Genomic Profiles of Lung vs. Head & Neck Squamous Cell Carcinoma

Diagnostic and Clinical Considerations

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Disclosures

• No financial or COI disclosures
Objectives

• Review genomic characteristics of squamous cell carcinomas arising from the head & neck and the lung
• Discuss the predictive, prognostic, and/or diagnostic utility of select biomarkers in tumors arising from these two sites
2016 ACS Estimates
Cancer Incidence by Site

• Oral cavity, pharynx, & larynx
  – Male: 45,420    Female: 16,430
  – Approximately 90% of cases are SqCC
• Lung
  – Male: 117,920   Female: 106,470
  – Approximately 35% of cases are SqCC
• Etiologic factors
  – Tobacco, tobacco, tobacco, alcohol, HPV
Squame vs. Squame

Comprehensive genomic characterization of head and neck squamous cell carcinomas
The Cancer Genome Atlas Network*
JANUARY 2015 | VOL 517 | NATURE

Comprehensive genomic characterization of squamous cell lung cancers
The Cancer Genome Atlas Research Network*
27 SEPTEMBER 2012 | VOL 489 | NATURE
TCGA: Lung SqCC

• 178 patients, previously untreated
  – Stages I-IV (predominantly I-III)
  – 131 male      47 female
  – 96% had a smoking history
• “normal” tissue or peripheral blood
• DNA and RNA analyses
  – Mutation, CNA, Chr Rearrangement, mRNA expression, miRNA expression, DNA methylation
TCGA: Lung SqCC

- Relatively high burden of genomic alteration
- 360 sequence mutations
- 323 copy number alterations (CNA)
  - Less than OvCa
  - Greater than BrCa, GBM, CRC, RCC
- 165 genomic rearrangements
TCGA LSqCC: CNAs

• Many CNAs overlapped with lung adeno
• Notable exception: amplification of 3q
  – SOX2, TP63, PIK3CA
TCGA LSqCC: Mutations

- MutSig: 10 genes recurrently mutated
- Supervised analysis: 12 additional genes
  - Includes: EGFR, BRAF, HRAS, NF1, FBXW7, SMAD4, others
  - EGFR mutation spectrum distinct from lung adenocarcinoma
TCGA LSqCC: Somatically Altered Pathways

- Oxidative Stress Response: cell response to damage 2/2 chemo- and radiotherapy
- Squamous differentiation: cell of origin or mutation gained on the road to malignancy?
Lung Squamous Cell Carcinoma mRNA Expression Subtypes Are Reproducible, Clinically Important, and Correspond to Normal Cell Types

Primitive subtype: lower OS and DFS
TCGA LSqCC: Is it actionable?

- 96% with alterations in some kinase, GPCR, protease, or phosphatase
- 69% of cases with alterations (genomic or expression) in PI3K or RAS pathways
- 64% of cases with alterations targeted by agents that are FDA approved or in clinical trial
TCGA: H&N SqCC

• 279 patients
  – Stages I-IV (half Stage IV)
  – Male: 203   Female: 76
  – 81% smoking hx; 67% EtOH hx

• Anatomic Sites
  – Oral cavity 62%
  – Oropharynx 12%
  – Laryngeal 26%
TCGA: H&N SqCC

- HPV detected in 36 cases (13%)
  - 64% prevalence in oropharyngeal tumors
  - 6% in non-oropharyngeal tumors
- Approach and methods similar, except:
  - HPV status determined by >1000 mapped reads (RNAseq) to E6/E7 viral genes
  - Various other confirmatory methods and clinical data
TCGA: H&N SqCC

- Also a high genomic alteration burden
- 133 sequence mutations
- 141 copy number alterations
- 62 genomic rearrangements
- Mutation rates were not statistically different in HPV- vs. HPV+ cancers
TCGA HNSqCC: CNAs

- Similar to LSqCC: 3q gain (HPV +/-)
- HPV –
  - CDKN2A del (9p)
  - CCND1 amp (11q)
- HPV +
  - TRAF3 del (14q)
  - E2F1 amp (20q)
TCGA HNSqCC: Mutations

- 11 recurrent mutations with FDR $q < 0.1$
  - HPV neg
    - CDKN2A
    - TP53
    - Wnt: FAT1, AJUBA
  - CASP8\textsuperscript{mut}, HRAS\textsuperscript{mut}, TP53\textsuperscript{wt}
    combo = better outcomes
  - HPV pos
    - Different spectrum of PIK3CA mutations
  - NSD1: epigenetic modifier
  - HLA-A and KMT2D
    - Defective immuno-surveillance?
    - Shared with LSqCC
TCGA HNSqCC: Somatically Altered Pathways
TCGA HNSqCC: Is it Actionable?

- Similar level of actionability as LSqCC in the Usual Suspects
- PI3K, EGFR, CDKs
- Low frequency but cumulative alterations in other RTKs
TCGA HNSqCC: Is it Prognostic?

Atypical ≠ Primitive (from LSqCC GEP)

Interestingly: RB1 mut is heavily enriched in LSqCC primitive type
TCGA HNSqCC: Is it Prognostic?
# Squame vs. Squame

<table>
<thead>
<tr>
<th>Lung SqCC</th>
<th>Head &amp; Neck SqCC</th>
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<tbody>
<tr>
<td>3q amplification</td>
<td>3q amplification</td>
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<tr>
<td>(TP63, SOX2)</td>
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<tr>
<td>NOTCH1 mutation</td>
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<tr>
<td>TP53, PIK3CA, CDKN2A, HRAS mutation</td>
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<tr>
<td>KMT2D (MLL2), HLA-A mutation</td>
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<tr>
<td>NFE2L2, KEAP1, CUL3 mutation</td>
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Standard Treatment Decisions

**Lung SqCC**
- N0-1: surgical resection if possible (comorbidities)
- Otherwise: RT+Chemo
- Cisplatin/gemcitabine for squamous histology
- PD1 inhibitors (front line)
  - PD-L1 IHC for pembro
- Consider EGFR, ALK, ROS1 evaluation

**Head and Neck SqCC**
- Multi-modal RT, Chemo, and/or surgery to best preserve form and function while maximizing survival
- Platinum based regimens
- Cetuximab
  - Irrespective of “genomic” alterations
- PD1 therapy second line

NCCN 2016 Guidelines
Where art thou from?

- Chemotherapy regimens, including targeted agents and need for special testing are different.
- Clinical management of metastatic HNSqCC to the lung is fundamentally different than management of a new primary lung SqCC.
Differential Diagnosis

- Generally requires clinical, radiologic, and pathologic correlation
  - IHC algorithm? Ichinose et al. (2016) PMID: 27597287
- HPV status
  - HPV+ primary LSqCC is “rarer than hen’s teeth” van Boerdenk et al. (2013) PMID: 23571474
  - However, HPV prevalence in HNSqCC is only ~40% in aggregate and varies highly based on site of primary
- Gene Expression Classifier
A gene expression profile test to resolve head & neck squamous versus lung squamous cancers

Anita Lal¹, Rebecca Panos¹, Mira Marjanovic¹, Michael Walker¹, Eloisa Fuentes¹, Gregory J Kubicek², W David Henner³, Ljubomir J Buturovic¹ and Meredith Halks-Miller¹

- 2160 gene classifier (Affymetrix array)
  - Developed on ~500 sample discovery set
- 80 validation FFPE samples
  - 95% pass rate
- 61% had a “definitive” score
  - 96% accuracy (CI 85-99)
  - AUC = 0.91
- Pathwork → Response → Cancer Genetics Inc.
  - FDA cleared
  - Cost? Reimbursement?
Interesting Points

• Mutation rates are high consistent with carcinogen exposure mediated tumorigenesis
  – Tumor suppressor LOF > Oncogene GOF
• Cell of origin vs. Altered differentiation pathways?
  – SqCC from multiple sites share the same genetic aberrations that affect keratinocyte differentiation
• Cell cycle dysregulation is key
  – Exogenous vs. endogenous mechanism might affect prognosis?
• Oxidative stress response alterations causing therapy resistance
• Immune evasion via common genomic mechanisms
Take Home

- Head & Neck and Lung squamous cell carcinomas share many common biologic/genomic features
  - Especially HPV neg HNSqCC and LSqCC
- HPV is the most robust biomarker for prognostic purposes in Head & Neck SqCC
- Emerging (but not prime time) prognostic signatures/ biomarkers in lung
- Data on effectiveness of immune checkpoint therapy is accumulating
- Hope for additional targeted therapy relies on on-going clinical trials primarily for RTKs, PI3K, or CDKs
  - May complicate the predictive biomarker space as combinations of CNA, mutation analysis, and perhaps even pathway activation may be needed
Genetic Landscape of Human Papillomavirus–Associated Head and Neck Cancer and Comparison to Tobacco-Related Tumors

D. Neil Hayes, Carter Van Waes, and Tanguy Y. Seiwert

Fig 1. Role of E6 and E7 in the cell cycle pathways and gene alterations as a function of human papillomavirus (HPV) tumor status. Genes altered in HPV-positive or viral oncogenes (red) or in HPV-negative tumors (black). RB, retinoblastoma tumor-suppressor protein.
Lung Squamous Cell Carcinoma mRNA Expression Subtypes Are Reproducible, Clinically Important, and Correspond to Normal Cell Types

Matthew D. Wilkerson¹, Xiaoying Yin¹, Katherine A. Hoadley¹,2, Yufeng Liu¹,4, Michele C. Hayward¹, Christopher R. Cabanski², Kenneth Muldrew², C. Ryan Miller¹,5, Scott H. Randell¹,6, Mark A. Socinski¹,7, Aiden M. Parsons², William K. Funkhouser¹,5, Carrie B. Lee¹,7, Patrick J. Roberts¹, Leigh Thorne¹,5, Philip S. Bernard⁶, Charles M. Perou¹,², and D. Neil Hayes¹,7

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