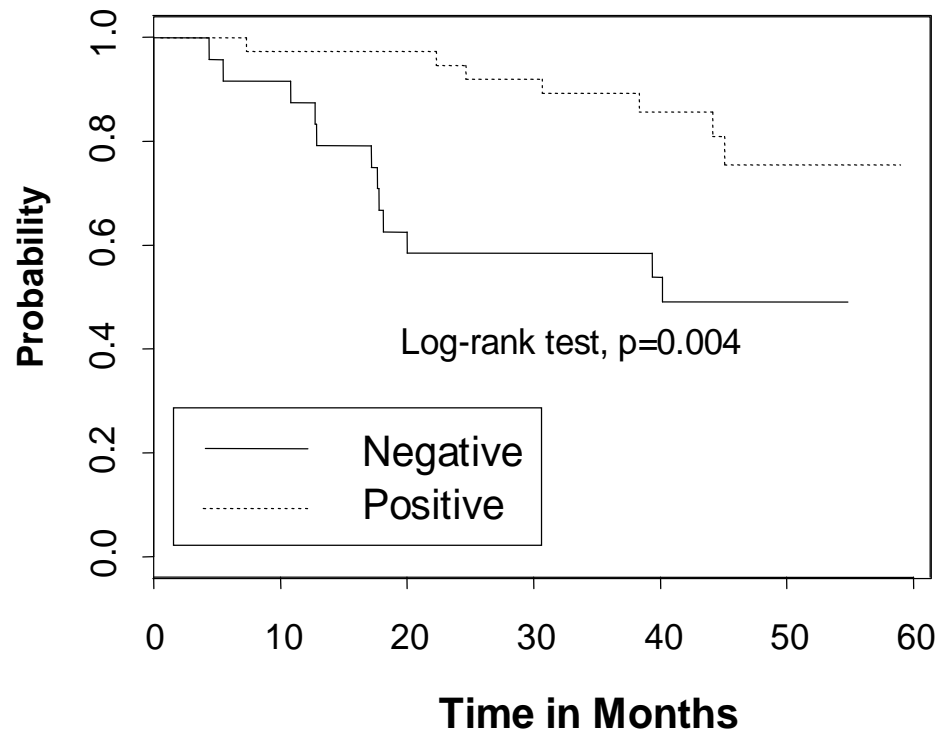
119
34

30
9

ECOG 2399: Sequential Therapy



ECOG 2399: Sequential Therapy



ECOG 2399: Sequential Therapy

	HPV +	HPV -
Number	38	24
Progression	5 (13%)	9 (38%)
 LRF	2 (5%)	8 (33%)
 DM	3 (8%)	1 (4%)
Deaths	7 (18%)	12 (50%)

HPV Infection And Response to Therapy

- HPV+ Respond Better Than HPV- Patients, Independent of the Therapy Used
- This Appears to Be A Distinct Disease Entity, Based on Epidemiology, Response to Therapy
- What Are the Implications of This?
- What Should Be the Basis for Our Treatment Decisions?

What Is the Origin of the Difference In HPV-Related Outcomes?

- RTOG 0129—Ph III Study Concurrent ChemoRT
 - 70 Gy/35 Fx, Bolus CDDP X3
 - 72 Gy/42 Fx/6 Wks, Bolus CDDP X2
- 2 Year Data Separated by HPV Status Presented by Gillison et al, at ASCO 2009 and ASTRO/ASCO Head/Neck Conference 2/10 Phoenix, AZ
- Examination of Patterns of Failure

HPV Infection And Response to Therapy—Patterns of Failure

	HPV+	HPV-	p
OS	87.9%	65.8%	<0.001
PFS	71.8%	50.4%	<0.001
LRF	13.6%	24.8%	0.004
DM	9.7%	12.9%	0.26
2 nd Primary	3.9%	11.1%	0.01
A-D 2 nd Primary	2.9%	7.7%	0.04

What Is the Origin of the Difference In HPV-Related Outcomes?

- What Do These Data Tell Us?
- Basis For Improvement In HPV+ Patients:
 - Increased Risk of 2nd Primaries for HPV-
 - Better LR Control for HPV+ Patients
- Non-Significant Differences
 - Rate of Distant Metastases

What Are the Options for Altering Therapy Based on HPV Status?

- We “Know” These Patients Do Better, So Should We Recommend That Intensity of Therapy Be Decreased?
- Is the Approach That Patients Are Younger So We Should Prioritize Minimizing Toxicity? Or, Since They Are Younger, Do We Intensify Therapy to Optimize Years of Life?
- What Information Might Help Us to Make a Rational Decision? Are There Additional Prognostic Factors?

Identification of Prognostic Factor for HPV+ (-) Patients

- Within the Group of HPV+ Patients, Are There Other Important Prognostic Factors?
- ASCO 2009 Head Neck Session: Additional Stratification Factors: p16, Tobacco Data
- Will This Allow Us to Further Identify Groups That Would Be Appropriate for De-intensification of Therapy?

Prognostic Factor for HPV+ (-)

Patients: Role of p16

- Stage III/IV Treated with Radiation, CDDP \pm Tirapazamine
 - OPX Primary, >60 Gy, No XRT Deviations
 - HPV16/18 In Situ, p16 by IHC
 - Population Studied: 384 (of 861) OPX, 195 for HPV, 186 for p16, 173 Both
- Effect of HPV (+/-)
 - 2 yr OS 94% vs 77% (p=0.007)
 - After Adjusting for Stage, etc: OS HR 0.29 (p=0.018)
- Effect of p16 (+/-)
 - 2 yr OS 92% vs 75% (p=0.003)
 - After Adjusting for Stage, etc: OS HR 0.39 (p=0.013)

Prognostic Factor for HPV+ (-) Patients: Role of p16

Hazard Ratios (% Patients)

	p16+	p16-
HPV+	0.35 (26%)	0 (2%)
HPV-	0.73 (33%)	1.79 (39%)

Prognostic Factor for HPV+ (-)

Patients: Role of Tobacco

- Stage III/IV Treated on Two ChemoRT Trials
 - OPX Primary, HPV, Tobacco Hx Assessed (P-Y, Never, Former, Current)
 - Population Studied: 124 Pts, 100 (81%) HPV+, 24 (19%) HPV-
- For HPV+
 - Overall, **22 (22%) Progression**
 - Never T Users—**3% Progression**; 28/32 NED, 1 Died Lung Mets, 3 of Other Causes
 - Former T Users—37/46 Alive
 - >20 yr stopped, **12% (3/26) w/Progression**, [2 DM, 1 2nd 1^o]
 - <20 yr stopped, **35% (7/20) w/Progression**, [3 LR, 3 DM, 1 2nd 1^o]
 - Current T Users, **36% (8/22) w/Progression** 15/22 Alive,
- For HPV-
 - Overall, **50% 12/24 w/Progression**
 - Current T Users 8/17 w/Progression

Prognostic Factor for HPV+ (-) Patients: Role of Tobacco

- RTOG 0129—Ph III Study Concurrent ChemoRT
 - 70 Gy/35 Fx, Bolus CDDP X3
 - 72 Gy/42 Fx/6 Wks, Bolus CDDP X2
- For HPV+/- 2 year OS: 87.9% vs 65.8% ($p < 0.001$)
- Examine Stratification Based On Extent of Prior Smoking: $>$, $<$ 20 Pack-years

Prognostic Factor for HPV+ (-) Patients: Role of Tobacco

	HR	95% CI	2 year OS
HPV+, <20 py	1.0	-	95%
HPV+, >20 py	1.91	1.20-3.05	80%
HPV-, <20 py	2.25	1.44-3.50	71%
HPV-, >20 py	4.30	2.40-7.71	63%

Considerations In Altering Therapy

- Since These Patients (HPV+, +/- Further Stratification), Do So Well and Standard Treatment With Chemotherapy and Radiation Has Known Toxicities, Should We Decrease Intensity of Therapy?
- When We Go Too Low, We May Find Out by Sacrificing Survival (DFS, OS)
- Never Recommend A De-Escalation Approach Ad Hoc; Currently, There Is No Basis For Doing This
- Dose De-Escalation Trials Are On the Horizon....

RTOG Study Concept

- “Phase II-III Trial of Moderate Dose De-Escalation of Chemotherapy and Radiation in Favorable Risk, Locally Advanced, HPV-Related Oropharynx Cancer”
- **Hypothesis to Be Tested:** Modest Dose Reductions of Chemotherapy (33%) and RT (14%) Will Maintain Tumor Control, Including DM with Decreased Toxicity and Improved QoL/Function
- Phase II Objectives
 - Choose Experimental Arm (PFS, Toxicity) for Phase III Study
 - Comparison of Sequential Therapy w/Concurrent; Confirm Favorable Outcomes for HPV+/Minimal Smoking Pts
- Phase III Objectives
 - Examine De-intensified Treatment with Standard of Care in Terms of Morbidity/QoL, w/o Compromising OS

RTOG Study Concept

- Use of RTOG 0129 To Define Oropharynx Risk Groups:
 - **High Risk:** 1) HPV-, >10 py OR 2) HPV-, <10 py, T4 [46%]
 - **Intermediate Risk:** 1) HPV-, <10 py T2-3 OR 2) HPV+, >10 py, N2b-3 [71%]
- Eligibility for Proposed Trial (Low Risk):
 - Currently Defined Oropharynx “Low Risk Group” [93%]
 - Oropharynx Primary, p16+
 - <10 py and T2, N2a/N3 OR T3-T4, any N
 - >10 py and T2N2a OR T3-4 w/N0-N2a

RTOG Study Concept

- Arm 1 (Control): Accelerated RT—70 Gy in 6 Weeks, CDDP (100 mg/M² X2)
- Arm 2 (Reduced Dose RT): 60 Gy in 6 Weeks, Weekly CDDP (35 mg/M²/week X6)
- Arm 3 (Modified Induction): Induction TPF X2, Reduced Dose Conventional RT 60 Gy in 6 weeks, IF CR/PR/SD at Primary Site
- For Phase II, Patients Randomized to One of 3 Arms w/Plan to Choose One of the Two Experimental Arms for the Phase III Trial

DFCI Trial—Sequential Therapy w/Radiation Dose De-Escalation

- Primary Objective: LRC at 2, 5 Years
- Secondary Objectives:
 - PFS at 2, 5 Years
 - OS at 2 Years
 - Acute/Chronic Toxicity of Reduced Rads at 2, 5 Years
- Model: Use of Intermediate Dose Assessment to Determine Patients for Dose De-Escalation

DFCI Trial—Sequential Therapy w/Radiation Dose De-Escalation

- Basic Concept Is to Use Response to Induction To Stratify Dose De-Escalation Candidates
- Eligible: HPV16 & p16 +, Stage III/IV w/o DM
- Treatment Plan:
 - TPF Induction X3 Cycles
 - Clinical/Radiographic Response Assessment
 - Concurrent XRT/Carbo/Erbix
 - Radiation Dose Determined by Response to Induction

DFCI Trial—Sequential Therapy w/Radiation Dose De-Escalation

- Response Assessment
 - If CR 1°/CR Neck, Reduced Dosing
 - If PR at Either Site, Need to Analyze Further
 - Primary: No Residual Mass; Distorted Anatomy Accepted
 - Nodes: PET, Size Criteria
- Radiation Dosing (w/ Concurrent Carbo/Erbitux)
 - **Standard:** 70 Gy “GTV”, 64/60 CTV (35 Fx)
 - **Reduced:** 60 Gy “GTV”, 60/54 CTV (30 Fx)
w/Reduction in Normal Tissue Dose Constraints

Underlying Question

You Have a Patient in Your Office with a T3/4 N2b SCC of the Base of Tongue. How Would You Alter Treatment If This Were:

- A) 55 yo with a 60 py Smoking History, Drinks 2-3 Beers per Day and Has An HPV- Tumor
- B) 45 yo Non-Smoker, Drinks Rarely and An HPV+ Pathology Report

Summary

- HPV+ and HPV- SCCHN Represent Two Distinct Disease Entities
- HPV+ Patients Demonstrate Markedly Better Responses to a Range of Therapies
- This Differential Response Allows Us to Consider Customizing Treatment
- De-Escalation of Dose Should Only Be Considered Under Well Controlled Situations