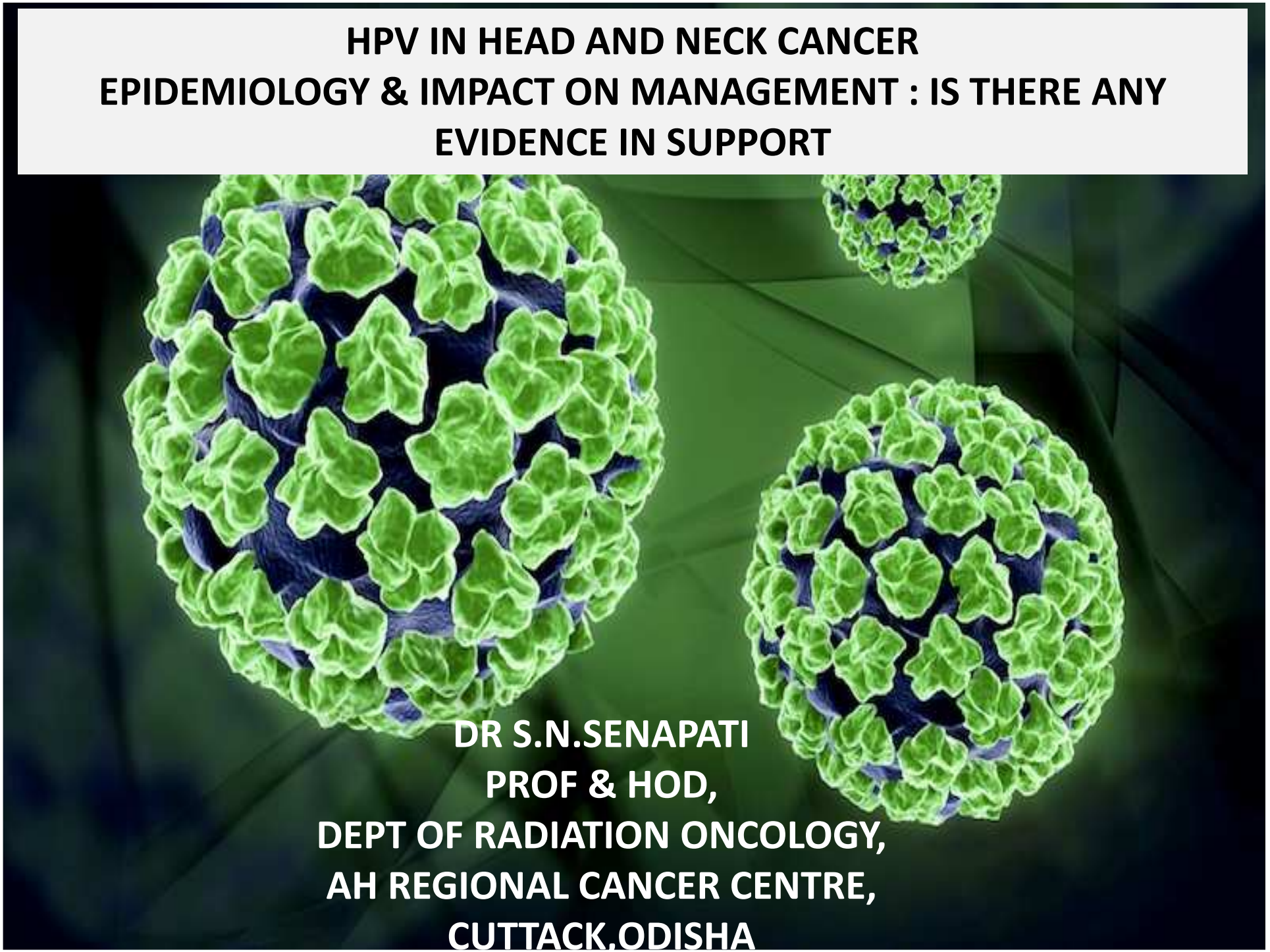
HPV IN HEAD AND NECK CANCER
EPIDEMIOLOGY & IMPACT ON MANAGEMENT : IS THERE ANY EVIDENCE IN SUPPORT



DR S.N.SENAPATI
PROF & HOD,
DEPT OF RADIATION ONCOLOGY,
AH REGIONAL CANCER CENTRE,
CUTTACK,ODISHA

HISTORY

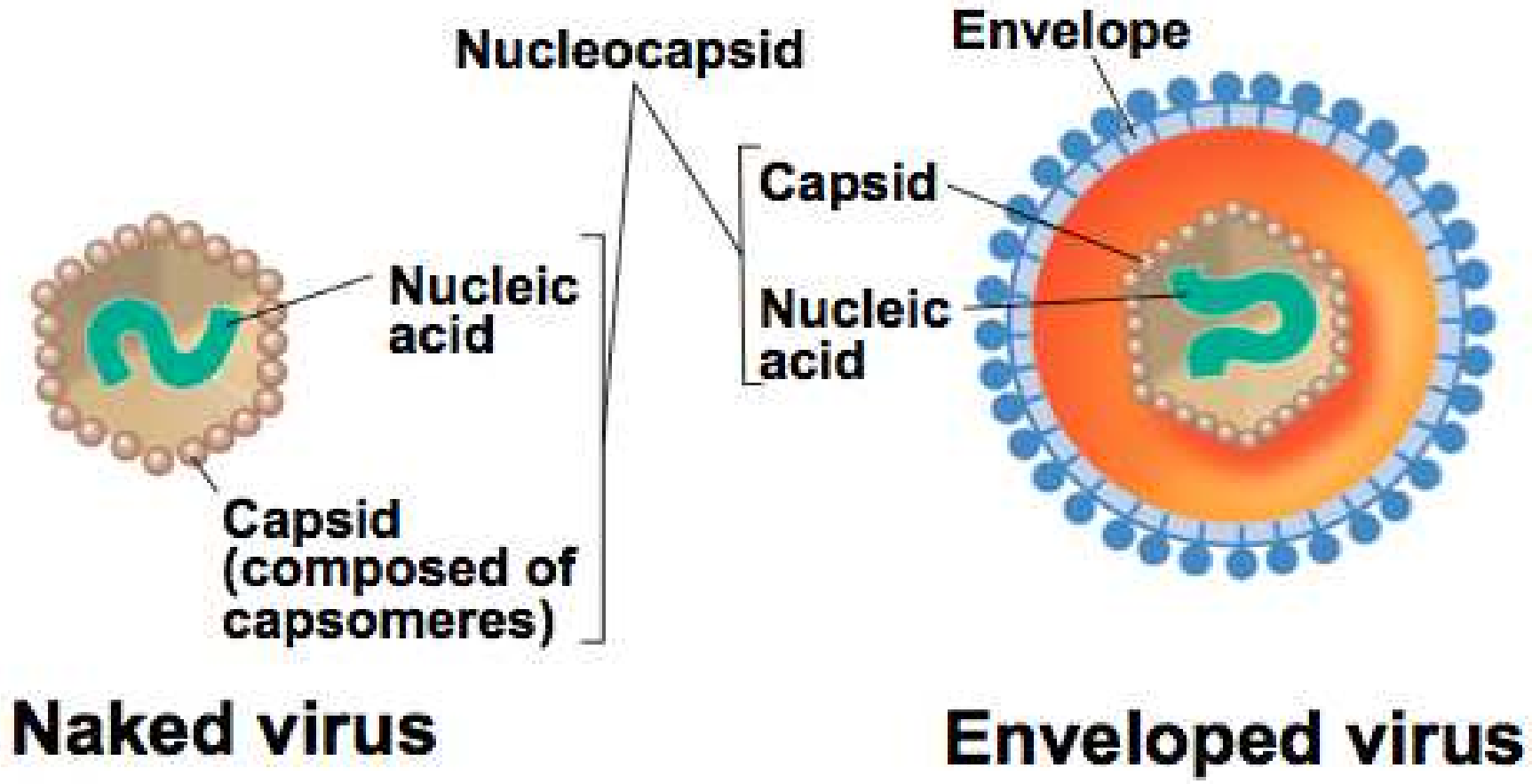
- 1983 - HISTOPATHOLOGICAL FEATURES OF HPV NOTICED IN ORAL CANCERS
- 1985 - HPV 16 DETECTED IN ORAL CARCINOMA
- 1990 - VIRAL DNA AND VIRAL ONCOGENE EXPRESSION N TONSILLAR CARCINOMAS
- 2000 - ONCOGENIC HPV 16 IN OROPHARYNX CARCINOMAS HIGH COPY NUMBER INTEGRATED INTO HOST CHROMOSOMAL DNA IN TUMOR CELL NUCLEI.

- THE TWO MAIN CAUSATIVE FACTORS IN **ABOUT 80%** OF ORAL, OROPHARYNGEAL, AND LARYNGEAL CARCINOMAS ARE SMOKING AND ALCOHOL USE.

BUT

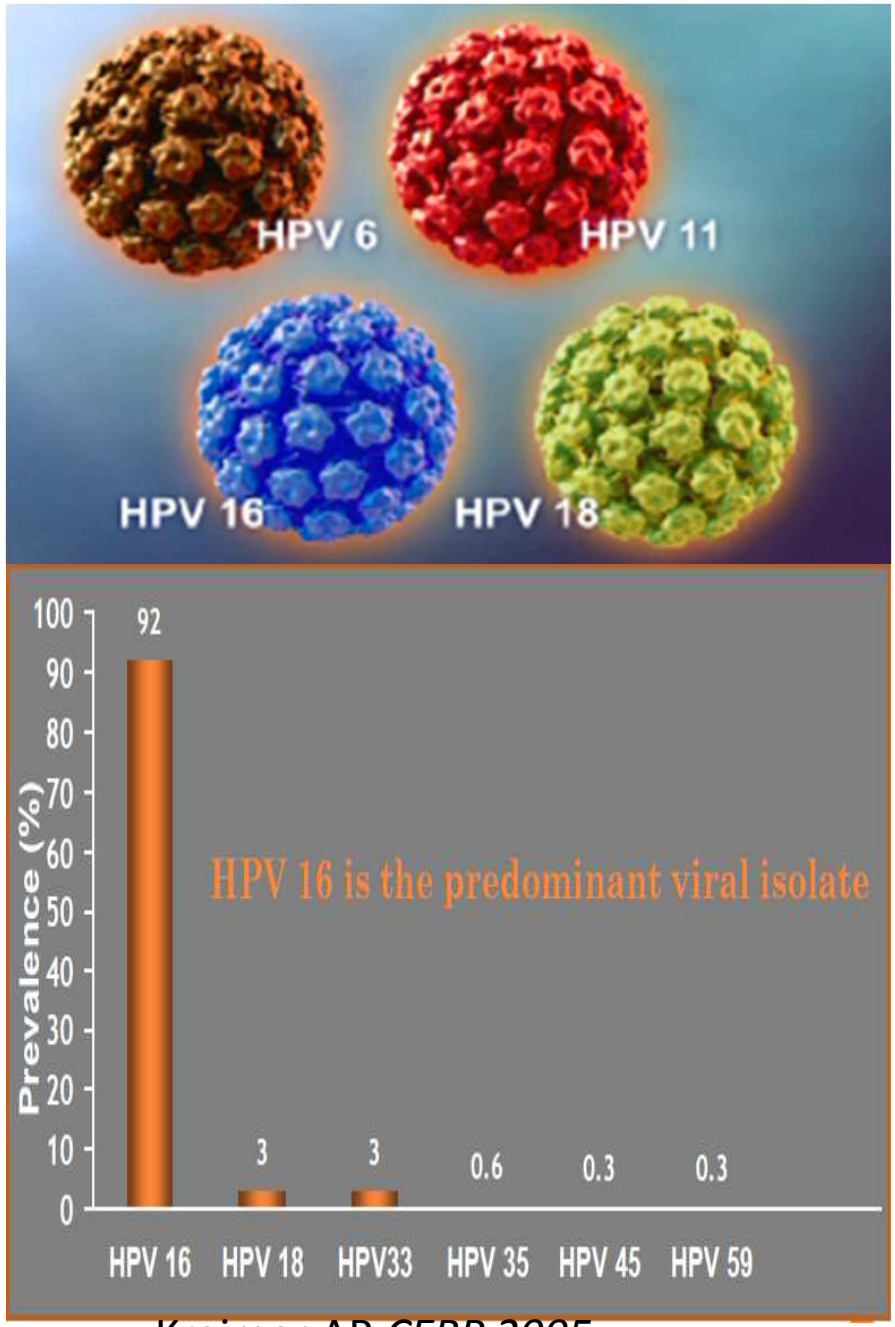
- ***20% ARE NOT RELATED TO SMOKING***
- WE ARE SEEING YOUNGER PATIENTS WITH OPSCC WHO HAVE **NEVER SMOKED**
- REASON : ***HPV***
- THIS RATE INCREASED BY **28% FROM 1988 TO 2004**, LARGELY BECAUSE OF THE ***INCREASE IN HPV-ASSOCIATED OROPHARYNGEAL CANCER*** WHEREAS *HPV-UNASSOCIATED OROPHARYNGEAL CANCER DECLINED BY 50%* OVER THE SAME TIME PERIOD**.**
- ABOUT 80% OF POPULATION HAVE HPV EXPOSURE
- 99.1% CLEAR THE INFECTION

STRUCTURE OF A VIRUS



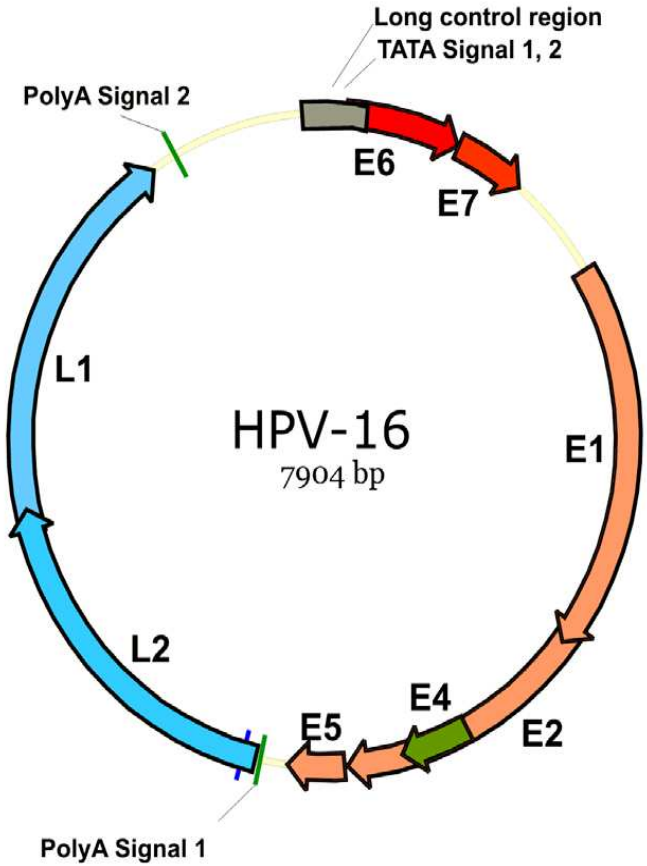
HPV

- SMALL DNA VIRUS (55 NM)
- OVER 120 UNIQUE TYPES
- HUMANS ONLY KNOWN HOST
- INFECTION COMMON
- INFECTS EPITHELIAL CELLS OF SKIN AND MUCOSA
- BENIGN WARTS, PRECANCER, CANCER
- HIGH RISK--**HPV 16, 18, 31, 33, 35, 52,58, 59, 68, 73, 82**
- LOW RISK-**HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81**

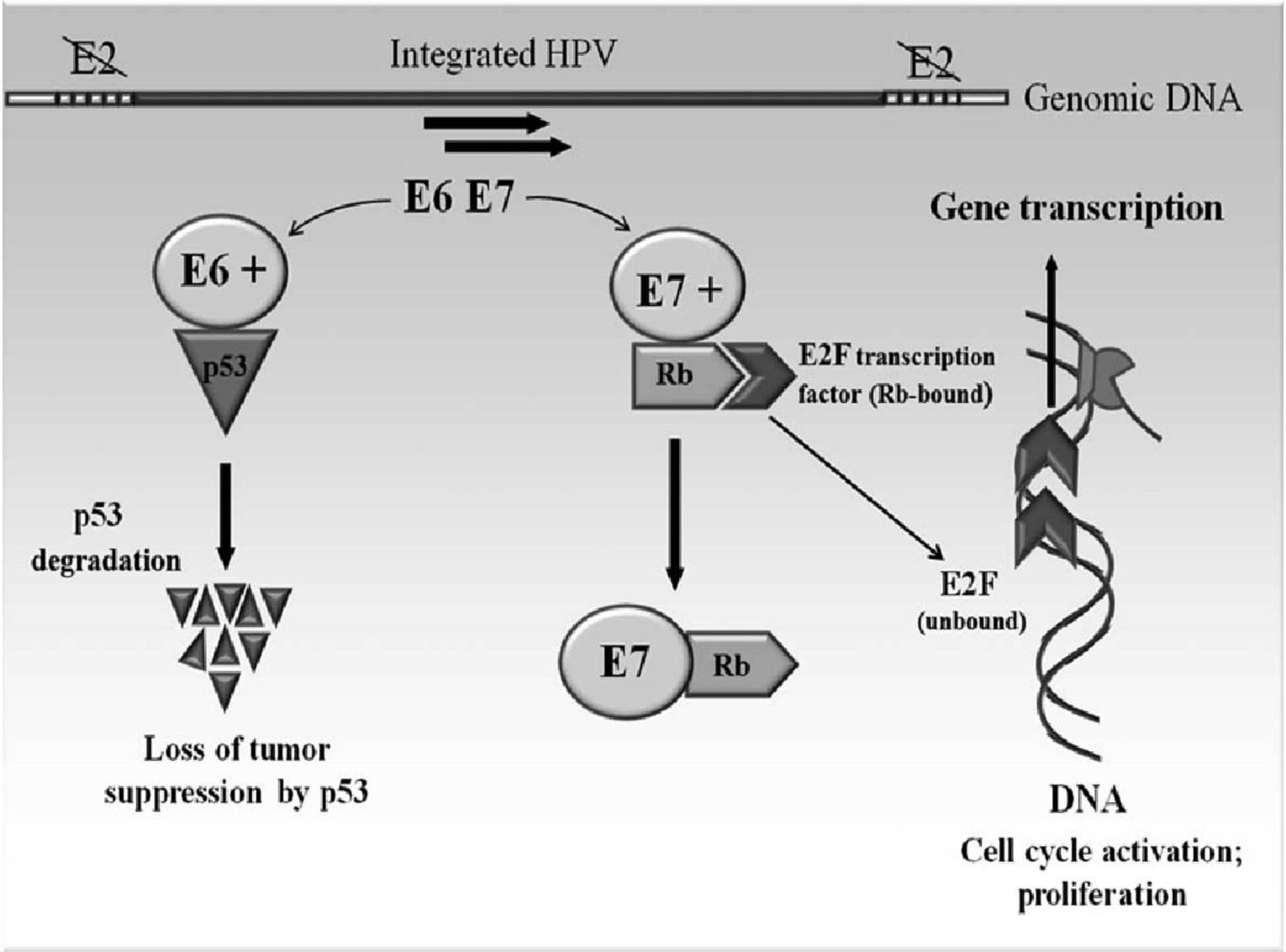


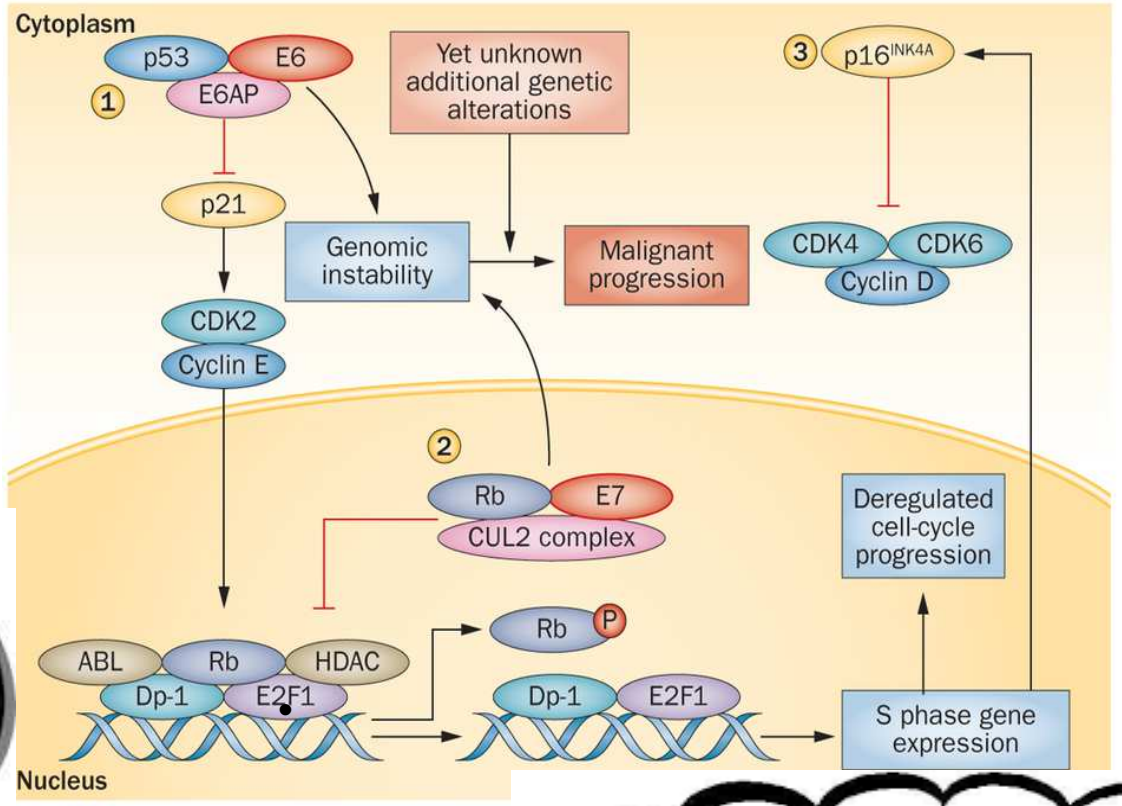
Kreimer AR *CEBP 2005*

HPV GENOME



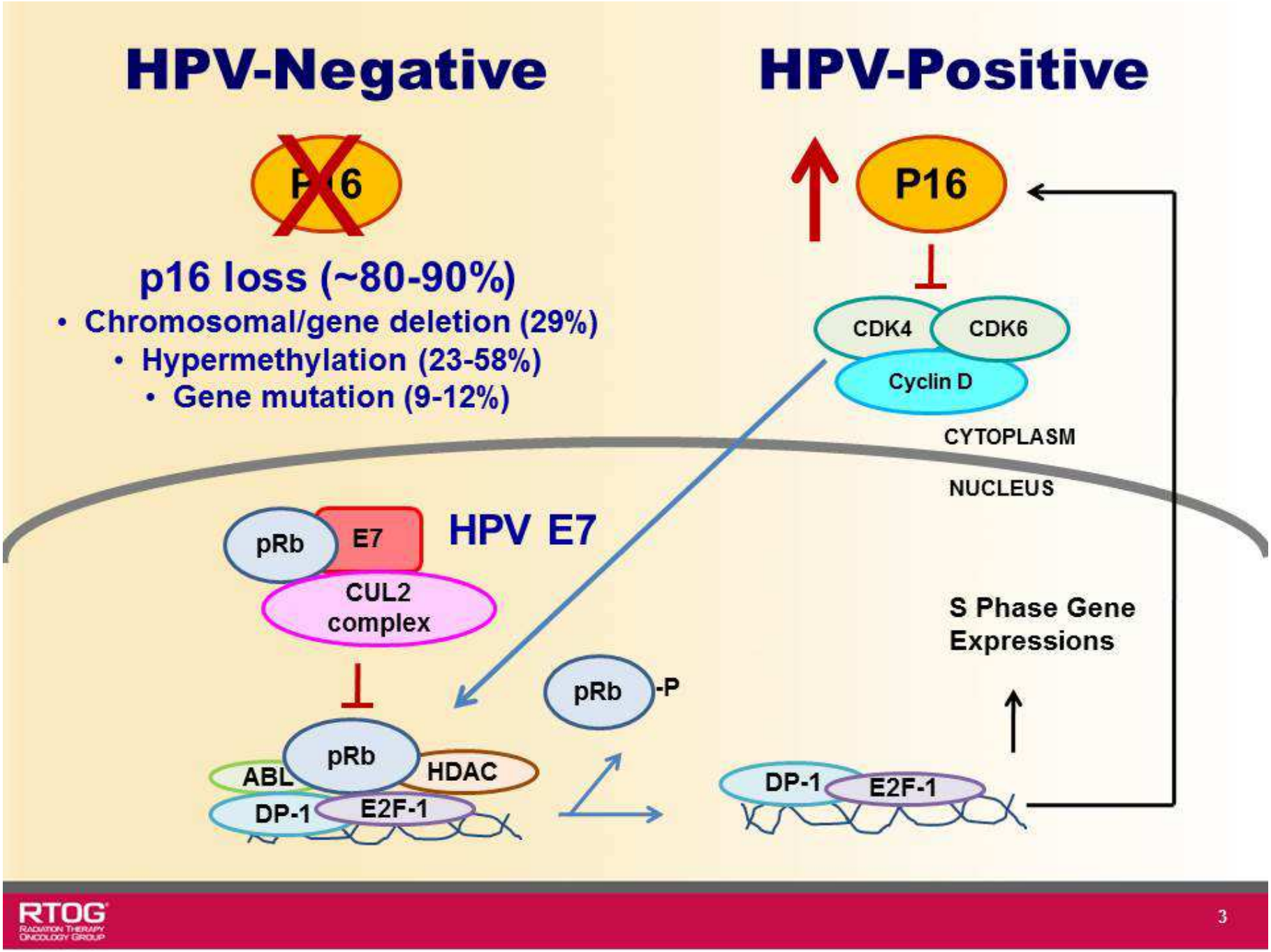
	FUNCTION
E6	DESRUCTION OF P53 TUMOR SUPRESSOR PROTEIN
E7	INACTIVATION OF pRB TUMOR SUPRESOR PROTEIN
E1	VIRAL DNA REPLICATION
E2	VIRAL DNA REPLICATION AND REPRESSION OF E6 AND E7
E5	INTERACTION WITH EPIDERMAL GROWTH FACTOR
L1	MAJOR CAPSID PROTEIN
L2	MINOR CAPSID PROTEIN


E2
Integrated HPV
E2
Genomic DNA
E6 E7
E6 +
p53
E7 +
Rb
E2F transcription factor (Rb-bound)
Gene transcription
p53 degradation
E7
Rb
E2F (unbound)
Loss of tumor suppression by p53
DNA
Cell cycle activation; proliferation



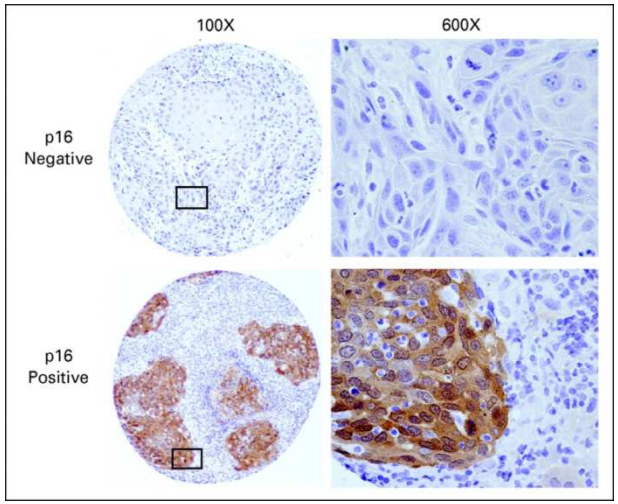
HOW THE E6 AND E7 WORKS ????

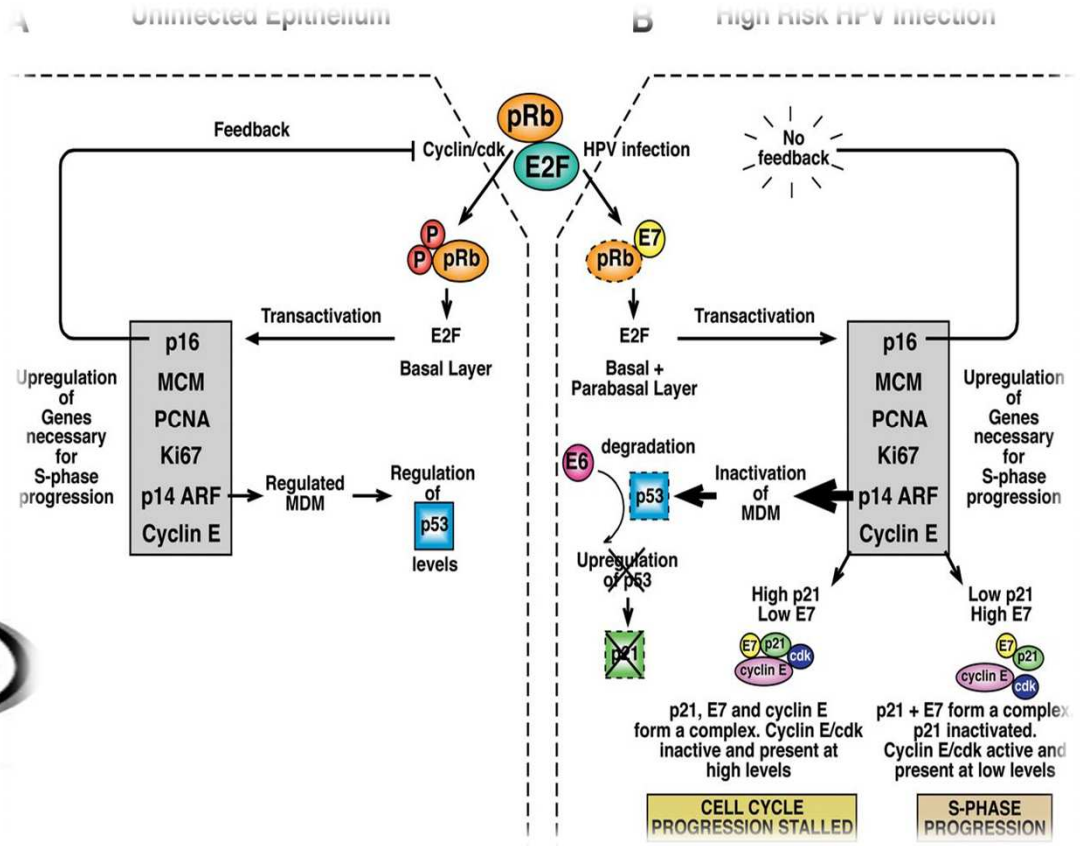
- E6 ACTS ON P53 TUMOR SUPPRESSOR GENE AND LEADS TO ITS UBIQUITIN MEDIATED DEGRADATION
- E7 BINDS WITH RB GENE INTERFERING WITH CENTROSOME DUPLICATION LEADING TO ANEUPLOIDY



Presented By Christine H. Chung, MD at 2013 ASCO Annual Meeting

HOW TO TEST HPV





- **WHY P16 IS A SURROGATE MARKER ? ISH OR PCR, WHICH IS BETTER**

- REGARDING THE DETECTION METHODS, PCR-BASED STUDIES REPORT A HIGHER PREVALENCE RATE THAN FOR IN SITU HYBRIDIZATION (ISH)-BASED RATES (34.8 VS 32.9%) ESPECIALLY IN THE OSCC SUBGROUP (OSCC PCR-BASED: 39.9%).

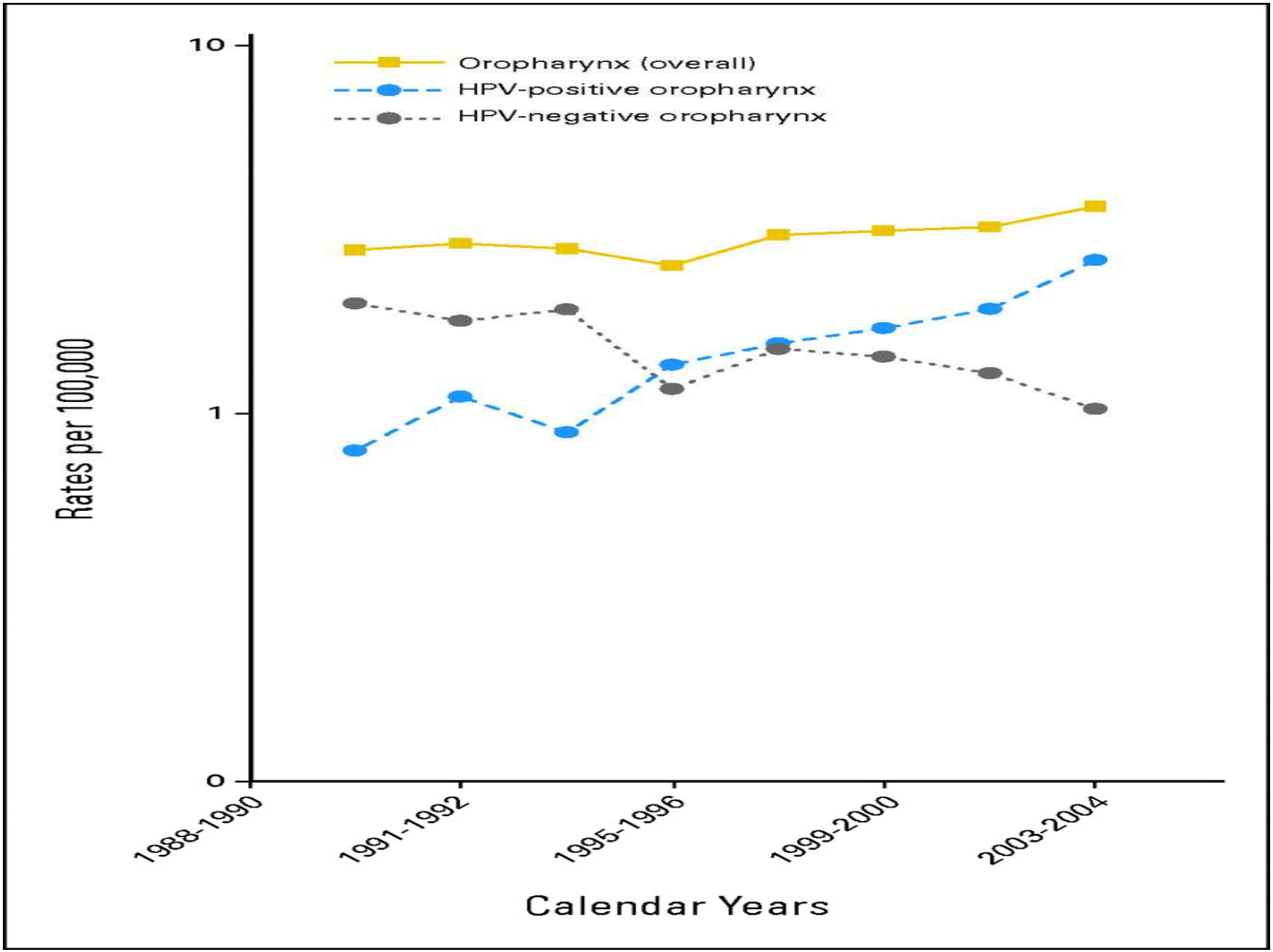
- IF + THEN HPV SUBTYPE WITH ISH OR PCR FOR CONFIRMATION

BEST METHOD OF DETECTION OF HPV-
WHAT ABOUT SALIVA???

- **HPV IN SALIVA AND ORAL EXFOLIATED CELLS HAS BEEN DETECTED IN SOME RECENT STUDIES, BUT THE SENSITIVITY AND SPECIFCITY FOR HPV-RELATED HNSCC ARE TOO LOW AND THE ROLE OF HPV DETECTION**
- **IN SALIVA AND ORAL EXFOLIATED CELLS SEEMS UNCERTAIN .**

PCR>ISH IN PARAFFIN BLOCK

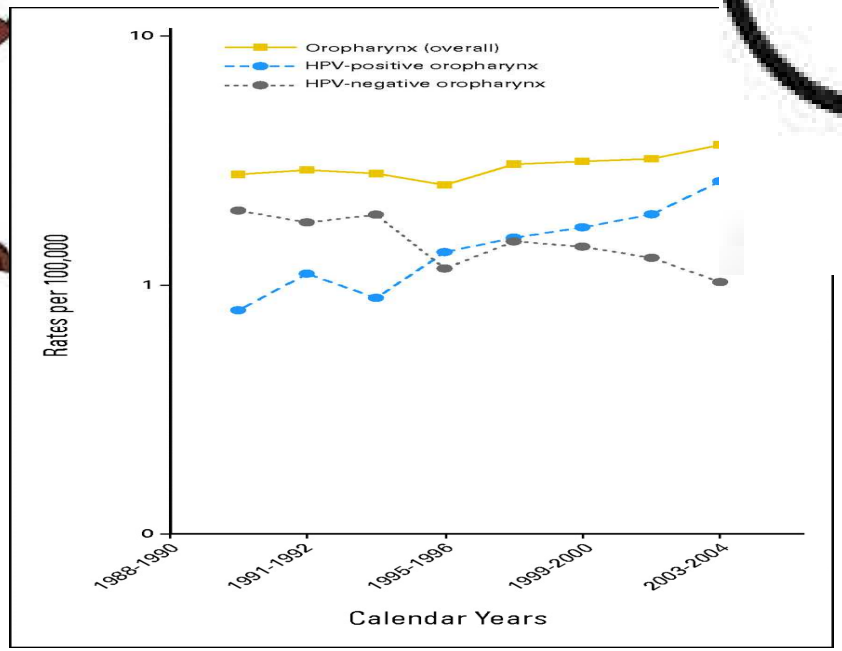
Zhao M Rosenbaum E et.al, Int J of Cancer,2005;117:605-10



Chaturvedi A K et al. JCO 2011

IS THE INCIDENCE OF HPV + OPV IS RISING TREND

1. MORE AWARENESS ABOUT THE ADVERSE EFFECT OF CIGARETTE SMOKING
2. MORE PREVALENCE
3. HIGH CLASS PEOPLE, MARIJUANA USE, ORAL SEX PATTERN



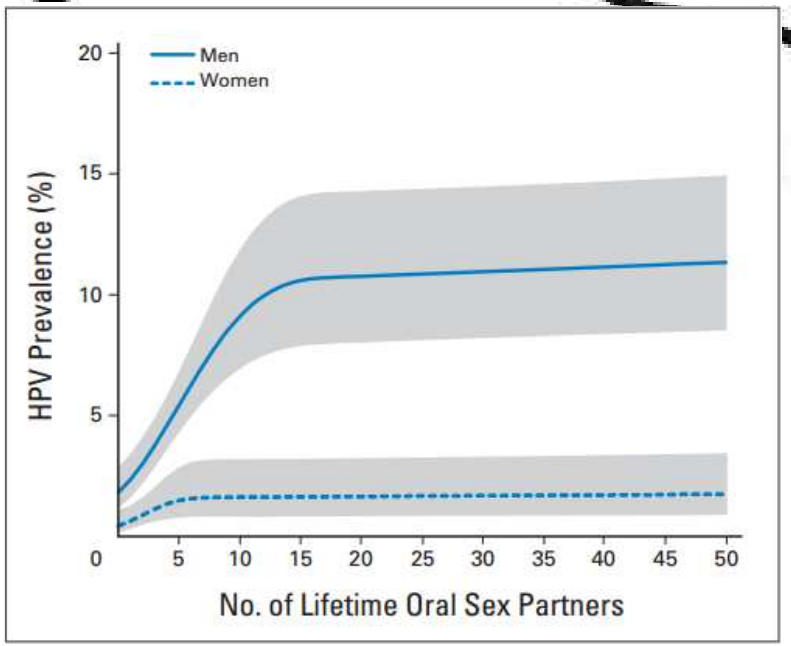
Chaturvedi A K et al. JCO 2011

MALE VS. FEMALE HPV INFECTION

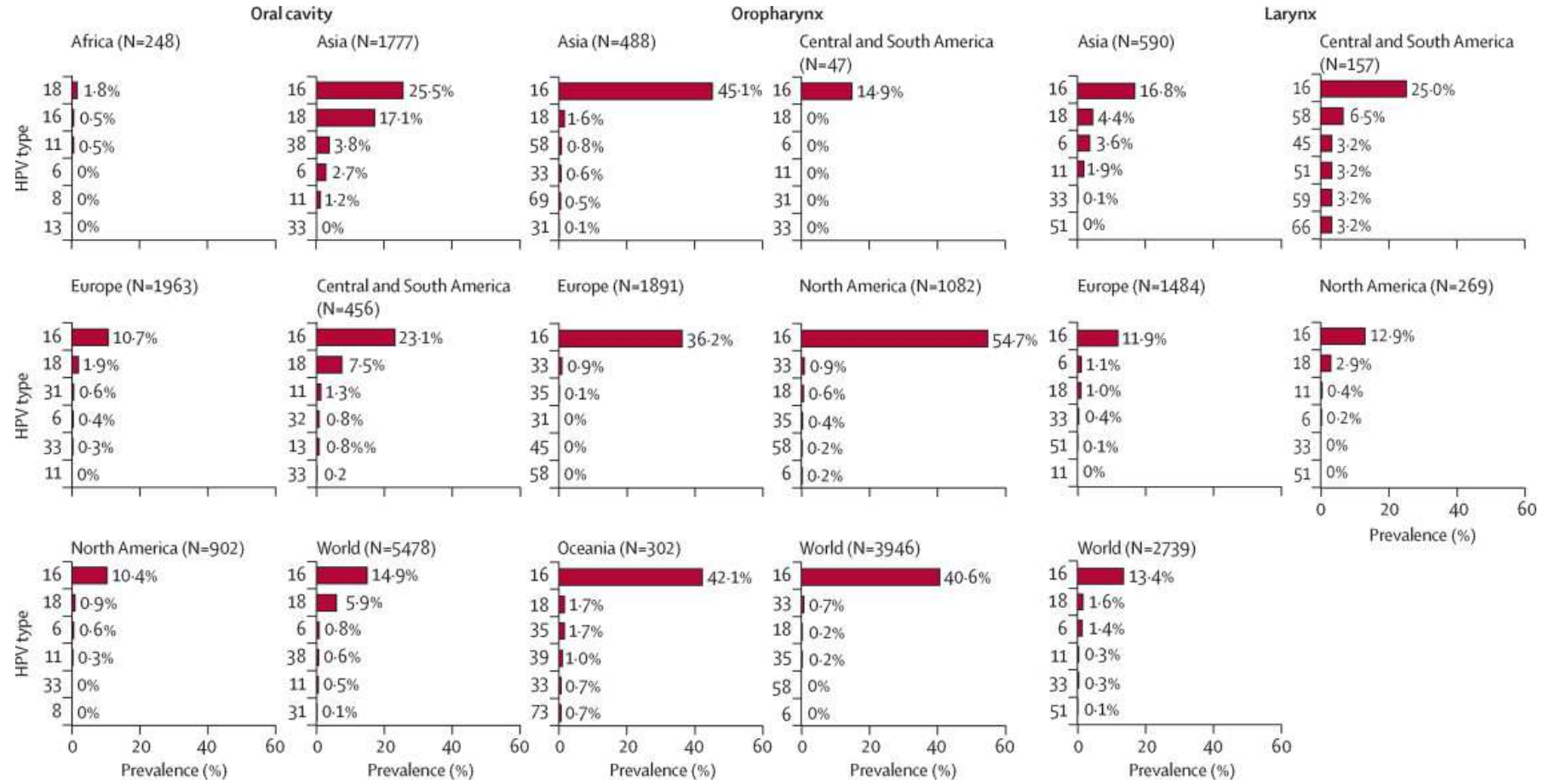
U ARE MORE PRONE, NOT I BCOZ
IN FEMALES INCREASED BODY IMMUNITY DUE TO SEROCONVERSION

MALE ARE MORE PRONE DUE TO

1. MULTIPLE SEXUAL PARTNER



Chaturvedi A K et al. JCO 2012



MOST COMMON SITE & MOST COMMON TYPE

- OROPHARYNX IS THE MOST COMMON TYPE.
- HPV 16 IS THE MOST COMMON MOST COMMON

Cathy Ndiaye et.al, The Lancet Journal

HPV in Indian Scenario

- DATA ON HPV PREVALENCE IS NOT ROBUST..
- PREVELENCE DATA AVAILABLE SPECIFICALLY FOR ORAL CAVITY MALIGNANCIES.
- THE HPV PREVALENCE IN INDIA VARIES WITH REGIONAL DIFFERENCES.
  - 33.6% IN THE EASTERN REGION
  - 67% IN SOUTH INDIA
  - 15% WESTERN INDIA.

BALARAM P ET AL, INT J CANCER 1995;61:450–4.

D'COSTA J ET AL, ORAL ONCOL 1998;34:413–20.

- ONLY 1 PROSPECTIVE STUDY FROM INDIA PREVALENCE OF HPV IN OROPHARYNGEAL SITE (22.8%)

*BAHL A ET AL, HEAD NECK, 2014, **36(4):** 505-10*

Table 1. Prevalence of HPV in malignant head and neck lesions

Study	Year	Type and location of lesion	Method	No. positive cases	%	HPV type
Syrjanen et al. (60)	1987	LSCC	ISH	15/116	13	11, 16, 6, 30
Syrjanen et al. (61)	1988	OSCC	ISH	6/51	12	16, 18
Chang et al. (62)	1990	OSCC	ISH/PCR	11/40	28	16, 18, 6
Zeuss et al. (26)	1991	OSCC	ISH	0/15	0	–
Holladay et al. (63)	1993	OSCC	PCR	7/37	19	16, 18
Ostwald et al. (64)	1994	OSCC	PCR/SB	16/26	62	16, 18, 6, 11
Balaram et al. (65)	1995	OSCC	PCR	67/91	74	16, 18, 6, 11
Cruz et al. (66)	1996	OSCC	PCR	19/35	55	16
Wilczynski et al. (67)	1998	TSCC	PCR	14/21	64	16, 33, 59
Van Houten et al. (68)	2001	HNSCC	PCR/E6R-PCR	20/84	24	16
Kojima et al. (69)	2002	OSCC	PCR	35/53	66	38
Sugiyama et al. (70)	2003	OSCC	PCR	30/86	35	16
Smith et al. (71)	2004	OSCC/OPSCC	RT-PCR	38/193	20	16, 18, 33
Koppikar et al. (72)	2005	OSCC	PCR	6/102	6	16, 18
Slebos et al. (73)	2006	HNSCC	RT-PCR	8/36	22	16
Luo et al. (74)	2007	OSCC	PCR	13/51	25	16, 18, 33, 52
Zhang et al. (43)	2008	HNSCC	ISH	10/30	33	–
Chuang et al. (42)	2008	HNSCC	RT-PCR	20/59	34	16
Simonato et al. (53)	2008	OSCC	nPCR	5/29	17	–
Luginbuhl et al. (75)	2009	TSCC	ISH	17/48	35	–
Avissar et al. (76)	2009	HNSCC	PCR	19/109	17	16
Lohavanichbutr et al. (23)	2009	OSCC/OPSCC	PCR	41/119	35	16
Gallo et al. (77)	2009	LSCC	PCR	0/40	0	–
Khovidhunkit et al. (78)	2008	OSCC	PCR	1/65	2	–
Gudleviciene et al. (79)	2009	HNSCC	PCR	13/48	27	16
Attner et al. (80)	2009	BTSCC	PCR	71/95	75	16, 33
Näsman et al. (2)	2009	TSCC	PCR	43/46	93	16, 33, 35, 59
Shi et al. (31)	2009	OPSCC	PCR/ISH/IHC	73/111	66	16
Straetmans et al. (49)	2009	TSCC	ISH	33/81	41	16
Weinberger et al. (81)	2009	OPSCC	PCR/IHC	47/77	61	16
Lassen et al. (51)	2010	HNSCC	IHC	84/131	25	–
Bennett et al. (82)	2010	TSCC	PCR	9/16	56	16
Hoffmann et al. (83)	2010	TSCC	RT-PCR/IHC	21/39	53	16

HPV, human papillomavirus; OSCC, oral squamous cell carcinoma; TSCC, tonsillar squamous cell carcinoma;

MOST COMMON SITE IN HEAD AND NECK CANCER

- **OROPHARYNX:-126 PTS**
- **OROCAVITY:-60 PTS**
- **HYPOPHARYNX:-35 PTS**

RANDALL J. KIMPLE AND PAUL M. HARARI et al,

- **HOBBS ET AL. FOUND THAT THE ASSOCIATION BETWEEN HPV16 AND CANCER WAS THE**
- **STRONGEST FOR THE PHARYNGEAL TONSILS (OR:15.1),**
- **INTERMEDIATE FOR THE OROPHARYNX (OR:4.3),**
- **AND WEAKEST FOR THE ORAL CAVITY (OR: 2.0)AND THE LARYNX (OR: 2.0)**

HPV 16 EXPOSURE AND RISK OF HNSCC

site	Odds ratio*	95% CI
Lip	0.5	0.1-2.1
Tongue	2.8	1.2-6.7
Oral Cavity	3.6	0.5-26.3
Oropharynx	***14.4***	***3.6-58.1***
Nasal Cavity/Sinuses	2.6	0.5-14.1
Larynx	2.4	1.0-5.6

- ***HPV SEROPOSITIVITY PRECEDED A CANCER DIAGNOSIS BY 9 YEARS ON AVERAGE***

MORK et.al. NEJM 2001

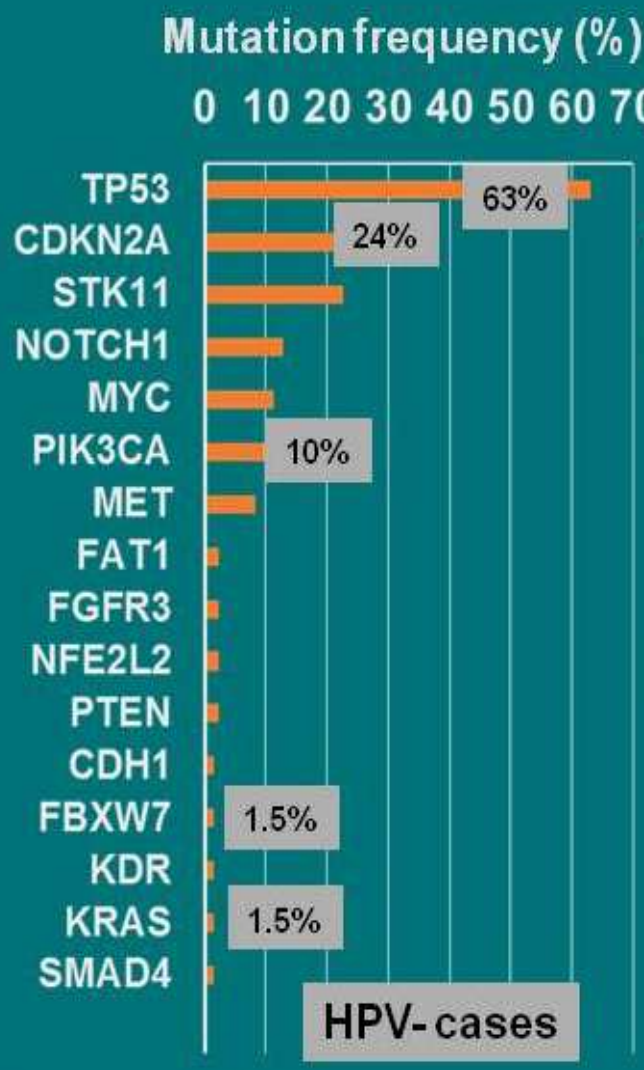
SPECIAL CHARACTERISTICS OF HPV-POSITIVE TUMOURS

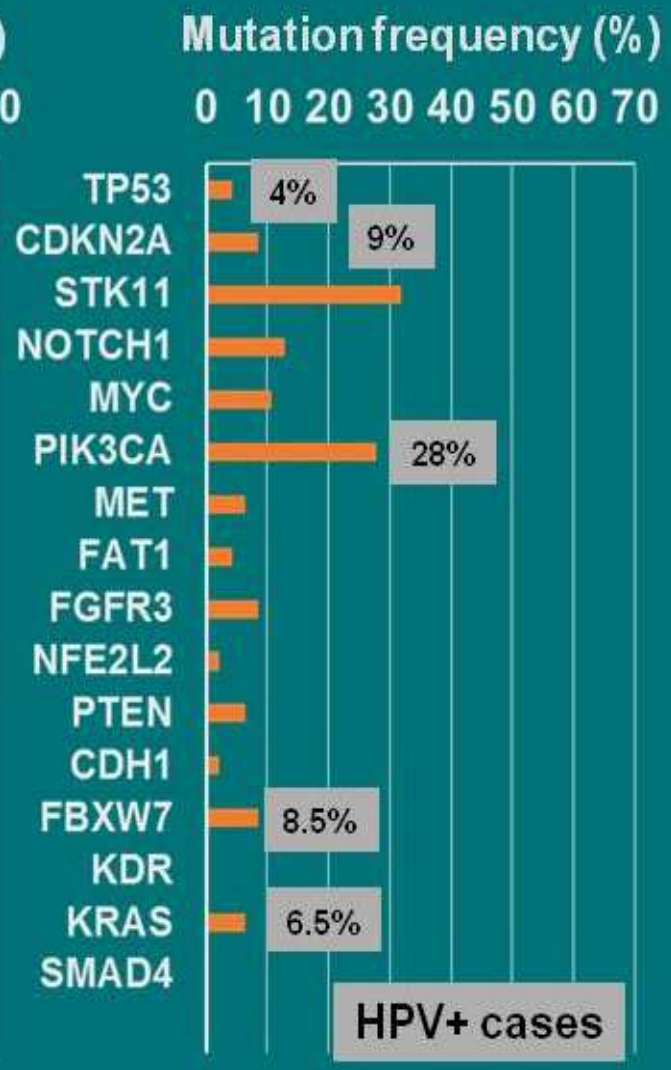
	HPV POSITIVE	HPV NEGATIVE
ANATOMICAL SITE	TONSIL, BOT	ALL SITES
HISTOLOGY	NON-KERATINISING, UNDIFFERENTIATED, BASALOID VERITY	KERATINISING
AGE	YOUNGER	OLDER
SEX RATIO(M:F)	3:1	3:1
STAGE	TXT1-2	VARIABLE
RISK FACTORS	SEXUAL BEHAVIOR, HIGHER SOCIO ECONOMIC STATUS, HIGHER EDUCATION	ALCOHOL,TOBACCO
INCIDENCE	INCREASING	DECREASING

MARUR S ET AL. LANCET ONCOL 2010;11:781-89.

Results

Significant differences in mutational patterns of HPV+ and HPV- cases

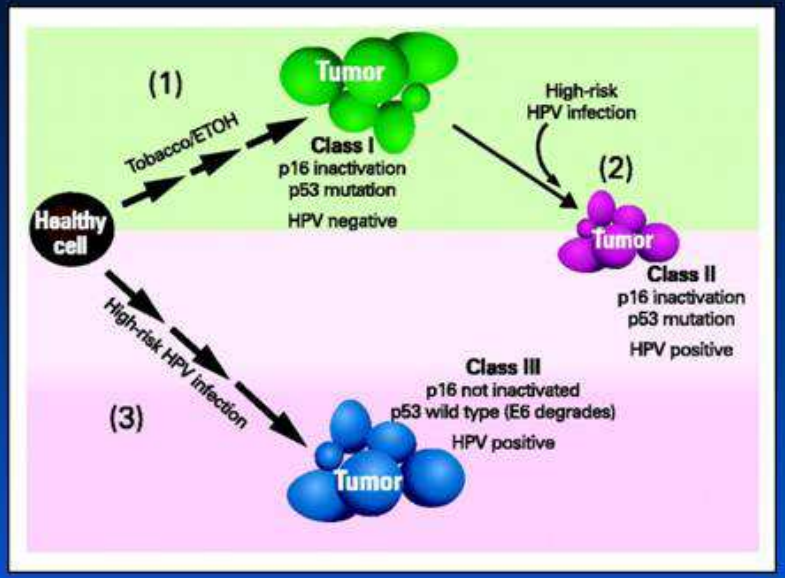


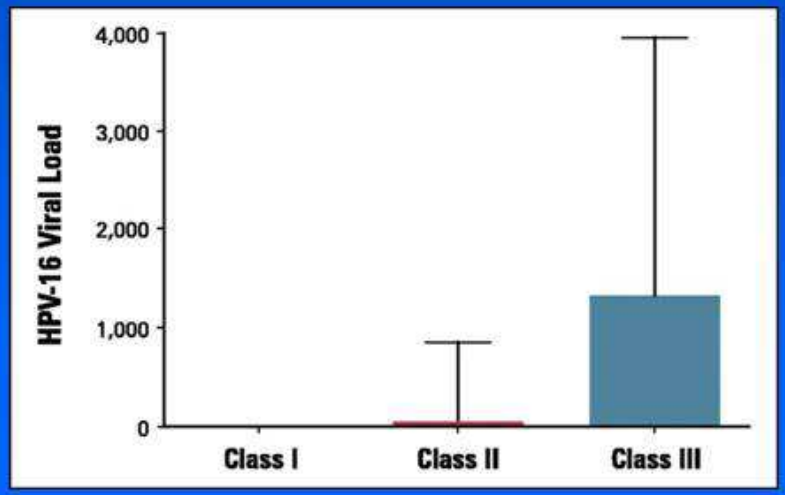


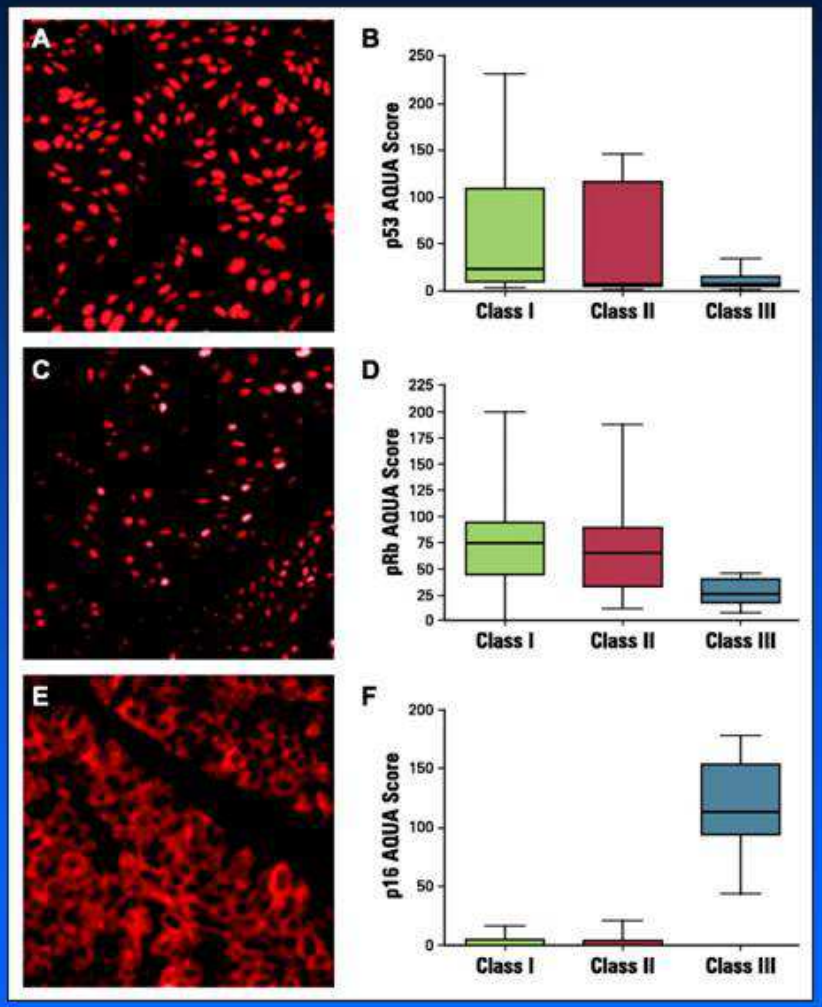
PRESENTED AT: ASCO Annual '15 Meeting

Presented By Inge Tinhofer at 2015 ASCO Annual Meeting

Oropharynx Carcinogenesis: 3 classes





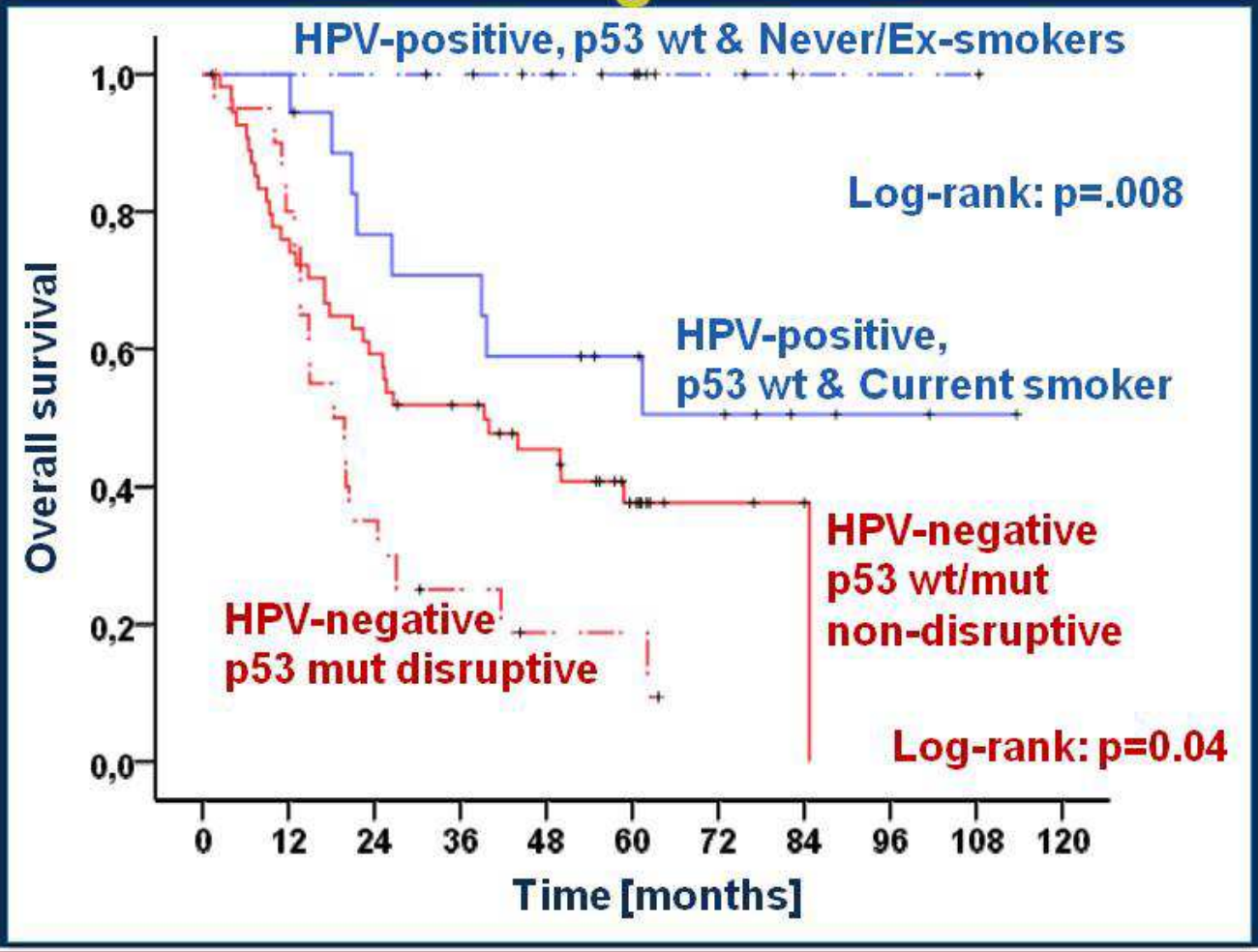


Weinberger PM et al. J Clin Oncol 2006;24:736-47.

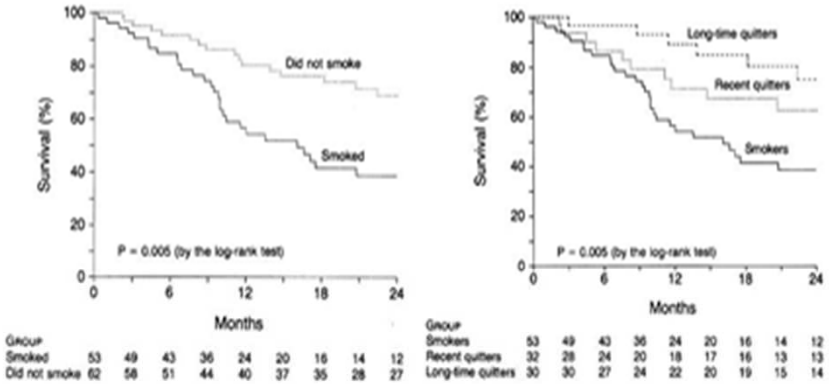
p16 is a diagnostic marker

Presented By John Ridge at 2014 ASCO Annual Meeting

Results: OS according to TP53 mutations, HPV and Smoking



Smoking and Head/Neck Cancer Treatment



- 115 Stage III-IV SCCA of H/N treated with XRT +/- fluorouracil
- 41% decrease in 2-year OS in patients who smoked during XRT
  - No difference based upon fluorouracil vs. placebo
  - No difference in toxicity (smokers during XRT vs. nonsmokers)

Browman GP et al. (1993) *N Engl J Med* **328**: 159

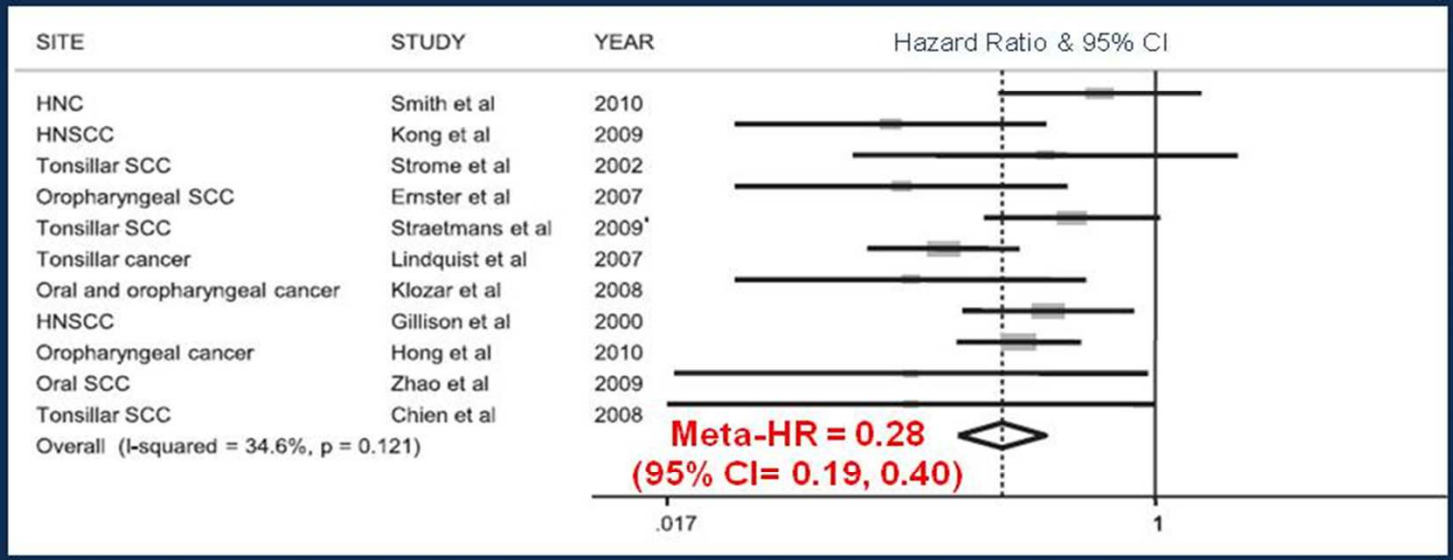
Presented By Graham Walter Warren, MD, PhD at 2013 ASCO Annual Meeting

HUMAN PAPILLOMAVIRUS ,TOBACCO AND SURVIVAL OF PATIENTS WITH OROPHARYNGEAL CANCER

	HR	95% CI	2 yr Survival
HPV +, <20py	1.0		95%
HPV +, >20py	1.91	1.2-3.05	80%
HPV -, <20py	2.25	1.44-3.5	71%
HPV -, >20py	4.30	2.4-7.71	63%

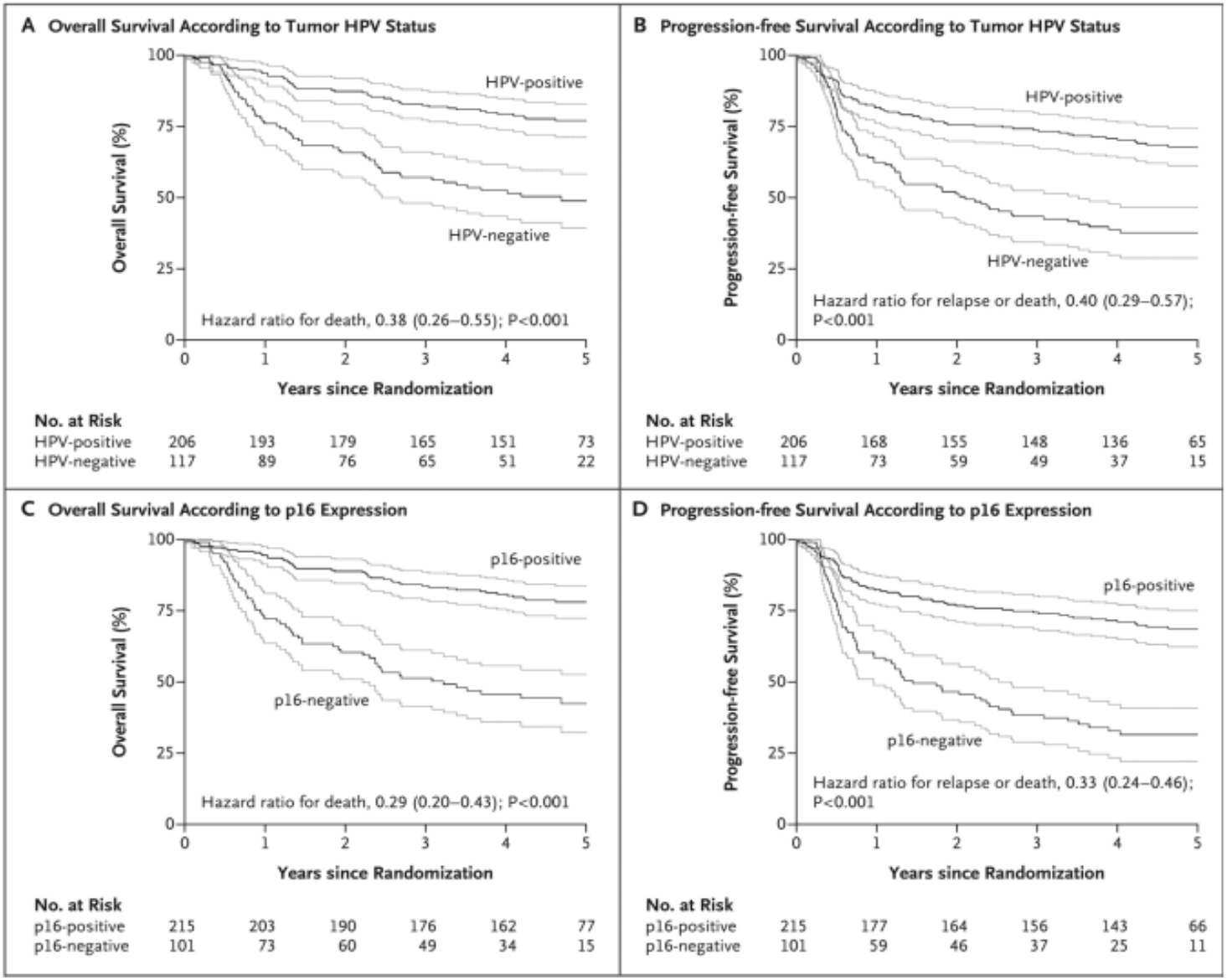
ANG ET AL. NEJM 2010

HPV-Related HNSCC are Associated with Favorable Prognosis



O'Rorke et al. Oral Oncol 48:1191-1201, 2012.

HUMAN PAPILLOMAVIRUS AND SURVIVAL OF PATIENTS WITH OROPHARYNGEAL CANCER K. KIAN ANG, M.D., PH.D.



WHY BETTER OUTCOME IN HPV+ve PATIENTS

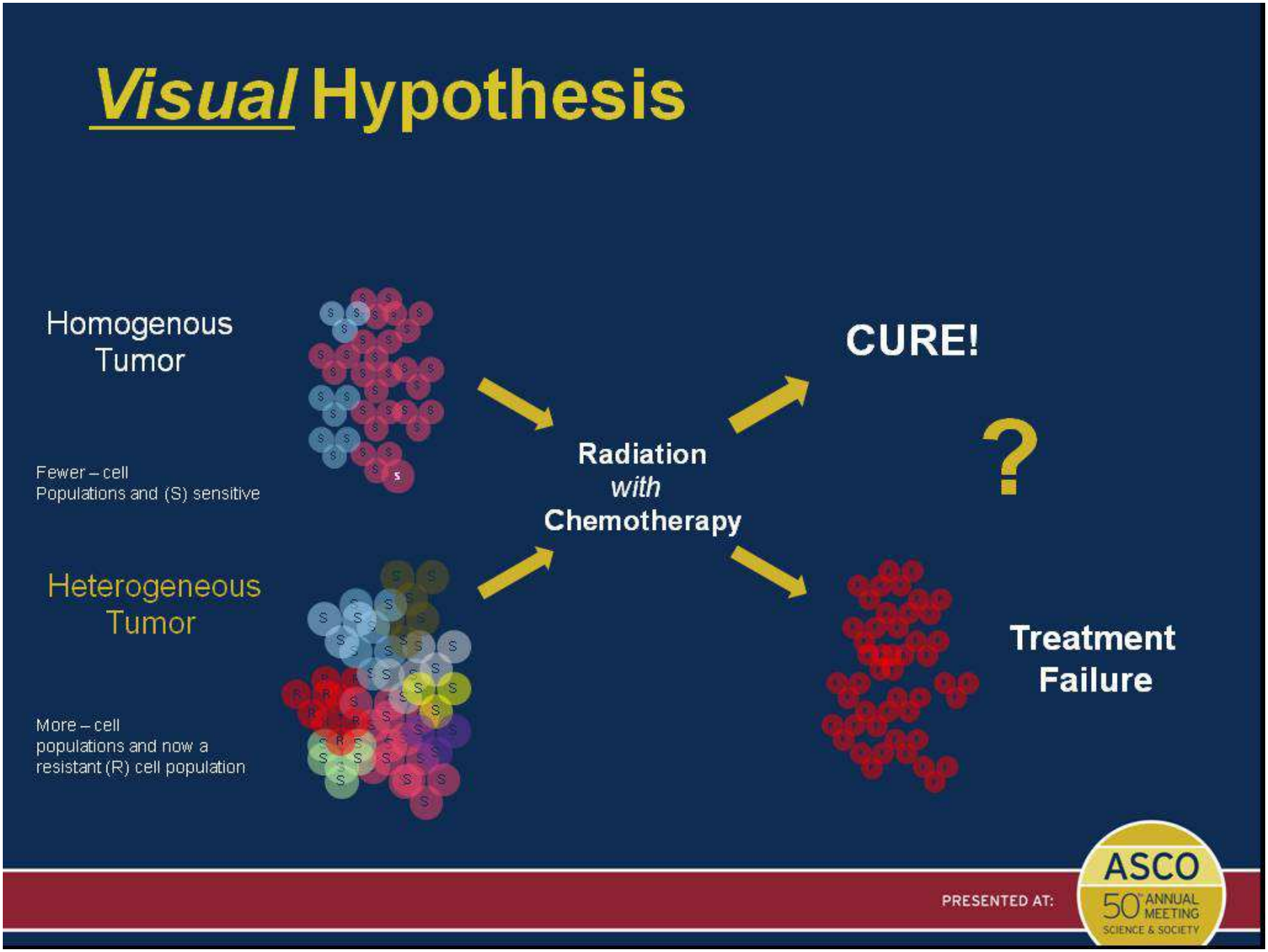
1. **HARBOUR *FEWER DIFFERENT GENETIC ALTERATIONS*, WHICH CAN BE ASSOCIATED WITH BETTER RESPONSE TO THERAPY**

2. **THE *ABSENCE OF FIELD CANCERISATION***

3. ***IMMUNOLOGIC RESPONSE* PLAY A ROLE IN THE IMPROVED RESPONSE TO CHEMO RADIATION .**

4. ***YOUNGER AGE, GOOD PERFORMANCE STATUS, FEWER COMORBIDITIES OF HPV-POSITIVE OROPHARYNGEAL CANCER PATIENTS MAY ALSO CONTRIBUTE TO IMPROVED SURVIVAL***
5. **HPV-ASSOCIATED TUMORS MAY BE *LESS HYPOXIC*, WHICH COULD INCREASE RESPONSIVENESS TO RADIOTHERAPY.**

Visual Hypothesis



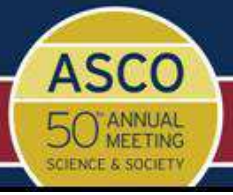
Presented By David Raben at 2014 ASCO Annual Meeting

What is "MATH"?

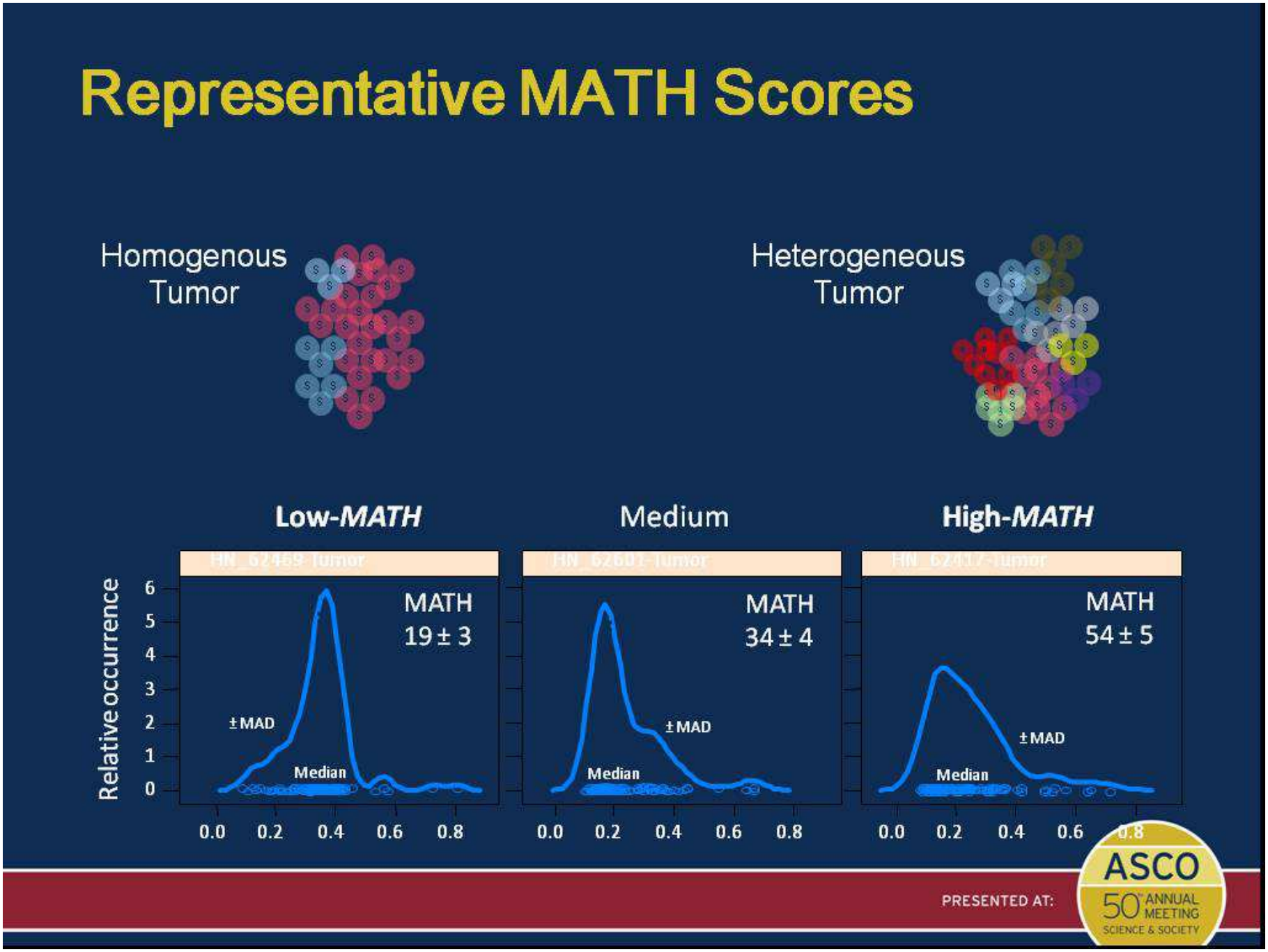
- Rocco et al developed a quantitative measure of intratumor genetic heterogeneity, based on differences among mutated loci in the mutant-allele fractions determined by NGS of tumor DNA
- Emphasizes overall genetic diversity regardless of which genes are mutated

Presented by:

PRESENTED AT:

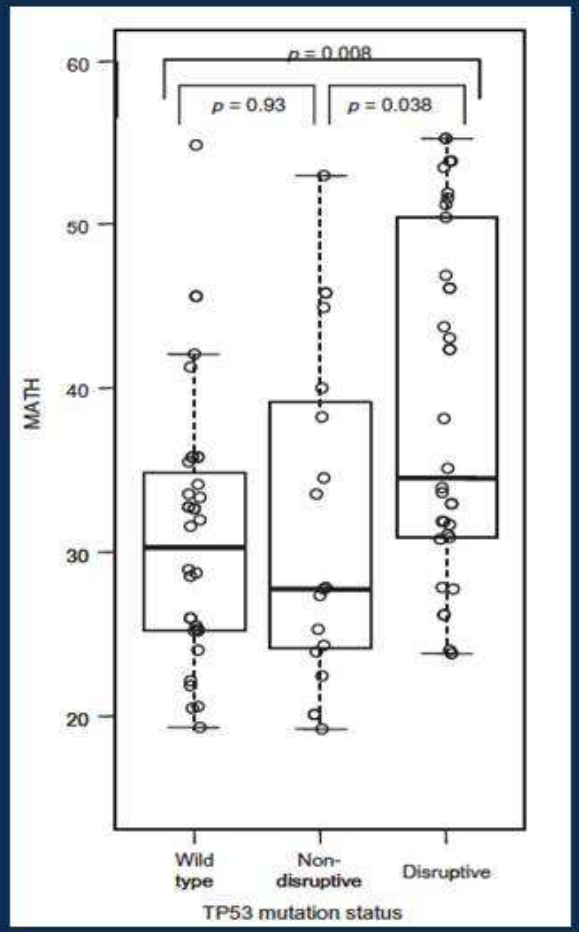


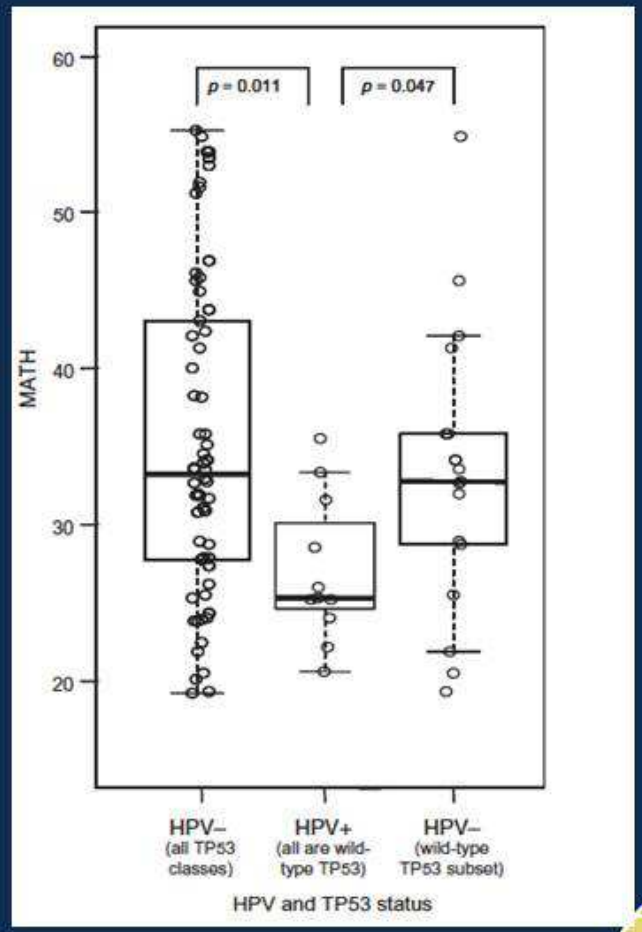
Representative MATH Scores



Presented By David Raben at 2014 ASCO Annual Meeting

Higher MATH scores related to disruptive p53 mutations





Mroz, et al. Oral Oncology 49 (2013) 211–215 PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

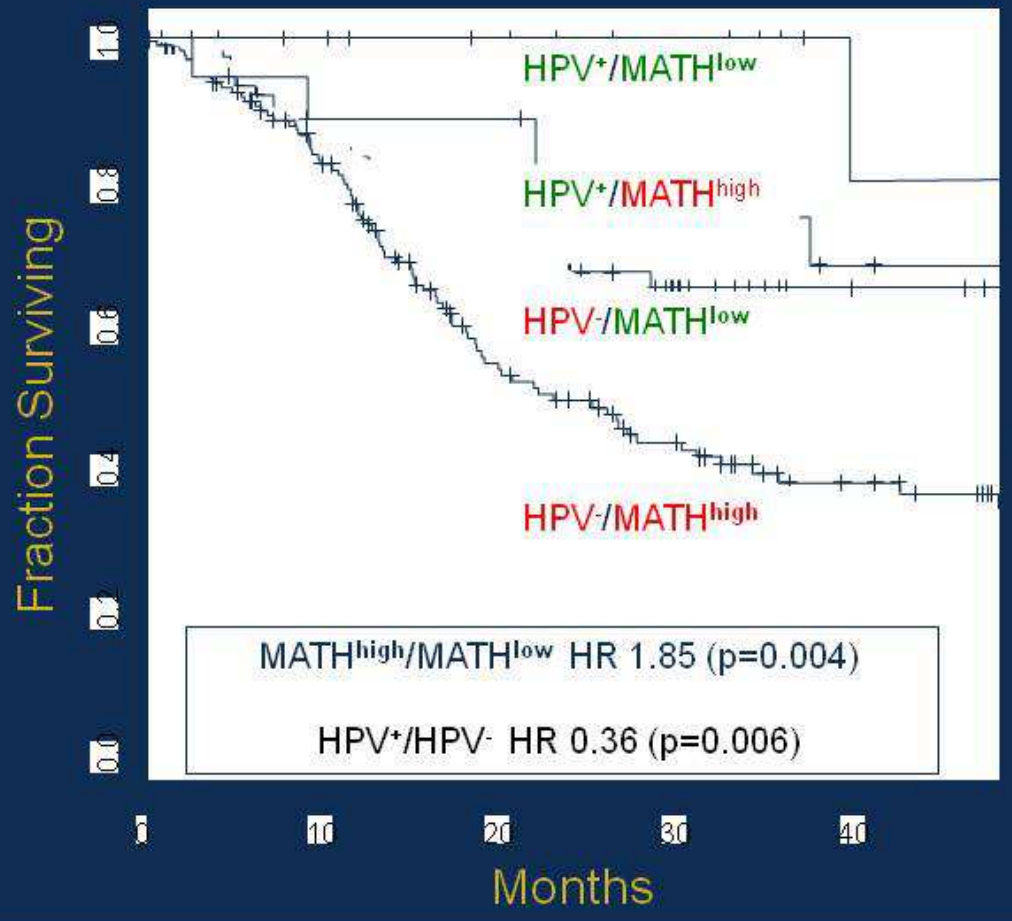
Presented By David Raben at 2014 ASCO Annual Meeting

Relations of MATH to HPV and Clinical Characteristics

- HPV^+ tumors had significantly lower MATH than HPV^- tumors (33.9+/-13.5 vs. 39.8+/-11.2; p=0.004)
- With HPV status taken into account MATH **was** significantly related to the clinical characteristics of:
  - *age*
  - *tumor grade*
  - *N classification*
  - *LVI*
- MATH **was not** related to ethnicity, race, tumor site, alcohol consumption, smoking history, margin status, PNI or TNM stage.
- Weak - *but not significant* - relations to gender, T-classification and ECS were noted

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

MATH and HPV status provide greater prognostic information



?

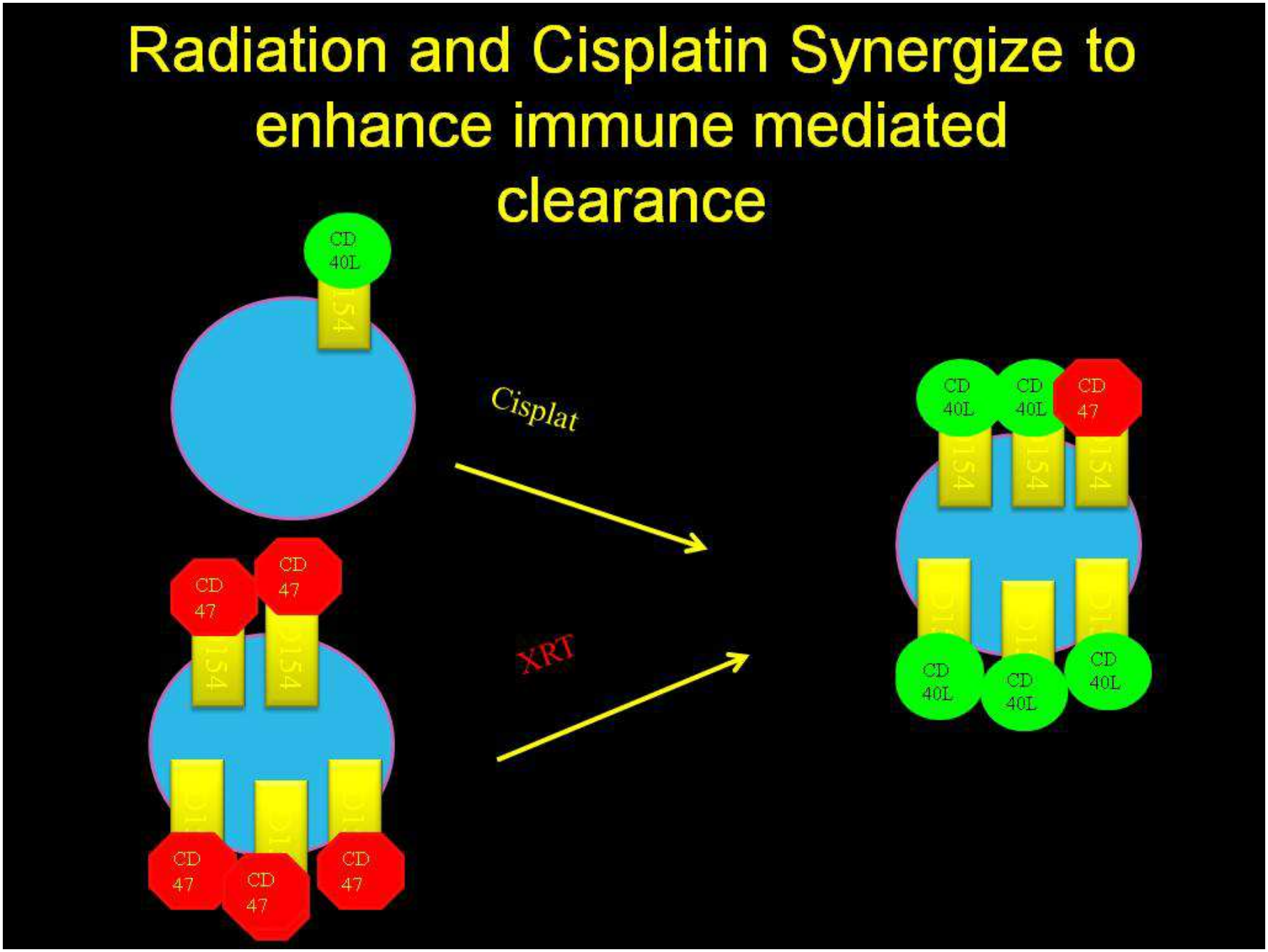
?

higher EGFR
DNA repair
cMET
TGFb
Undiscovered mutations

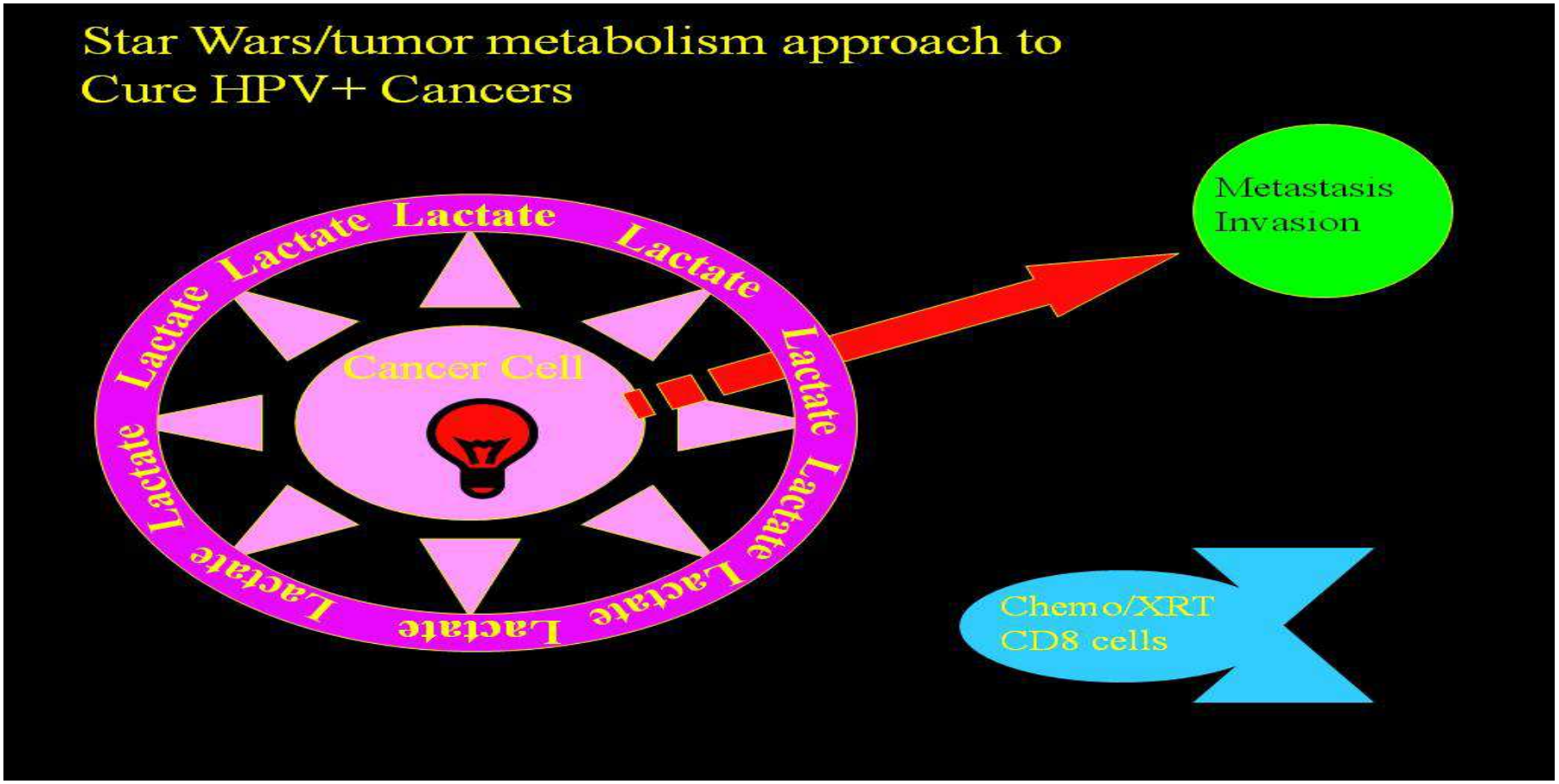
PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By David Raben at 2014 ASCO Annual Meeting



Presented By John Lee at 2014 ASCO Annual Meeting



- Tumor Lacate Production prevents immune mediated clearance of HPV+ HNSCC- possibly all antigenic cancers
- Decreasing Lactate enhances immune mediated clearance

HPV INFECTION AND RESPONSE TO THERAPY—OVERALL SURVIVAL A PROSPECTIVE STUDY & SECONDARY ANALYSIS FROM DIFFERENT PROSPECTIVE TRIALS

Table 2: Tumor HPV Status and Survival Outcomes in Reported Prospective Clinical Trials

Author	Cooperative Group	N	XRT	Induction	Concurrent	Median F/U	HPV+	Time	HPV+	HPV-	P-value	HAZARD RATIO HPV+ vs -
Fakhry	ECOG	96	70Gy	2 cycles paclitaxel 175mg/m2 carbo AUC6	weekly paclitaxel 30mg/m2 x 7	39 mo	40%	2-year	95%	62%	0.005	0.36
Rischin	TROG	195	70Gy	none	cisplatin +/- tirapazamine	27 mo	28%	2-year	94%	77%	0.007	0.29
Gillison	RTOG 0129	323	70-72Gy	none	cisplatin 100mg/m2 x2 or 3	4.8 yrs	64%	3-year	79%	46%	0.002	0.44
Settle	TAX324	119	70-74Gy	3 cycles taxotere 75mg/m2 cisplatin 100mg/m2 5-FU 1000mg/m2/day x 4	weekly carboplatin AUC 1.5 x 7	67 mo	50%	5-year	93%	35%	<0.001	0.2
Lassen	DHANCA5	156	62-68Gy	none	nimorazale 1200mg/m2/day x 30	>60 mo	22%	5-year	62%	26%	0.003	0.44

Int. J. Cancer: **121,** 1813–1820 (2007)

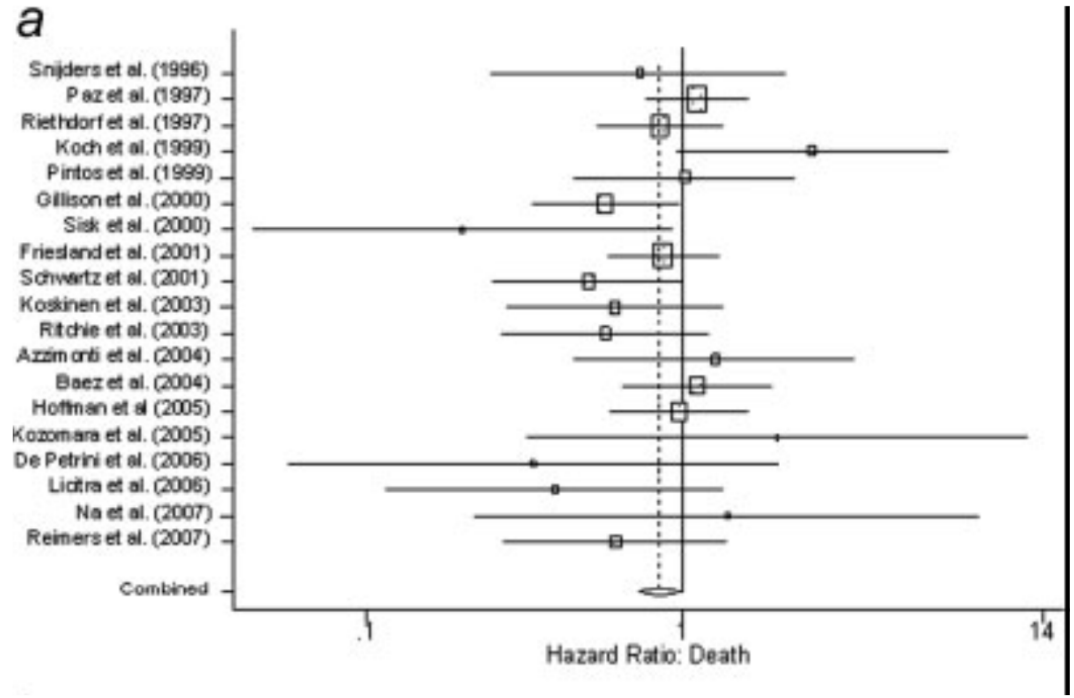
Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis

Camille C.R. Ragin[1,2]* and Emanuela Taioli[1,2]

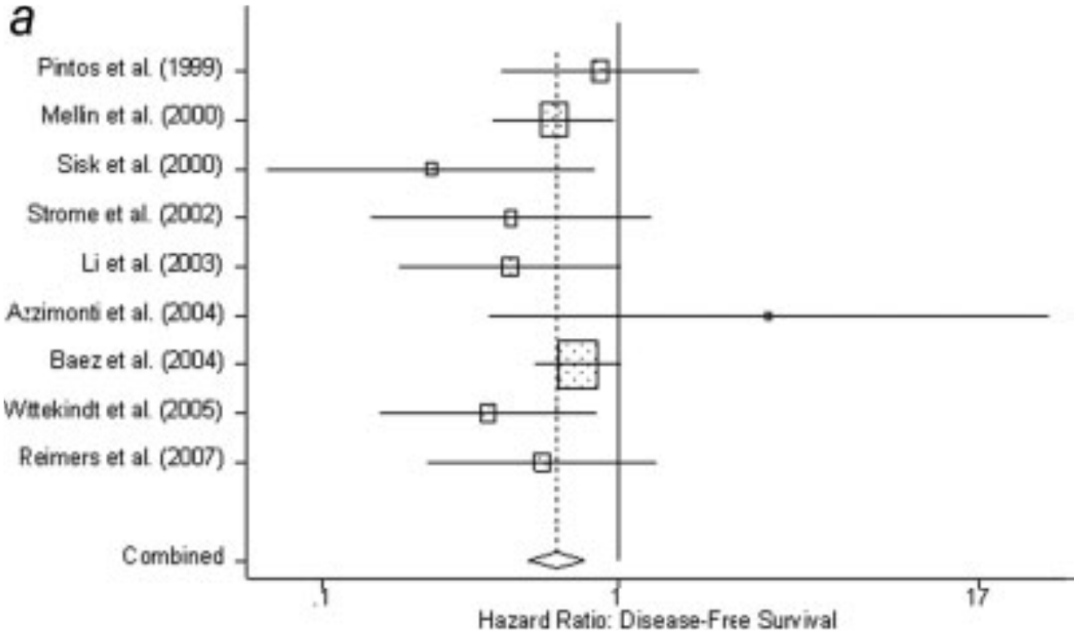
[1]*Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA*
[2]*Division of Cancer Prevention and Population Science, University of Pittsburgh Cancer Institute, Pittsburgh, PA*

RESULTS OF SEVERAL RETROSPECTIVE STUDIES:

- PATIENTS WITH HPV-POSITIVE HNSCC LOWER RISK OF DYING (HR:0.85, 95% CI: 0.7–1.0)
  AND LOWER RISK OF RECURRENCE (HR: 0.62, 95%CI: 0.5–0.8)
- **NO DIFFERENCE** IN OAS BETWEEN HPV-POSITIVE AND NEGATIVE **NON-OROPHARYNGEAL** CANCER PATIENTS.



OS HPV+Ve Vs HPV–Ve



DFS HPV+Ve Vs HPV-Ve

p16 expression as a human papillomavirus (HPV)-independent prognostic biomarker of non-oropharyngeal squamous cell carcinoma (non-OPSCC)

Chung, CH; Zhang, Q; Kong, C; Harris, J; Ang, K ; Harari, P; Wang, D; Redmond, K; Shenouda, G; Trotti, A; Raben, D; Gillison, M; Jordan, R; Le, Q-T

Presented By Christine H. Chung, MD at 2013 ASCO Annual Meeting

p16 and HPV Result Summary

Study ID (n=Total # non-OPSCC)	RTOG 0129 (n=288)	RTOG 0234 (n=129)	RTOG 0522 (n=266)	Total (n=683)
p16 data available	85 (30%)	95 (74%)	142 (53%)	322 (47%)
p16-positive	12 (14%)	23 (24%)	27 (19%)	62 (19%)
p16-negative	73 (86%)	72 (76%)	115 (81%)	260 (81%)
HPV data available	93 (32%)	103 (80%)	101 (38%)	297 (43%)
HPV-positive	6 (6%)	15 (15%)	7 (7%)	28 (9%)
HPV-negative	87 (94%)	88 (85%)	94 (93%)	269 (91%)

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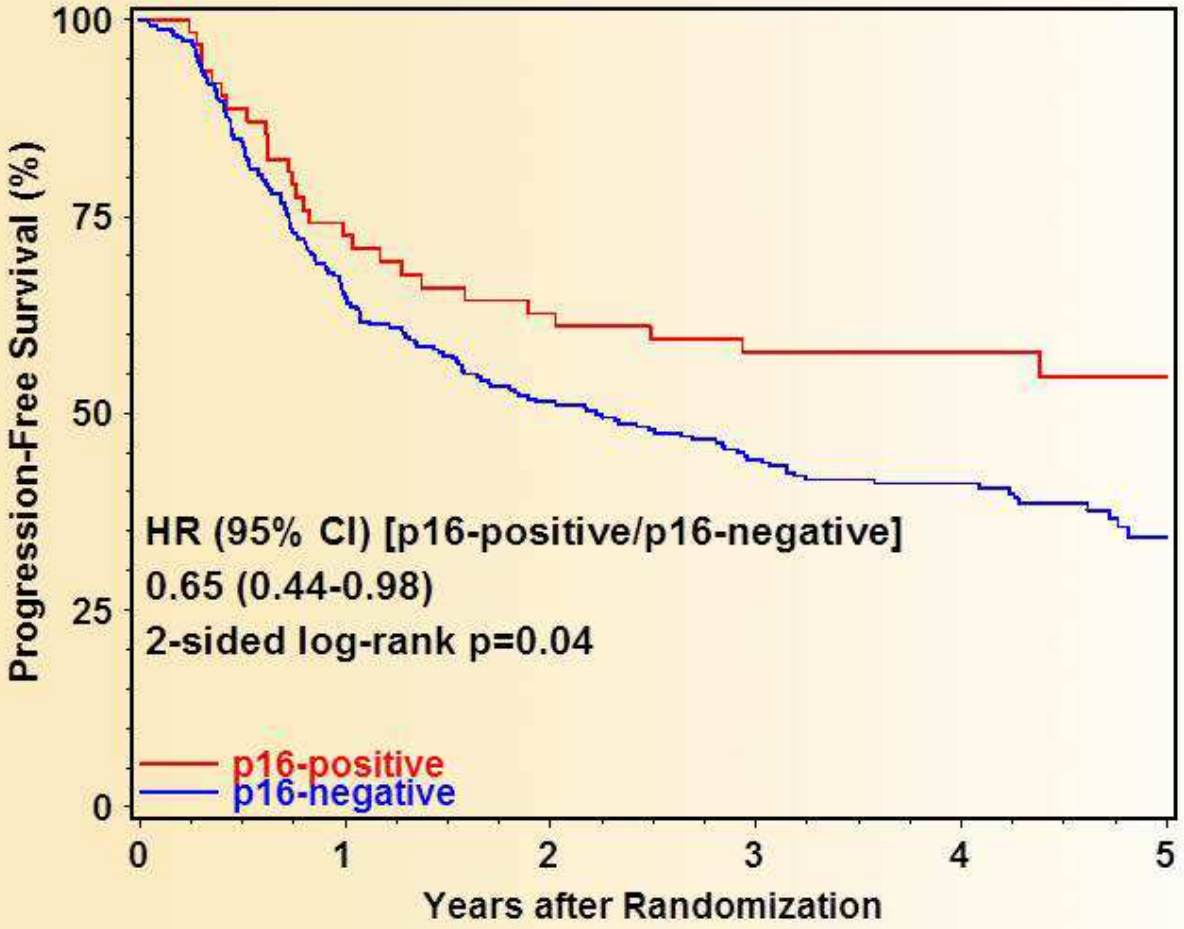
Progression-free survival



Patients at Risk						
p16-positive	62	45	38	34	23	10
p16-negative	260	167	131	106	74	23

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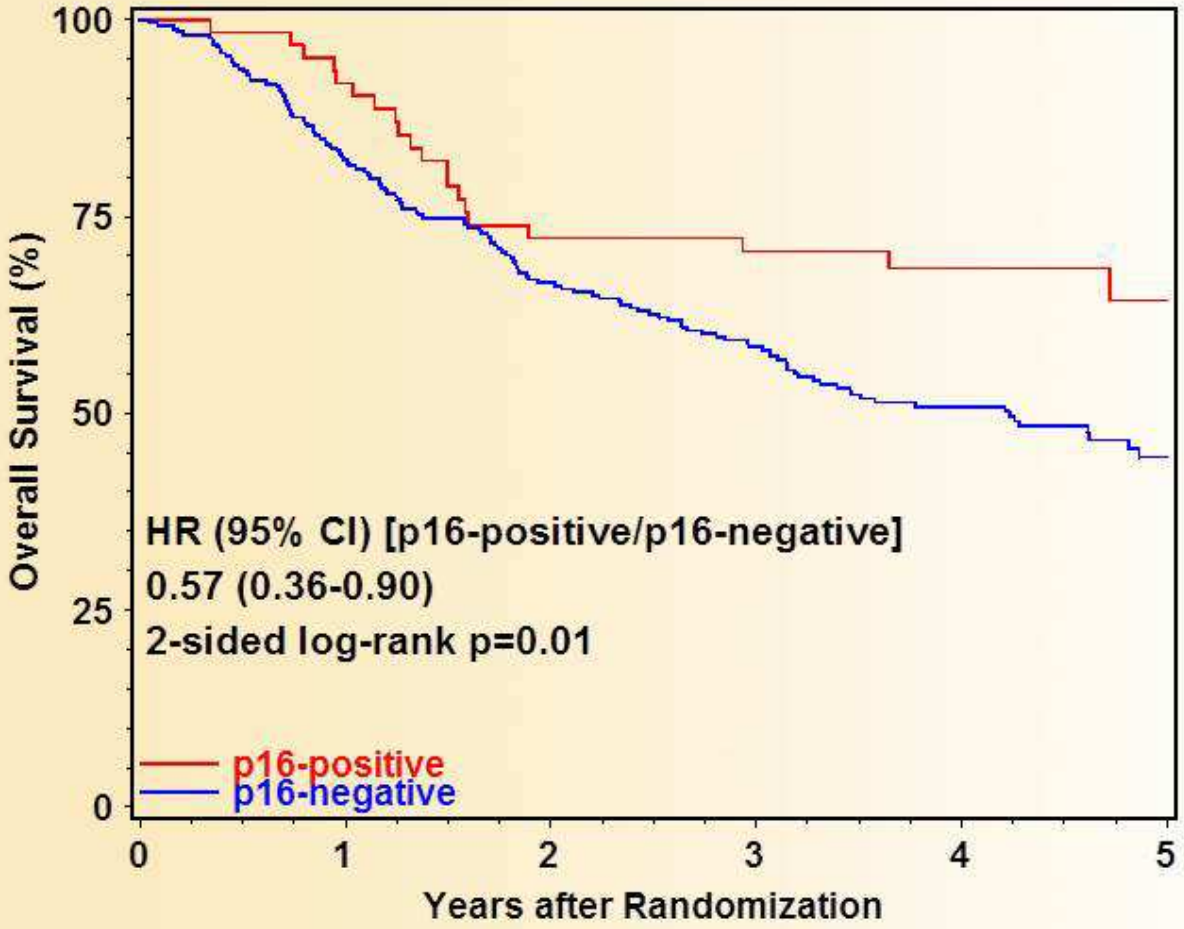
Overall survival



Patients at Risk						
p16-positive	62	57	44	41	28	13
p16-negative	260	212	170	140	91	33

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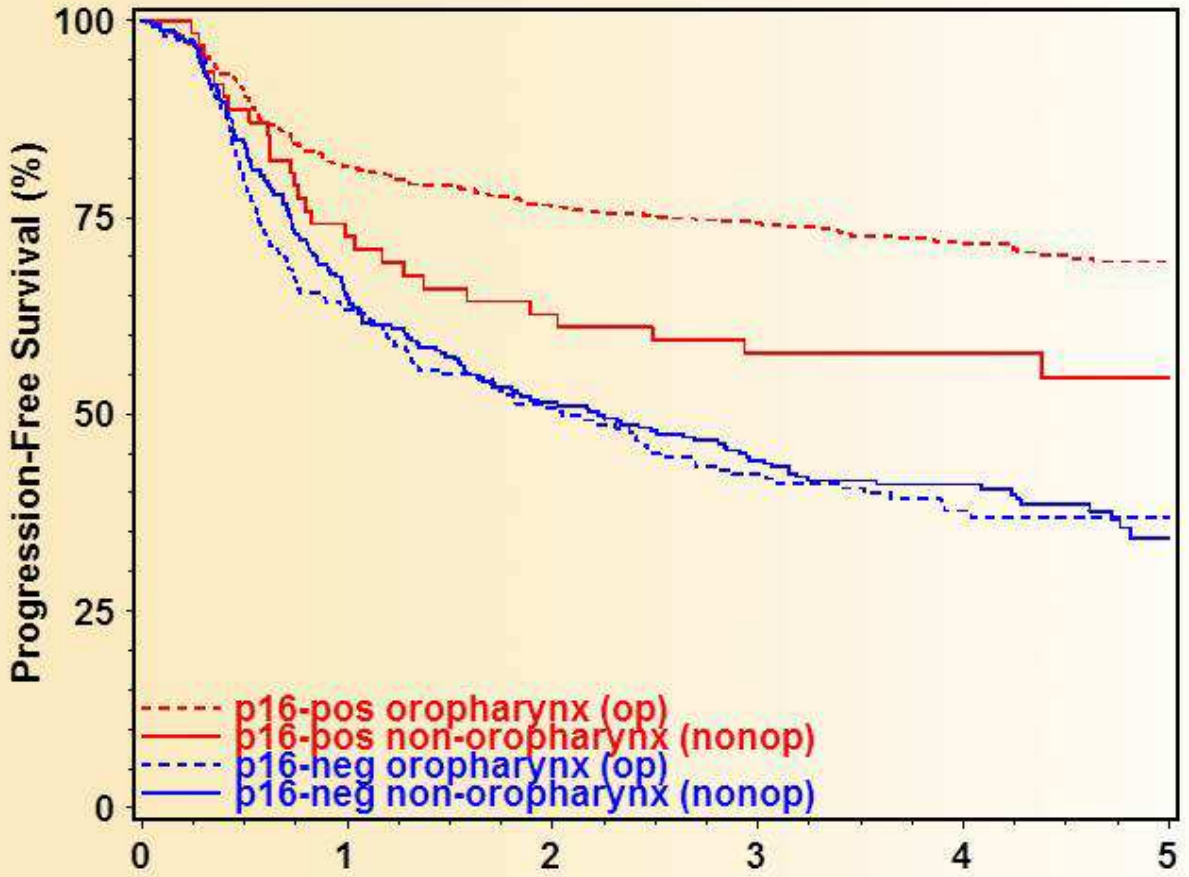
Progression-free survival



Patients at Risk						
p16-pos op	493	399	370	347	253	105
p16-pos nonop	62	45	38	34	23	10
p16-neg op	198	123	96	78	45	21
p16-neg nonop	260	167	131	106	74	23

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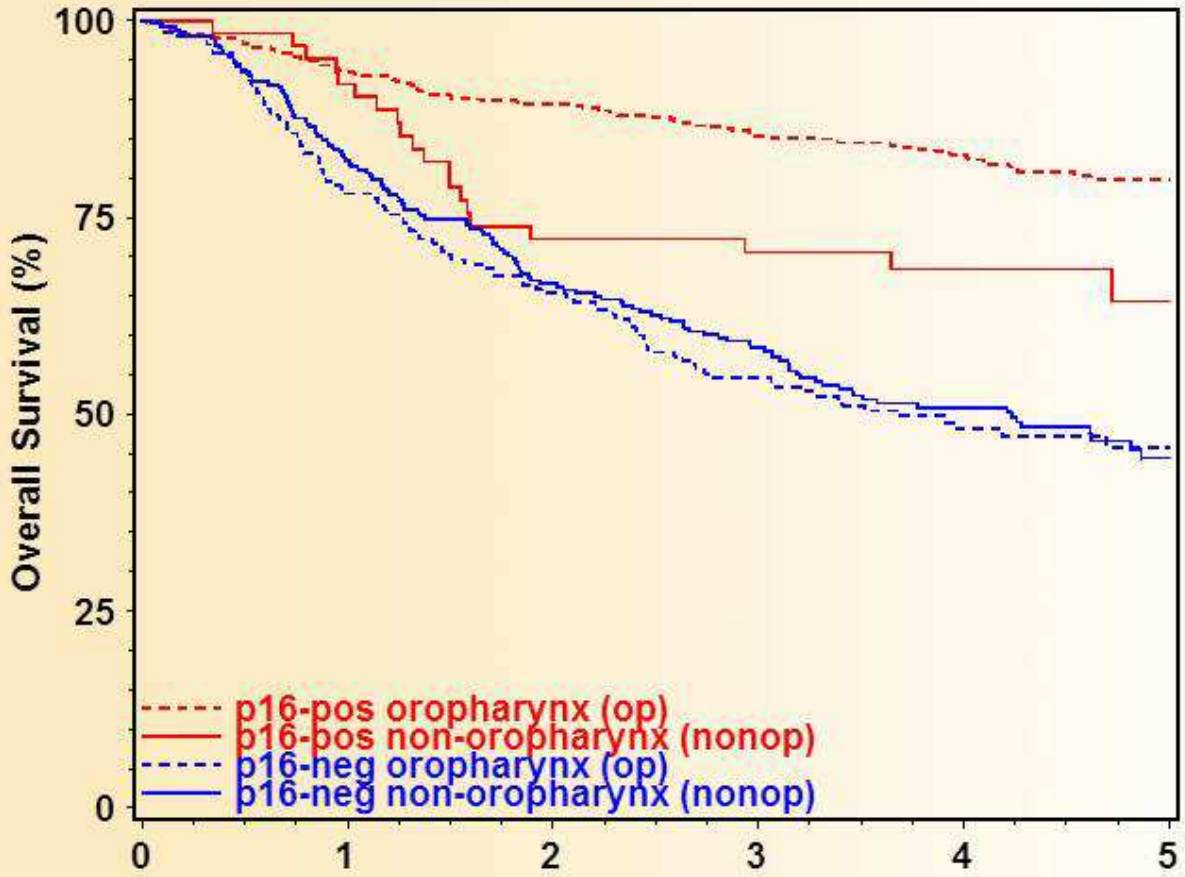
Overall survival



Patients at Risk						
p16-pos op	493	457	433	399	290	119
p16-pos nonop	62	57	44	41	28	13
p16-neg op	198	151	122	99	56	25
p16-neg nonop	260	212	170	140	91	33

Interaction of p16 status and Primary site in survival outcomes

	Comparison	Subsite	HR (95% CI)
PFS	p16-pos vs. p16-neg	OPSCC	0.37 (0.29-0.47)
		Non-OPSCC	0.67 (0.45-1.00)
	OPSCC vs. non-OPSCC	p16-pos	0.54 (0.36-0.82)
		p16-neg	0.99 (0.77-1.26)
		p-value for interaction	0.01
OS	p16-pos vs. p16-neg	OPSCC	0.29 (0.22-0.38)
		Non-OPSCC	0.58 (0.36-0.91)
	OPSCC vs. non-OPSCC	p16-pos	0.48 (0.30-0.78)
		p16-neg	0.97 (0.74-1.27)
		p-value for interaction	0.01

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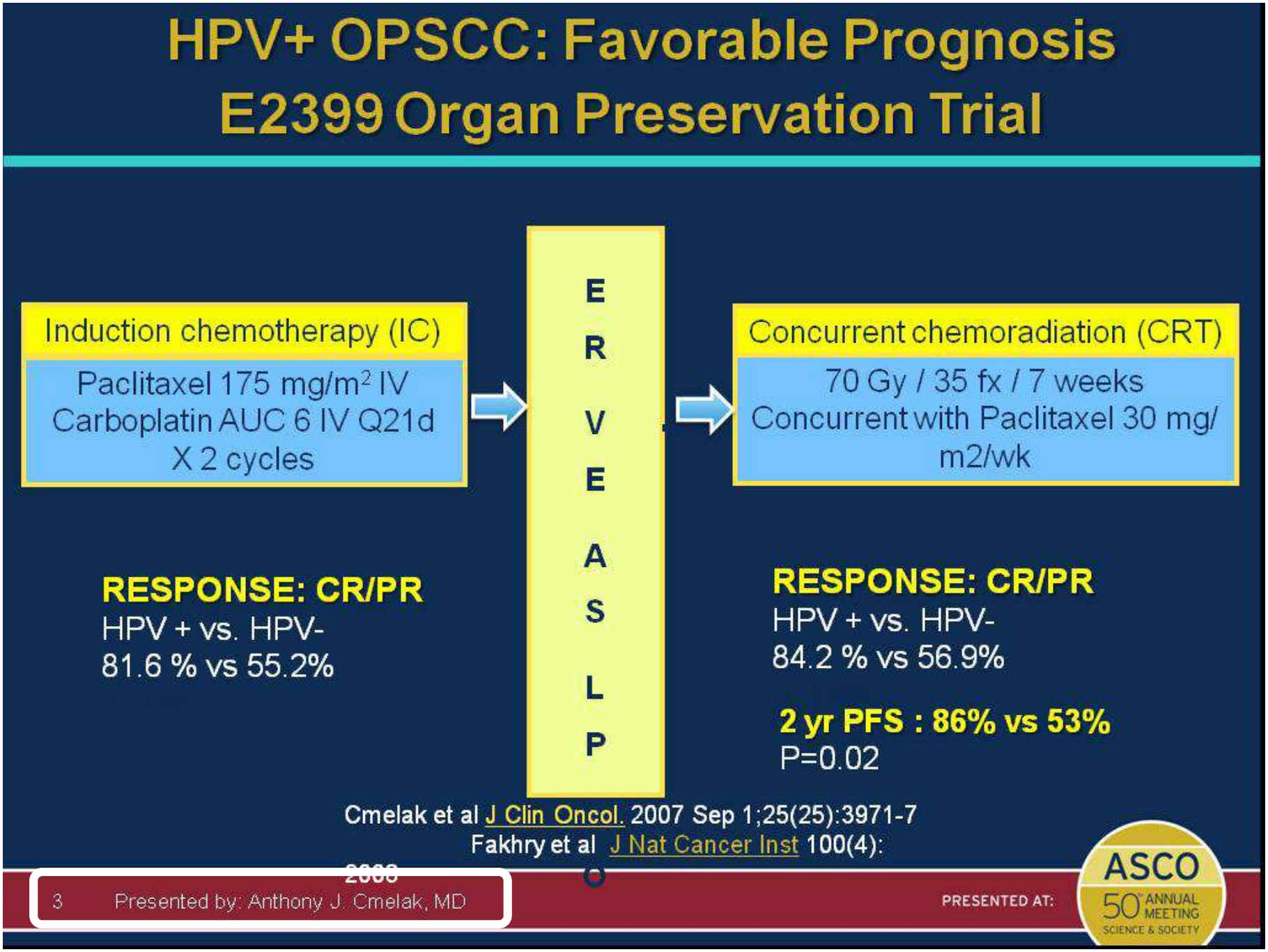
HPV+ OPSCC: Favorable Prognosis
E2399 Organ Preservation Trial



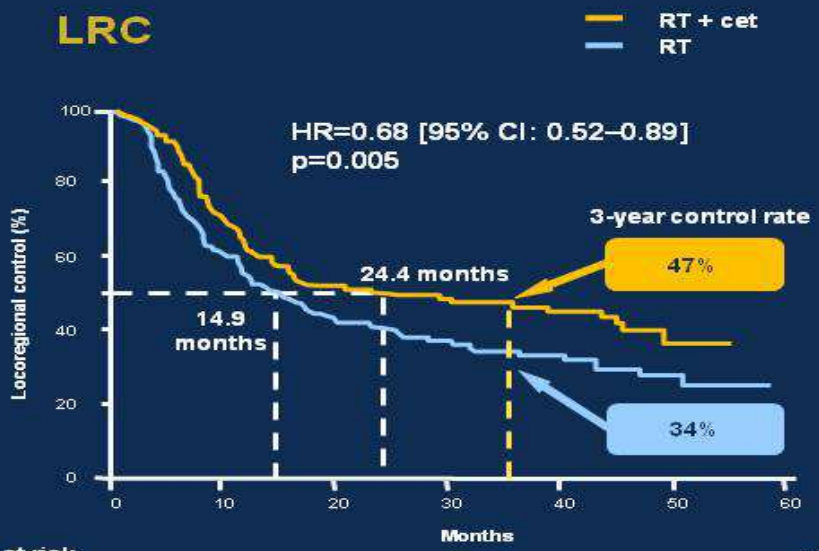
Presented By Anthony Cmelak at 2014 ASCO Annual Meeting

Impact of p16 status on the results of the phase III cetuximab/radiotherapy 'Bonner' registration trial for locoregionally advanced squamous cell carcinoma of the head and neck

David I. Rosenthal*, Paul M. Harari, Jordi Giralt, Diana Bell, David Raben, Joyce Liu, Jeltje Schulten, K. Kian Ang, James A. Bonner

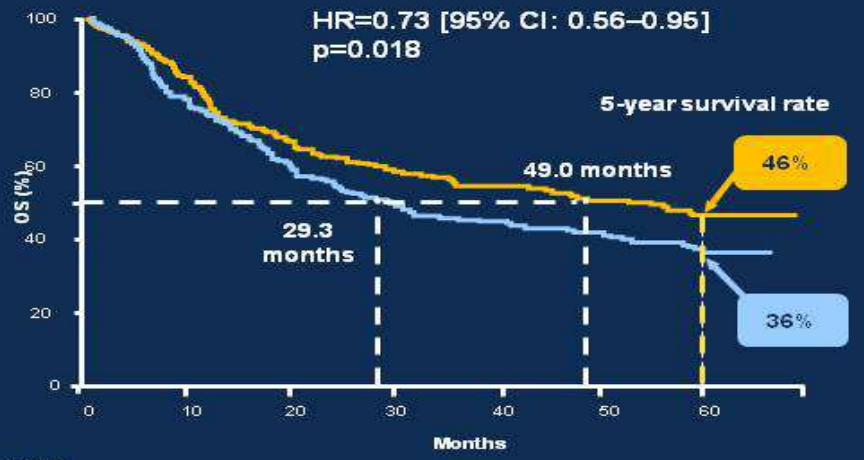
RT + cetuximab significantly improves LRC and 5-year OS

LRC



No. at risk						
RT	213	122	80	51	30	10
RT + cet	211	143	101	66	35	9

OS



No. at risk							
RT	213	162	122	98	85	77	49
RT + cet	211	177	136	117	105	90	49

HR, hazard ratio; LA-SCCHN, locally advanced squamous cell carcinoma of the head & neck; LRC, locoregional control; RT, radiotherapy.

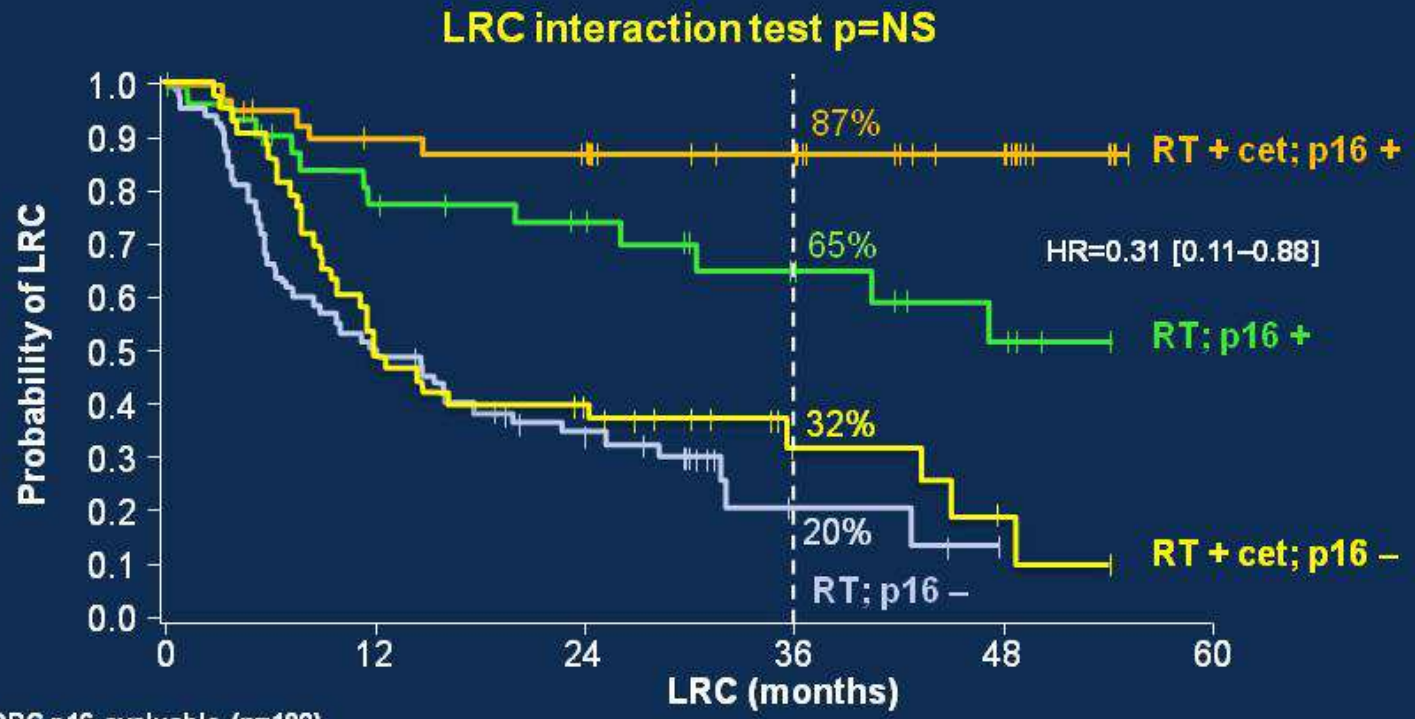
Bonner JA, et al. N Engl J Med 2006;354:567-78.
Bonner JA, et al. Lancet Oncol 2010;11:21–28.

Presented by: David I. Rosenthal

PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

LRC in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs RT alone



No. at risk OPC p16 evaluable (n=182)

RT p16 negative	64	31	17	3	0	0
RT p16 positive	34	24	20	12	6	0
RT + cet p16 negative	43	21	16	6	2	0
RT + cet p16 positive	41	33	30	21	12	0

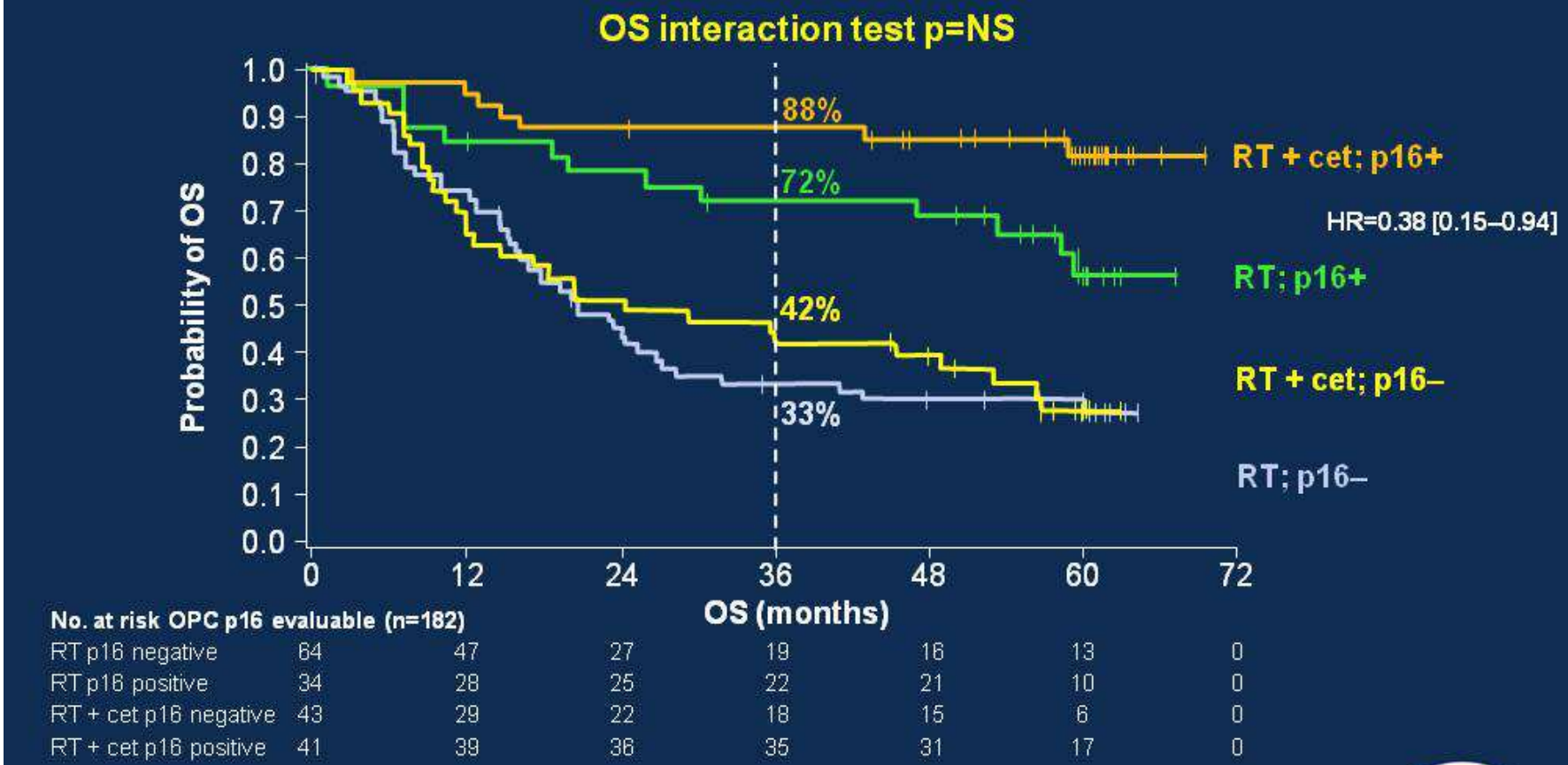
p16-, p16-negative.

Presented by: David I. Rosenthal

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Vassiliki Papadimitrakopoulou at 2014 ASCO Annual Meeting

OS in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs RT alone



No. at risk OPC p16 evaluable (n=182)							
RT p16 negative	64	47	27	19	16	13	0
RT p16 positive	34	28	25	22	21	10	0
RT + cet p16 negative	43	29	22	18	15	6	0
RT + cet p16 positive	41	39	36	35	31	17	0

Presented by: David I. Rosenthal

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Vassiliki Papadimitrakopoulou at 2014 ASCO Annual Meeting

Why Deintensification?

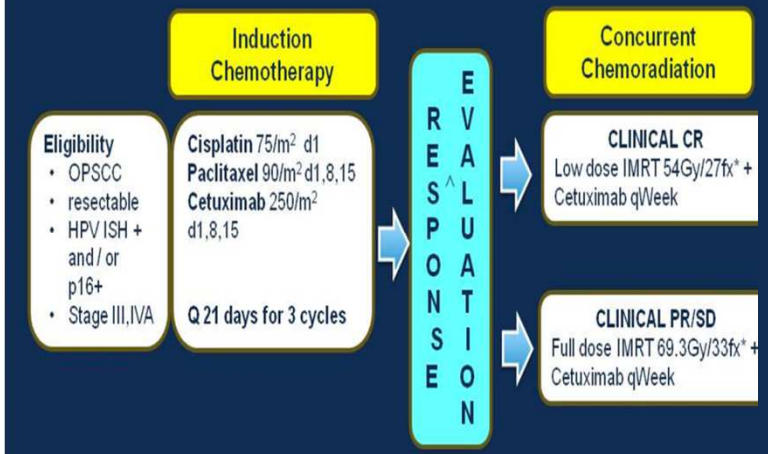
- Patients with HPV-associated cancer have improved cure rates after conventional chemoradiation
- Current CRT regimens developed among HPV-negative patients
- Deintensified therapy might
  - Reduce acute discomforts and risks of treatment
  - Reduce late effects on swallowing, pain, xerostomia, psychological health, and non-cancer mortality
  - Conserve health care resources

PRESENTED AT: ASCO Annual '15 Meeting

E1308: A Phase II Trial of Induction Chemotherapy Followed by Cetuximab with Low Dose vs. Standard Dose IMRT in Patients with HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx

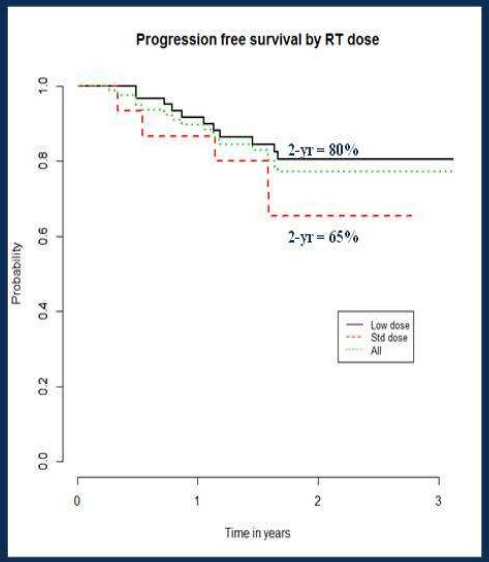
Anthony Cmelak, Shuli Li, Shanthi Marur, Weiqiang Zhao, Zhang W, William Westra, Christine Chung, Maura Gillison, Jill Gilbert, Julie Bauman, Lynne Wagner, Robert Ferris, David Trevarthen, Dimitri Colevas, Balkrishna Jahagirdar, Barbara Burtness

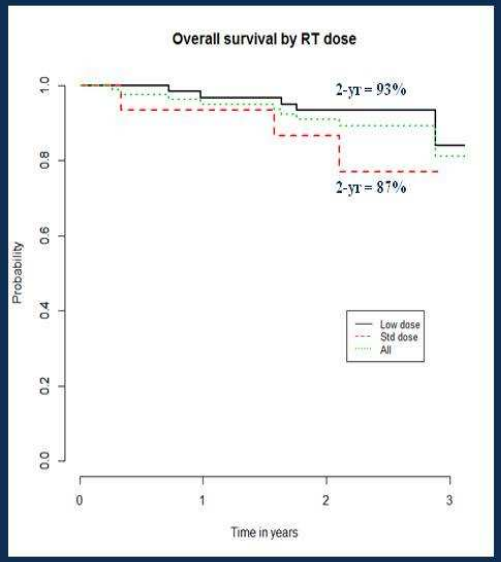
ECOG 1308: Phase II Schema



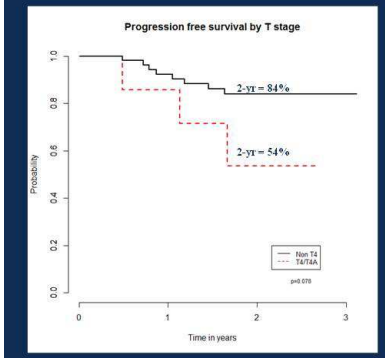
IMRT margins for primary: 1.0 to 1.5cm around gross dz
Nodal margin: 1cm margin minimum, treat entire nodal level

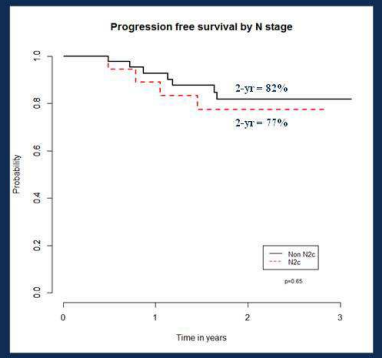
PFS and Survival: Dose





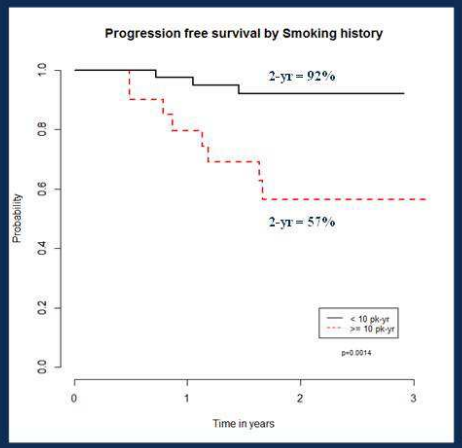
Low Dose: T stage and N stage

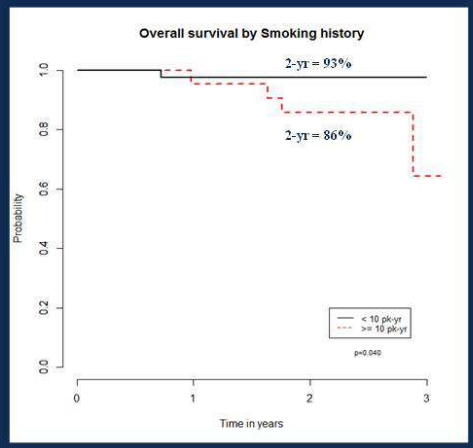




17 Presented by: Anthony J. Cmelak, MD PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Smoking: PFS and Survival





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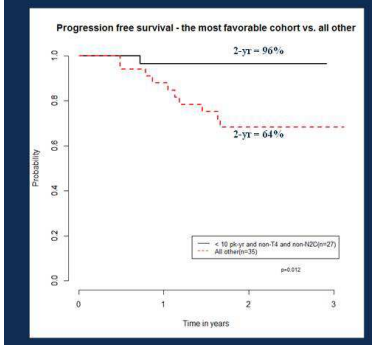
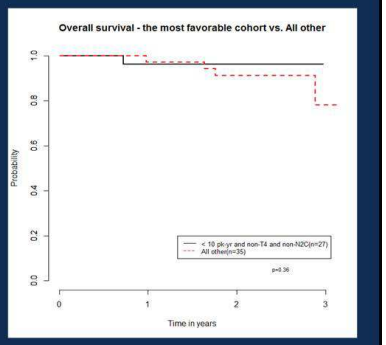
Best Outcome: <T4, T1-N2b, <10 pk-yr





19 Presented by: Anthony J. Cmelak, MD PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Anthony Cmelak at 2014 ASCO Annual Meeting

Clinical Trials Testing Specific Treatments for HPV-Related HNSCC

- RTOG 1333 (Phase III) – DESIGN

Result awaited

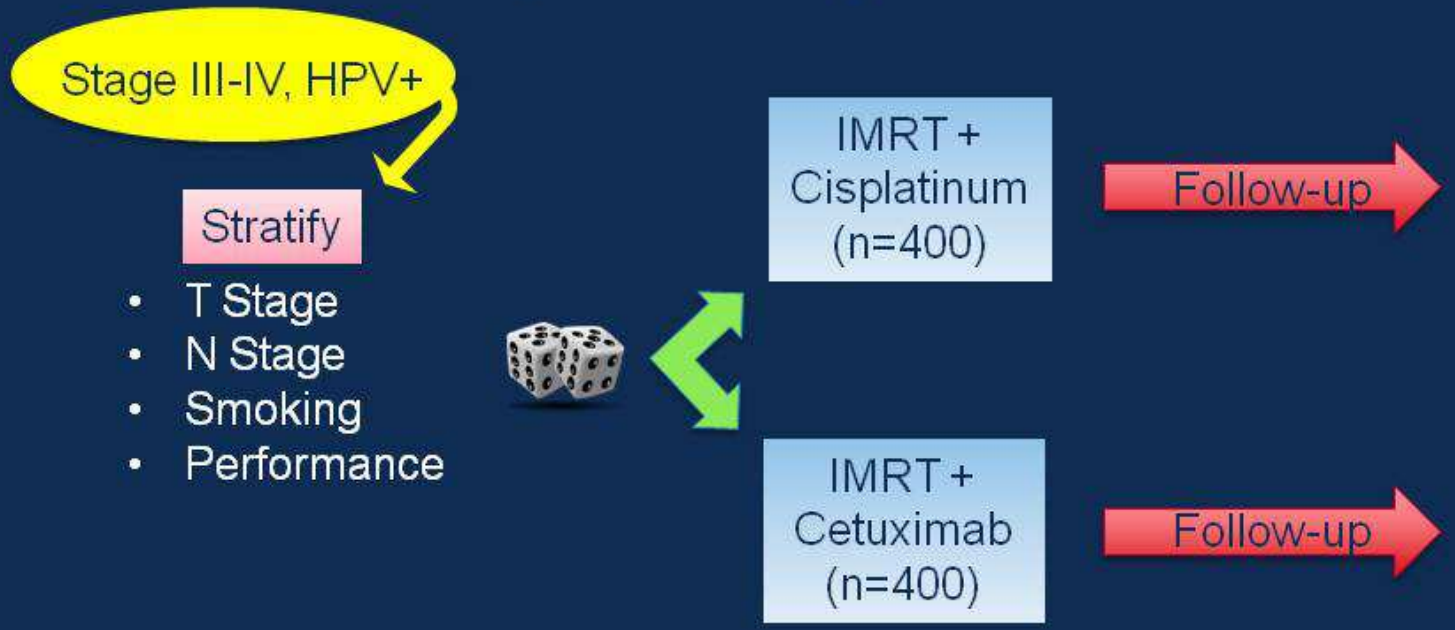
Presented By Stephen Schwartz at 2014 ASCO Annual Meeting

IS THERE ANY ROLE OF HYPOXIC SENSITISER IN HPV +VE PATIENTS

NO THERE IS NO ROLE

Clinical Trials Testing Specific Treatments for HPV-Related HNSCC

- RTOG 1016 (Phase III) – DESIGN



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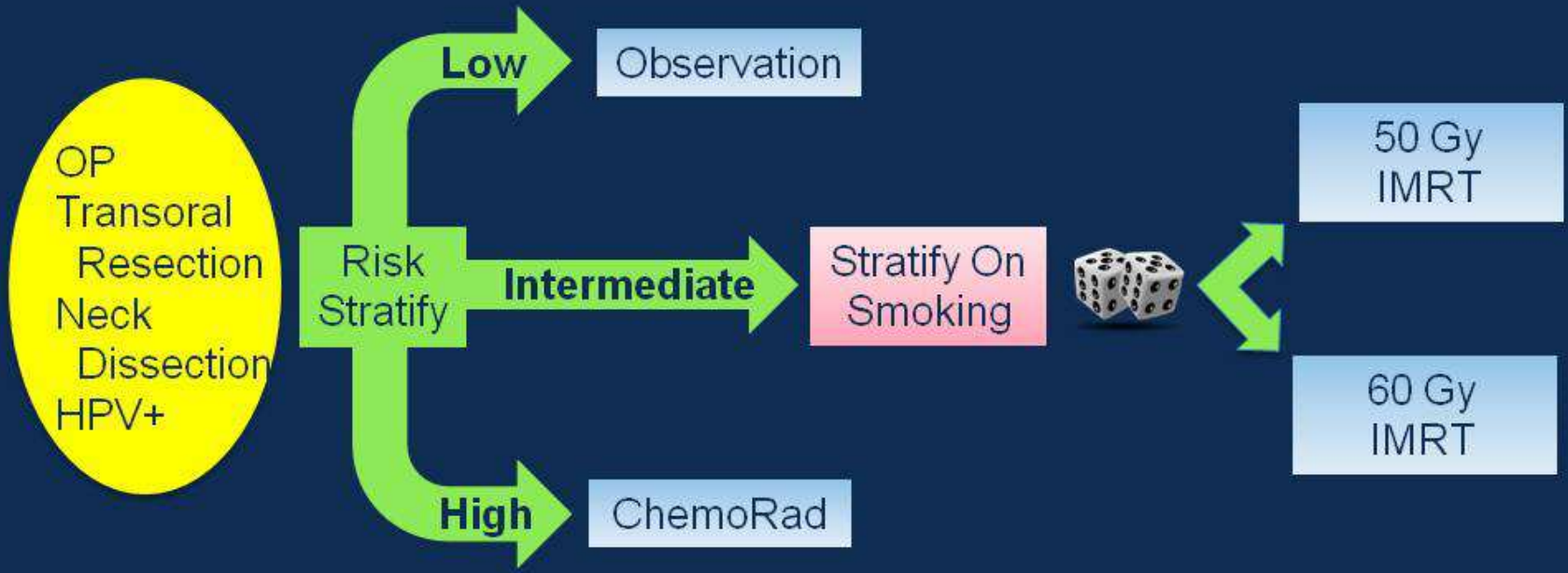
Clinical Trials Testing Specific Treatments for HPV-Related HNSCC

- ECOG 3311 (Phase III) – DESIGN



Presented By Stephen Schwartz at 2014 ASCO Annual Meeting

SHOULD WE VACCINATE *TO PREVENT HPV-RELATED OROPHARYNGEAL CARCINOMAS?*

- PROPHYLACTIC VACCINE COMPOSED OF ***HPV-16 VIRAL CAPSID PROTEINS***
- ***PREVENTS PERSISTENT HPV-16 INFECTION.***
- ***PREVENTS DEVELOPMENT OF CERVICAL DYSPLASIA .***
- **NO DATA YET ON ORAL HPV INFECTION CANINE AND HAMSTER WORK PROMISING**

- HPV-16 IS RESPONSIBLE FOR ONLY 50-60% OF CERVICAL CANCERS
- IN HPV + OROPHARYNGEAL CANCER, HPV-16 SUBTYPE IS PRESENT IN 94% OF THESE CANCERS
- ***THE HPV VACCINE SHOULD BE EVEN MORE EFFECTIVE IN HEAD AND NECK CANCER***

HPV VACCINES

1. GARDASIL (QUADRIVALENT, HPV 16, 18, 6, 11)

- *DEVELOPED BY RESEARCHERS AT GEORGETOWN, UNIV OF ROCHESTER, UNIV OF QUEENSLAND, AND THE US NATIONAL CANCER INSTITUTE FROM WORK BEGUN IN THE 1980S.*
- *APPROVED BY FDA FOR GIRLS IN 2006*
- *APPROVED BY FDA FOR BOYS FOR PREVENTION OF GENITAL WARTS IN OCTOBER 2009*

2. CERVARIX (BIVALENT HPV 16, 18)

APPROVED BY FDA IN 2009

BY 2020….

- THE ANNUAL NUMBER OF HPV-POSITIVE OPSCCS (APPROXIMATELY 8,700 PATIENTS) WILL SURPASS THE ANNUAL NUMBER OF CERVICAL CANCERS (APPROXIMATELY 7,700 PATIENTS) WITH THE MAJORITY OCCURRING AMONG MEN (APPROXIMATELY 7,400).
- BY 2030, OPSCC WILL LIKELY CONSTITUTE A MAJORITY (47%) OF ALL HEAD AND NECK CANCERS.

Chaturvedi A K et al. JCO 2011

TAKE HOME MESSAGE-1

- ***IN LAST TWO DECADES INCREASE IN HPV-ASSOCIATED OROPHARYNGEAL CANCER.***
- ***THIS UNCAPSULATED dsDNA VIRUS HAS 120 SEROTYPES, OF WHICH TYPE 16 IS MOST PREVALENT.***
- **E6 & E7 ARE MAIN PROTEINS BEHIND ITS ONCOGENESIS.**
- **BY DESRUCTION OF P53 TUMOR SUPRESSOR PROTEIN (P53 & Prb pathway respectively).**
- **P16 IS THE SURROGATE MARKER FOR HPV INFECTION.**
- **PCR IS THE MOST SENSITIVE TEST(SINCE SALIVA HAS A LOWER DETECTION RATE DUE TO POOR YIELD OF EXFOLIATED CELLS).**
- **RECENT STUDY SHOWS MORE PREVALENCE IN HIGH SCHOOL EDUCATED, HIGH ANNUAL INCOME, MARIJUANA USE, SEX BEHAVIOUR.**
- **MALE IS MORE PRONE AS EARLY INFECTION IN FEMALES CAUSE SEROCONVERSION AND CONSEQUENT INCREASED BODY IMMUNITY**
- **HPV +VE TUMOR HAS FAVOURABLE PROGNOSIS.**
- **A FEW TRIAL SHOWS FAVOURABLE RESPONSE TO INDAUCTION CT (TAXANE BASED) IN HPV +VE OPSCC**
- **ANTI EGFR ANTIBODY LIKE CETUXIMAB HAS INCREASED INCIDENCE OF COMPLETE RESPONSE IN CCRT**

TAKE HOME MESSAGE-2

- **RESPONSE IS DUE TO IMMUNOLOGICAL**
- **ON ACCOUNT OF ITS HIGH RESPONSE RATE RT DOSE DE INTENSIFICATION HAS BEEN TRIED WITH FAVOURABLE RESULT AND FEWER COMPLICATION IN HPV +VE OPSCC.**
- **FURTHER STUDIES ARE ON GOING TO FIND OUT SPECIFIC RISK STRATIFICATION ON THE BASIS OF LESS CIGARETTE SMOKING PACK YEAR, EARLY STAGES, HPV POSITIVITY**
- **AFTER INTRODUCTION OF VACCINES IN CERVICAL CANCER TEHRE IS ENTHUSIASM REGARDING ITS USE IN HPV+VE OPSCC. (VALIDATION IS FURTHER REQUIRED)**

THANK YOU