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 IN 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

Naked virus

Enveloped virus

Capsid (composed of capsomeres)

Nucleic acid

Nucleocapsid

Capsid

Nucleic acid

Envelope
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

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
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<tbody>
<tr>
<td>E6</td>
<td>Destruction of p53 tumor suppressor protein</td>
</tr>
<tr>
<td>E7</td>
<td>Inactivation of pRB tumor suppressor protein</td>
</tr>
<tr>
<td>E1</td>
<td>Viral DNA replication</td>
</tr>
<tr>
<td>E2</td>
<td>Viral DNA replication and repression of E6 and E7</td>
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<tr>
<td>E5</td>
<td>Interaction with epidermal growth factor</td>
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<tr>
<td>L1</td>
<td>Major capsid protein</td>
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<tr>
<td>L2</td>
<td>Minor capsid protein</td>
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</tbody>
</table>

**HPV-16**

7904 bp
Integrated HPV

Gene transcription

E6 + p53

p53 degradation

Loss of tumor suppression by p53

E7 + Rb

E2F transcription factor (Rb-bound)

E2F (unbound)

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 CENTROSONE DUPLICATION LEADING TO ANEUPLOIDY
HPV-Negative

p16 loss (~80-90%)
- Chromosomal/gene deletion (29%)
- Hypermethylation (23-58%)
- Gene mutation (9-12%)

HPV-Positive

P16

CDK4
CDK6
Cyclin D

CYTOPLASM

NUCLEUS

S Phase Gene Expressions

Presented By Christine H. Chung, MD at 2013 ASCO Annual Meeting
HOW TO TEST HPV

• 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

WHY P16 IS A SURROGATE MARKER? ISH OR PCR, WHICH IS BETTER
HPV IN SALIVA AND ORAL EXFOLIATED CELLS HAS BEEN DETECTED IN SOME RECENT STUDIES, BUT THE SENSITIVITY AND SPECIFICITY FOR HPV-RELATED HNSCC ARE TOO LOW AND THE ROLE OF HPV DETECTION IN SALIVA AND ORAL EXFOLIATED CELLS SEEMS UNCERTAIN.

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

PCR>ISH IN PARAFFIN BLOCK

Zhao M Rosenbaum E et.al, Int J of Cancer, 2005;117:605-10
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
• OROPHARYNX IS THE MOST COMMON TYPE.
• HPV 16 IS THE MOST COMMON TYPE.
HPV in Indian Scenario

- DATA ON HPV PREVALENCE IS NOT ROBUST.

- PREVALENCE 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.


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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type and location of lesion</th>
<th>Method</th>
<th>No. positive cases</th>
<th>%</th>
<th>HPV type</th>
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<td>Syrjanen et al. (60)</td>
<td>1987</td>
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<td>Smith et al. (71)</td>
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<td>Shi et al. (31)</td>
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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

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

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

MORK et.al. NEJM 2001
## SPECIAL CHARACTERISTICS OF HPV-POSITIVE TUMOURS

<table>
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<tr>
<th></th>
<th>HPV POSITIVE</th>
<th>HPV NEGATIVE</th>
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<td><strong>ANATOMICAL SITE</strong></td>
<td>TONSIL, BOT</td>
<td>ALL SITES</td>
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<td><strong>HISTOLOGY</strong></td>
<td>NON-KERATINISING, UNDIFFERENTIATED, BASALOID VERITY</td>
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<td><strong>AGE</strong></td>
<td>YOUNGER</td>
<td>OLDER</td>
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<td><strong>SEX RATIO(M:F)</strong></td>
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<td><strong>STAGE</strong></td>
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<td><strong>RISK FACTORS</strong></td>
<td>SEXUAL BEHAVIOR, HIGHER SOCIO ECONOMIC STATUS, HIGHER EDUCATION</td>
<td>ALCOHOL, TOBACCO</td>
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<tr>
<td><strong>INCIDENCE</strong></td>
<td>INCREASING</td>
<td>DECREASING</td>
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Results

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

Mutation frequency (%)
0  10  20  30  40  50  60  70

HPV- cases
TP53  CDKN2A  STK11  NOTCH1  MYC  PIK3CA  MET  FAT1  FGFR3  NFE2L2  PTEN  CDH1  FBXW7  KDR  KRAS  SMAD4
24%  63%

HPV+ cases
TP53  CDKN2A  STK11  NOTCH1  MYC  PIK3CA  MET  FAT1  FGFR3  NFE2L2  PTEN  CDH1  FBXW7  KDR  KRAS  SMAD4
4%  9%  28%

Presented By Inge Tinhofer at 2015 ASCO Annual Meeting
Oropharynx Carcinogenesis: 3 classes

Class I
- p16 inactivation
- p53 mutation
- HPV negative

Class II
- p16 inactivation
- p53 mutation
- HPV positive

Class III
- p16 not inactivated
- p53 wild type (E6 degrades)
- HPV present

p16 is a diagnostic marker

Results: OS according to TP53 mutations, HPV and Smoking

- HPV-positive, p53 wt & Never/Ex-smokers
- HPV-positive, p53 wt & Current smoker
- HPV-negative p53 mut disruptive
- HPV-negative p53 wt/mut non-disruptive

Log-rank: p = 0.008
Log-rank: p = 0.04

Time [months]
Overall survival
Smoking HAS IT ANY IMPACT ON SURVIVAL

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)

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

YES
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<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>2 yr Survival</th>
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<td>HPV +, &lt;20py</td>
<td>1.0</td>
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<tr>
<td>HPV +, &gt;20py</td>
<td>1.91</td>
<td>1.2-3.05</td>
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<td>HPV -, &lt;20py</td>
<td>2.25</td>
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<tr>
<td>HPV -, &gt;20py</td>
<td>4.30</td>
<td>2.4-7.71</td>
<td>63%</td>
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Does tobacco alter the survival in HPV +ve malignancy?

Yes, sure

Ang et al. NEJM 2010
HPV-Related HNSCC are Associated with Favorable Prognosis

<table>
<thead>
<tr>
<th>SITE</th>
<th>STUDY</th>
<th>YEAR</th>
<th>Hazard Ratio &amp; 95% CI</th>
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<td>HNC</td>
<td>Smith et al</td>
<td>2010</td>
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<tr>
<td>HNSCC</td>
<td>Kong et al</td>
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<td>Tonsillar SCC</td>
<td>Strome et al</td>
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<td>Ernst et al</td>
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<td>Zhao et al</td>
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<td>Tonsillar SCC</td>
<td>Chien et al</td>
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<tr>
<td>Overall (I-squared = 34.6%, p = 0.121)</td>
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<td>Meta-HR = 0.28 (95% CI = 0.19, 0.40)</td>
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PRESENTED AT: ASCO 50th Annual Meeting Science & Society
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

Homogeneous Tumor

Fewer cell populations and (S) sensitive

Heterogeneous Tumor

More cell populations and now a resistant (R) cell population

Radiation with Chemotherapy

CURE!

Treatment Failure

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.
Representative MATH Scores

Homogenous Tumor

Heterogeneous Tumor

Low-MATH

MATH 19 ± 3

Medium

MATH 34 ± 4

High-MATH

MATH 54 ± 5

Presented By David Raben at 2014 ASCO Annual Meeting
Higher MATH scores related to disruptive p53 mutations


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
MATH and HPV status provide greater prognostic information

Presented By David Raben at 2014 ASCO Annual Meeting
Radiation and Cisplatin Synergize to enhance immune mediated clearance

Presented By John Lee at 2014 ASCO Annual Meeting
Star Wars/tumor metabolism approach to Cure HPV+ Cancers

- Tumor Lactate 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Cooperative Group</th>
<th>N</th>
<th>XRT</th>
<th>Induction</th>
<th>Concurrent</th>
<th>Median F/U</th>
<th>HPV+</th>
<th>Time</th>
<th>HPV+</th>
<th>HPV-</th>
<th>P-value</th>
<th>HAZARD RATIO HPV+ vs HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakhry</td>
<td>ECOG</td>
<td>96</td>
<td>70Gy</td>
<td>2 cycles paclitaxel 175mg/m2 carbo AUC6</td>
<td>weekly paclitaxel 30mg/m2 x 7</td>
<td>39 mo</td>
<td>40%</td>
<td>2-year</td>
<td>95%</td>
<td>62%</td>
<td>0.005</td>
<td>0.36</td>
</tr>
<tr>
<td>Rischin</td>
<td>TROG</td>
<td>195</td>
<td>70Gy</td>
<td>none</td>
<td>cisplatin +/- tirapazamine</td>
<td>27 mo</td>
<td>28%</td>
<td>2-year</td>
<td>94%</td>
<td>77%</td>
<td>0.007</td>
<td>0.29</td>
</tr>
<tr>
<td>Gillison</td>
<td>RTOG 0129</td>
<td>323</td>
<td>70-72Gy</td>
<td>none</td>
<td>cisplatin 100mg/m2 x2 or 3</td>
<td>4.8 yrs</td>
<td>64%</td>
<td>3-year</td>
<td>79%</td>
<td>46%</td>
<td>0.002</td>
<td>0.44</td>
</tr>
<tr>
<td>Settle</td>
<td>TAX32 4</td>
<td>119</td>
<td>70-74Gy</td>
<td>3 cycles taxotere 75mg/m2 cisplatin 100mg/m2 5-FU 1000mg/m2/day x 4</td>
<td>weekly carboplatin AUC 1.5 x 7</td>
<td>67 mo</td>
<td>50%</td>
<td>5-year</td>
<td>93%</td>
<td>35%</td>
<td>&lt;0.00</td>
<td>1</td>
</tr>
<tr>
<td>Lassen</td>
<td>DHANC A5</td>
<td>156</td>
<td>62-68Gy</td>
<td>none</td>
<td>nimorazole 1200mg/m2/day x 30</td>
<td>&gt;60 mo</td>
<td>22%</td>
<td>5-year</td>
<td>62%</td>
<td>26%</td>
<td>0.003</td>
<td>0.44</td>
</tr>
</tbody>
</table>
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
### p16 and HPV Result Summary

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

Presented By Christine H. Chung, MD at 2013 ASCO Annual Meeting
Progression-free survival

HR (95% CI) \([p16\text{-positive}/p16\text{-negative}]\)
0.65 (0.44-0.98)
2-sided log-rank \(p=0.04\)

Patients at Risk
\[\begin{array}{cccccccc}
p16\text{-positive} & 62 & 45 & 38 & 34 & 23 & 10 \\
p16\text{-negative} & 260 & 167 & 131 & 106 & 74 & 23 \\
\end{array}\]
Overall survival

HR (95% CI) [p16-positive/p16-negative]
0.57 (0.36-0.90)
2-sided log-rank p=0.01

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

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

Patients at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Years after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16-pos op</td>
<td>0</td>
</tr>
<tr>
<td>p16-pos nonop</td>
<td>62</td>
</tr>
<tr>
<td>p16-neg op</td>
<td>198</td>
</tr>
<tr>
<td>p16-neg nonop</td>
<td>260</td>
</tr>
</tbody>
</table>

Presented by Christine H. Chung, MD at 2013 ASCO Annual Meeting
# Interaction of p16 status and Primary site in survival outcomes

<table>
<thead>
<tr>
<th></th>
<th>Comparison</th>
<th>Subsite</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>p16-pos vs. p16-neg</td>
<td>OPSCC</td>
<td>0.37 (0.29-0.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-OPSCC</td>
<td>0.67 (0.45-1.00)</td>
</tr>
<tr>
<td></td>
<td>OPSCC vs. non-OPSCC</td>
<td>p16-pos</td>
<td>0.54 (0.36-0.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p16-neg</td>
<td>0.99 (0.77-1.26)</td>
</tr>
<tr>
<td></td>
<td>p-value for interaction</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>p16-pos vs. p16-neg</td>
<td>OPSCC</td>
<td>0.29 (0.22-0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-OPSCC</td>
<td>0.58 (0.36-0.91)</td>
</tr>
<tr>
<td></td>
<td>OPSCC vs. non-OPSCC</td>
<td>p16-pos</td>
<td>0.48 (0.30-0.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p16-neg</td>
<td>0.97 (0.74-1.27)</td>
</tr>
<tr>
<td></td>
<td>p-value for interaction</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>
HPV+ OPSCC: Favorable Prognosis E2399 Organ Preservation Trial

Induction chemotherapy (IC)
Paclitaxel 175 mg/m² IV
Carboplatin AUC 6 IV Q21d
X 2 cycles

Concurrent chemoradiation (CRT)
70 Gy / 35 fx / 7 weeks
Concurrent with Paclitaxel 30 mg/m²/wk

RESPONSE: CR/PR
HPV + vs. HPV-
81.6 % vs 55.2%

RESPONSE: CR/PR
HPV + vs. HPV-
84.2 % vs 56.9%
2 yr PFS: 86% vs 53%
P=0.02

Cmelak et al J Clin Oncol. 2007 Sep 1;25(25):3971-7
Fakhry et al J Nat Cancer Inst 100(4):

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

HR = 0.68 [95% CI: 0.52–0.89]  
\( p = 0.005 \)

3-year control rate

24.4 months  
RT: 47%  
RT + cet:

14.9 months  
RT: 34%  
RT + cet:

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>RT + cet</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>193</td>
<td>60</td>
</tr>
<tr>
<td>101</td>
<td>101</td>
<td>51</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

OS

HR = 0.73 [95% CI: 0.56–0.95]  
\( p = 0.018 \)

5-year survival rate

29.3 months  
RT: 36%  
RT + cet:

49.0 months  
RT: 46%  
RT + cet:

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>RT + cet</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>193</td>
<td>60</td>
</tr>
<tr>
<td>101</td>
<td>101</td>
<td>51</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

HR, hazard ratio; LA-SCCHN, locally advanced squamous cell carcinoma of the head and neck; LRC, locoregional control; RT, radiotherapy.
LRC in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs RT alone

LRC interaction test p=NS

<table>
<thead>
<tr>
<th>LRC (months)</th>
<th>Probability of LRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.9</td>
</tr>
<tr>
<td>24</td>
<td>0.8</td>
</tr>
<tr>
<td>36</td>
<td>0.7</td>
</tr>
<tr>
<td>48</td>
<td>0.6</td>
</tr>
<tr>
<td>60</td>
<td>0.5</td>
</tr>
<tr>
<td>72</td>
<td>0.4</td>
</tr>
<tr>
<td>84</td>
<td>0.3</td>
</tr>
<tr>
<td>96</td>
<td>0.2</td>
</tr>
<tr>
<td>108</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>p16 negative</th>
<th>p16 positive</th>
<th>RT + cet</th>
<th>p16 negative</th>
<th>RT + cet</th>
<th>p16 positive</th>
<th>p16 negative</th>
<th>RT + cet</th>
<th>p16 positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>34</td>
<td>31</td>
<td>17</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
</tbody>
</table>

HR=0.31 [0.11–0.88]

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

OS interaction test p=NS

RT + cet; p16+
HR=0.38 [0.15–0.94]
72%
RT: p16+
42%
RT + cet; p16−
RT: p16−
33%

No. at risk OPC p16 evaluable (n=182)
RT p16 negative 84 47 27 19 18 13 0
RT p16 positive 34 20 25 22 21 10 0
RT + cet p16 negative 43 29 22 18 15 6 0
RT + cet p16 positive 41 38 36 35 31 17 0

Presented by: David I. Rosenthal

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
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


ECOG 1308: Phase II Schema

**Induction Chemotherapy**
- Cisplatin 75mg²d⁻¹×1
- Paclitaxel 90mg²d⁻¹×8,15
- Cetuximab 250mg²d⁻¹×8,15
- Q 21 days for 3 cycles

**Concurrent Chemoradiation**
- CLINICAL CR
  - Low dose IMRT 54Gy/27fx + Cetuximab qWeek
- CLINICAL PR/SD
  - Full dose IMRT 69.3Gy/33fx + Cetuximab qWeek

PFS and Survival: Dose

**Progression free survival by RT dose**
- 2-yr = 92%
- 2-yr = 60%

**Overall survival by RT dose**
- 2-yr = 93%
- 2-yr = 81%

IMRT margins for primary: 1.0 to 1.5cm around gross tz
Nodal margin: 1cm margin minimum, treat entire nodal level
Low Dose: T stage and N stage

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

Smoking: PFS and Survival

Presented By Anthony Cmelak at 2014 ASCO Annual Meeting
Clinical Trials Testing Specific Treatments for HPV-Related HNSCC

- RTOG 1333 (Phase III) – DESIGN

OP
HPV+
≤10 pck-yrs
T1-T2, N1-N2b
T3, N0-N2b

ChemoRad
(60 Gy rad, cisplatinum)

Rad Only
(60 Gy rad)

Result awaited
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

  Stage III-IV, HPV+
  
  Stratify
  - T Stage
  - N Stage
  - Smoking
  - Performance

  IMRT + Cisplatinum (n=400)
  Follow-up

  IMRT + Cetuximab (n=400)
  Follow-up
Clinical Trials Testing Specific Treatments for HPV-Related HNSCC

- ECOG 3311 (Phase III) – DESIGN

- OP Transoral Resection Neck Dissection HPV+

- Low Risk Stratify
  - Observation

- Intermediate Risk Stratify
  - Stratify On Smoking
    - 50 Gy IMRT
    - 60 Gy IMRT

- High Risk Stratify
  - ChemoRad
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 DESTRUCTION 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