56th Annual Meeting
American Society for Radiation Oncology

Meet-the-Expert:
“Technology and Biology: The Next Generation of Progress”

Moderator: Laura A. Dawson, MD

Wednesday, Sept. 16, 2014
7 a.m. (PT)
Predictive Value of p16 Status on the Development of a Pathologic Complete Response (pCr) at Planned Neck Dissection after Cisplatin Based Chemoradiation – A Second Analysis of RTOG 0129

1TJ Galloway; 2QE Zhang; 3PF Nguyen-Tan; 4D Rosenthal; 3D Soulières; 5AFortin; 6C Silverman; 7M Daly; 1JA Ridge; 8JA Hammond; 9QT Le

1. Fox Chase Cancer Center; 2. NRG Oncology Statistics and Data Management Center; 3. Centre Hospitalier de l’Université de Montréal-Notre Dame; 4. University of Texas-MD Anderson Cancer Center; 5. L Hotel-Dieu de Quebec; 6. The James Brown Cancer Center – University of Louisville; 7. University of California Davis Medical Center; 8. London Regional Cancer Program; 9. Stanford University Medical Center
Background

• RTOG 0129 was a randomized phase III trial investigating chemotherapy and radiation for lymph node positive head and neck cancer.

• Many patients had the initially involved nodes removed after the completion of chemotherapy and radiation

• Pathologic response of the lymph nodes is prognostic.

• This analysis sought to determine if the recent emergence of HPV associated oropharynx cancer influenced pathologic response rates on the post-radiation neck dissection performed on RTOG 0129
Background

49 yo male, Lymph node positive SCCA of the tonsil, p16+

p16: Protein produced by HPV-associated oropharynx tumors.

Pre-chemoradiation

Post-chemoradiation
Background

RTOG 0129 Neck Dissection Analysis

721 patients

433 oropharynx cancer patients

316 patients with a known p16 status

23 with an N0 neck

46 with an N1 neck

247 with an N2a, N2b, N2c, N3 neck

193 initially involved necks observed

99 neck dissections within 180 days of the completion of chemoradiotherapy
Analysis

Post-chemoRT Neck Assessment

<table>
<thead>
<tr>
<th>Clinical/Radiographic Neck Assessment</th>
<th>HPV+ (n=69)</th>
<th>HPV- (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent abnormality</td>
<td>55%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>No disease</td>
<td>26%</td>
<td>27%</td>
<td>0.42</td>
</tr>
<tr>
<td>Unknown/no assessment</td>
<td>19%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic Neck Assessment</th>
<th>HPV+ (n=69)</th>
<th>HPV- (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Path CR</td>
<td>78%</td>
<td>53%</td>
<td>0.017</td>
</tr>
<tr>
<td>No Path CR</td>
<td>22%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>
# Analysis

## Local-regional Failure after Neck Dissection
(Cox model)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>If HPV-</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic CR (yes v no)</td>
<td></td>
<td>0.31 (0.11-0.88)</td>
<td>0.028</td>
</tr>
<tr>
<td>Pathologic CR (yes v no)</td>
<td>If HPV+</td>
<td>0.68 (0.18-2.59)</td>
<td>0.57</td>
</tr>
<tr>
<td>HPV status (pos v neg)</td>
<td>If not path CR</td>
<td>0.13 (0.03 – 0.48)</td>
<td>0.0025</td>
</tr>
<tr>
<td>HPV status (pos v neg)</td>
<td>If pathCR</td>
<td>0.28 (0.10 – 0.80)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

P-value for interaction between pathologic CR and p16 status: 0.3669
Comparison of Neck Dissection v. Neck Observation
## Results

Post-chemoradiotherapy Neck Status as Determined by Clinical/Radiographic Reporting

<table>
<thead>
<tr>
<th>Neck status after chemoRT</th>
<th>HPV+</th>
<th>p-value</th>
<th>HPV-</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck Dissected n = 69</td>
<td>55%</td>
<td>14%</td>
<td>43%</td>
<td>24%</td>
</tr>
<tr>
<td>Neck Observed n = 130</td>
<td>14%</td>
<td>27%</td>
<td>67%</td>
<td>0.001</td>
</tr>
<tr>
<td>Persistent abnormality</td>
<td>55%</td>
<td>14%</td>
<td>43%</td>
<td>24%</td>
</tr>
<tr>
<td>No disease</td>
<td>26%</td>
<td>72%</td>
<td>27%</td>
<td>67%</td>
</tr>
<tr>
<td>Unknown/no assessment</td>
<td>19%</td>
<td>14%</td>
<td>30%</td>
<td>10%</td>
</tr>
</tbody>
</table>
## Results

### Local-regional Failure

<table>
<thead>
<tr>
<th>2-year Local-Regional Failure (HPV+)</th>
<th>Patients</th>
<th>Estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed neck w/ clinical CR</td>
<td>94</td>
<td>9.9 (4.8-17.1)</td>
</tr>
<tr>
<td>pCR neck dissection</td>
<td>54</td>
<td>7.5 (2.4-16.7)</td>
</tr>
<tr>
<td>Persistent tumor neck dissection</td>
<td>15</td>
<td>20.0 (4.5-43.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-year Local-Regional Failure (HPV-)</th>
<th>Patients</th>
<th>Estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed neck w/ clinical CR</td>
<td>42</td>
<td>19.2 (8.9-32.5)</td>
</tr>
<tr>
<td>pCR neck dissection</td>
<td>16</td>
<td>26.0 (7.5-49.6)</td>
</tr>
<tr>
<td>Persistent tumor neck dissection</td>
<td>14</td>
<td>75.0 (36.0-92.2)</td>
</tr>
</tbody>
</table>
Conclusions

• Patients with p16+ tumors had significantly higher complete pathologic response rates than those with p16- tumors.

• Patients with a complete clinical/radiographic response in the neck were more likely to be managed without a neck dissection, and had a failure rate similar to patients with a complete pathologic response.
The Significance of p16 and p53 Expression on Clinical Outcome in Patients with Anal Cancer Treated with Chemoradiotherapy: *An Analysis of RTOG 98-11*

Corinne M. Doll; Kathryn Winter; Jaffer Ajani; Alexander Klimowicz; Christopher H. Crane; Lisa A. Kachnic; Gordon Okawara; Himanshu Lukka; Lawrence Berk; Kevin Roof; Mark Becker; David L Grisell; Chandan Guha; and Anthony M. Magliocco

Supported by NCI grants:
U10 CA21661, U10 CA37422, and U24 CA114734
Background

• Several studies show prognostic significance of human papillomavirus (HPV) and outcome in patients with squamous oropharyngeal cancers
  - Improved outcome in HPV+ tumors and chemoradiotherapy (CRT)

• Impact of HPV pathway activation on prognosis in patients with anal cancer not as well defined
Background

HPV Effect

• The HPV protein E6 binds p53 and targets the protein for degradation

• E7 protein binds and inactivates Rb protein, which causes p16 expression to increase
Background

RTOG 98-11

• Phase III RCT: 5FU, MMC and RT vs. 5FU, cisplatin and RT for carcinoma of the anal canal, n=682

• Concurrent chemoradiation with 5FU-MMC has a statistically significant impact on DFS and OS vs. induction + concurrent 5FU-CDDP

• Potential strategies to improve outcomes include treatment intensification/modification and individualized molecular-based treatment

Aims

• Measure expression of p16 (surrogate for HPV) and p53 (tumor suppressor protein) in pre-treatment tumor biopsies of anal cancer patients enrolled on RTOG 98-11

• Correlate expression with patient outcome
Methodology

• Retrospective analysis of RTOG 98-11, pre-treatment anal cancers, n=155 analyzed

• Quantitative immunohistochemistry expression of p16 and p53 proteins for each tumor sample (core)

• Protein expression was analyzed using X-tile cut-points defining high (H) vs. low (L) expression status, based on overall survival

• Associations between the tumor marker categories and clinical outcome parameters
  ▪ Cox proportional hazards models
Results

Fluorescence IHC and AQUA® Results for p16 and p53 in RTOG 98-11 Anal Cancers

Examples of p16 and p53 staining in:

- Normal tissue
- RTOG 98-11 cores with high p16/low p53 expression
- RTOG 98-11 cores with low p16/high p53 expression
### Results

**Patient/tumor characteristics by p16 and p53 status**

<table>
<thead>
<tr>
<th></th>
<th>H-p16/L-p53 (n=126, 81%)</th>
<th>Other (n=29, 19%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>RX</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>RT+5FU/MMC</td>
<td>66 52.4%</td>
<td>12 41.4%</td>
<td></td>
</tr>
<tr>
<td>RT+5FU/CDDP</td>
<td>60 47.6%</td>
<td>17 58.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>&lt; 55</td>
<td>56 44.4%</td>
<td>20 69.0%</td>
<td></td>
</tr>
<tr>
<td>≥ 55</td>
<td>70 55.6%</td>
<td>9 31.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td>0.0034</td>
</tr>
<tr>
<td>Male</td>
<td>34 27.0%</td>
<td>16 55.2%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92 73.0%</td>
<td>13 44.8%</td>
<td></td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td>60-80</td>
<td>21 16.7%</td>
<td>11 37.9%</td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td>105 83.3%</td>
<td>18 62.1%</td>
<td></td>
</tr>
<tr>
<td><strong>T-stage</strong></td>
<td></td>
<td></td>
<td>0.0084</td>
</tr>
<tr>
<td>T2</td>
<td>96 76.2%</td>
<td>15 51.7%</td>
<td></td>
</tr>
<tr>
<td>T3/T4</td>
<td>30 23.8%</td>
<td>14 48.3%</td>
<td></td>
</tr>
<tr>
<td><strong>N-stage</strong></td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>N0/NX</td>
<td>99 78.6%</td>
<td>23 79.3%</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>27 21.4%</td>
<td>6 20.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Largest T-size</strong></td>
<td></td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>≤ 5cm</td>
<td>99 78.6%</td>
<td>17 58.6%</td>
<td></td>
</tr>
<tr>
<td>&gt; 5cm</td>
<td>27 21.4%</td>
<td>12 41.4%</td>
<td></td>
</tr>
</tbody>
</table>

Patients whose tumors had high p16/low p53 status were more likely: **Female, better performance status, smaller tumors**

4-year OS for patients with high p16/low p53 was **88%** (95% CI: 80%, 92%) vs. **60%** (95% CI: 39%, 75%) for other
### Multivariate Analyses

Patients with high p16/low p53 expression had better outcomes

#### OS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>95% C.I. LL</th>
<th>95% C.I. UL</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-p16/L-p53</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>3.80</td>
<td>2.02</td>
<td>7.15</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

#### DFS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>95% C.I. LL</th>
<th>95% C.I. UL</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-p16/L-p53</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>2.15</td>
<td>1.23</td>
<td>3.75</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

†p-value from Chi-square test using the Cox proportional hazards model
Conclusions

• In this exploratory analysis of a subset of patients treated with CRT on the RTOG 98-11 protocol:
  ▪ High p16/low p53 tumor status was associated with better clinical outcomes
    o Independently associated with better OS, DFS, LRF

• Further exploration of the optimal biologic cut-point should be evaluated

• Differential treatment strategies could be considered for patients with these distinct tumor subtypes
TARGETING CANCER: TECHNOLOGY & BIOLOGY

ASTRO 56TH ANNUAL MEETING

Welcome
Metabolic Tumor Volume on FDG-PET Predicts Clinical Outcomes Following Chemoradiotherapy for Locally Advanced Non-small Cell Lung Cancer: A Secondary Analysis of ECOG-ACRIN 6668 / RTOG 0235

Nitin Ohri; Fenghai Duan; Mitchell Machtay; Jeremy Gorelick; Bradley Snyder; Abass Alavi; Barry Siegel; Douglas Johnson; Jeffrey Bradley; Albert DeNittis; Maria Werner-Wasik
Background

• Approximately 1/3 of the 220,000 patients diagnosed with non-small cell lung cancer (NSCLC) in the U.S. each year have stage III disease.

• $^{18}$F-FDG positron emission tomography (PET) is an important tool for the staging and radiotherapy planning for patients with NSCLC.

• ECOG-ACRIN 6668 / RTOG 0235:
  - A prospective, multi-institutional trial that evaluated the prognostic value of PET for patients treated with definitive chemoradiotherapy for locally advanced NSCLC.
  - PET was performed before radiotherapy and 12-16 weeks after radiotherapy.
  - Enrolled 251 patients.
Background
ECOG-ACRIN 6668 / RTOG 0235: Primary Analysis

Post-treatment Peak SUV

Survival (probability)

Time Since Post-Treatment PET (months)

J Clin Oncol 31:3823-3830
Purpose

• To evaluate associations between pre- and post-treatment PET metrics and clinical outcomes for stage III NSCLC patients treated with definitive, concurrent chemoradiotherapy.
Methodology

• PET Metrics:
  - Maximum SUV (SUVmax)
  - Metabolic Tumor Volume (MTV)
  - Total Glycolytic Activity (TGA)
Results

• Pre-Treatment PET and Local Control:
  ▪ 79/233 patients (34%) demonstrated local failure.
  ▪ Median time to local failure was 25.3 months after study registration.
  ▪ Independent predictors of local control:
    ○ RT Dose (HR = 0.960 per Gy, p = 0.002)
    ○ Pre-treatment MTV (HR = 1.036 per 10 cc, p = 0.004)

• Pre-Treatment PET and Survival:
  ▪ 159 deaths out of 214 patients (74%).
  ▪ Median survival was 20.0 months after study registration.
  ▪ Independent predictors of survival:
    ○ Age (HR = 1.022 per year, p = 0.030)
    ○ Performance Status (HR = 1.624, p = 0.006)
    ○ RT Dose (HR = 0.974 per Gy, p = 0.002)
    ○ Pre-treatment MTV (HR = 1.040 per 10 cc, p < 0.001)
Results

• Post-Treatment PET and Local Control:
  - 68/164 patients (41%) demonstrated local failure.
  - Median time to local failure was 18.6 months after post-treatment PET.
  - Independent predictors of local control:
    o Post-treatment SUVmax (HR = 1.135, p = 0.002)

• Post-Treatment PET and Survival:
  - 119 deaths out of 170 patients (70%).
  - Median survival was 18.2 months after post-treatment PET.
  - Independent predictors of survival:
    o Age (HR = 1.034 per year, p = 0.006)
    o Performance Status (HR = 1.585, p = 0.021)
    o Pre-treatment MTV (HR = 1.029 per 10 cc, p = 0.019)
    o Post-treatment SUVmax (HR = 1.106, p < 0.001)
Results

Pre-Treatment PET and Survival

MTV

- > 57.2 cc (above median)
- ≤57.2 cc (below median)

p < 0.0001
Conclusion

• PET metrics are strong predictors of clinical outcomes for stage III NSCLC patients treated with definitive chemoradiotherapy.
  ▪ Pre-treatment MTV
  ▪ Post-treatment SUVmax
Targeting Cancer: Technology & Biology

ASTRO 56th Annual Meeting

Welcome
Questions?

Contact ASTRO’s Press Office
In San Francisco, Sept. 14-17, 2014: 415-978-3503
Via email: press@astro.org

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