Mutant-Allele Tumor Heterogeneity (MATH) in head and neck squamous cell carcinoma patients is an effective marker, along with HPV status, of improved patient outcome

Scottsdale, Ariz., February 20, 2014—Evaluating next-generation sequencing (NGS) data and associated clinical records of head and neck squamous cell carcinoma (HNSCC) patients from several institutions, made available through The Cancer Genome Atlas (TCGA), showed that combining Mutant-Allele Tumor Heterogeneity (MATH) as a biomarker with the patient’s HPV status provides an effective indicator of improved patient outcome, according to research presented today at the 2014 Multidisciplinary Head and Neck Cancer Symposium.

The TCGA data available for HNSCC patients included 302 patients, with 35 HPV-positive patients. The researchers’ examination confirmed that high tumor MATH at time of surgery is an indicator of poor outcome (high-MATH hazard ratio (HR) = 2.1; 95 percent confidence interval (CI), 1.4 to 3.2; p = 0.0002, logrank test) and that HPV-positive HNSCC patients have lower average MATH values than HPV-negative HNSCC patients. In bivariate analysis, both MATH and HPV were significantly associated with survival. When stratified by HPV status, MATH was similarly related to outcome in clinically defined subsets of patients regardless of clinical characteristics (tumor margins, nodal classification or tumor staging). Median follow-up with the 173 surviving patients was 22 months.
A tumor can contain many different types of cancer cells. Standard DNA sequencing discovers both the DNA mutations that differ among cancer cells and gives a measure of diversity. Genetic heterogeneity of each tumor was assessed by MATH, the percentage ratio of the width to the center of the distribution of tumor-specific mutant-allele fractions. In order to compare to previous studies, analysis was limited to mutant-allele fractions no less than 0.075, and the high-MATH cutoff value of 32, previously found to distinguish outcome classes, was used. Cox proportional hazards analysis was used to evaluate the relations of MATH and HPV to overall survival.

“Calculating patients’ MATH marker as well as their HPV status is a more reliable predictor of patient survival, and the methodology that we used to measure MATH is simple enough that it could be adopted readily in the clinic,” said author James Rocco, MD, PhD, a head and neck surgical oncologist at Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary, and the Daniel Miller Chair in Otology and Laryngology at Harvard Medical School in Boston. “Now that we know that both HPV status and intra-tumor heterogeneity matter for patient outcome, we are in a better position to personalize therapy for our patients. We can try less toxic therapies in patients likely to be cured, and try new or alternate therapies in patients likely to fail. In addition, it may help identify the patients most likely to benefit from clinical trials.”

The abstract, “Mutant-Allele Tumor Heterogeneity (MATH) Adds to Human Papillomavirus (HPV) Status in Predicting Outcome in Head and Neck Squamous Cell Carcinoma (HNSCC),” will be presented in detail during a scientific session at 10:30 a.m. Mountain time on Friday, February 21, 2014, at the 2014 Multidisciplinary Head and Neck Cancer Symposium. To speak with Dr. Rocco, contact Michelle Kirkwood on February 20–21, 2014 in the ASTRO Press Office at the JW Marriott Camelback Inn Resort and Spa in Scottsdale, Ariz., at 480-596-7085 or email michellek@astro.org.

The 2014 Multidisciplinary Head and Neck Cancer Symposium is sponsored by the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO) and the American Head & Neck Society (AHNS). The two-and-a-half day meeting includes interactive educational sessions focused on topics such as supportive care, directed therapy, new surgical and radiotherapeutic techniques, as well as 12 oral abstract presentations of the current science of
relevance to the head and neck cancer community. A total of 189 abstracts will be presented including 177 posters. Keynote speakers include Jennifer Grandis, MD, of the University of Pittsburgh, to present “The Molecular Road to Defining and Targeting High-risk Head and Neck Patients;” and Julia H. Rowland, PhD, of the National Cancer Institute, to present “Cancer Survivorship: Research Opportunities on the Path to Where We Want to Be.”

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Mutant-Allele Tumor Heterogeneity (MATH) Adds to Human Papillomavirus (HPV) Status in Predicting Outcome in Head and Neck Squamous Cell Carcinoma (HNSCC)

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Background: Next-generation sequencing (NGS) data and associated clinical data made available by multiple institutions through The Cancer Genome Atlas (TCGA) provide opportunities for testing clinical hypotheses in HNSCC. Based on 74 cases from a single institution, we had previously shown that a measure of intratumor genetic heterogeneity derived from NGS data, MATH, is related to outcome in HNSCC (Oral Oncology 49: 211, 2013; Cancer 119: 3034, 2013). Only a limited number of HPV-positive cases were available for that initial study. We sought to determine, in the larger TCGA HNSCC dataset with over 300 cases, whether the MATH biomarker of intratumor genetic heterogeneity improves HNSCC outcome prediction based on HPV status.

Methods and Materials: We examined exome NGS data and associated clinical data on HNSCC available from TCGA. Genetic heterogeneity of each tumor was assessed by MATH, the percentage ratio of the width to the center of the distribution of tumor-specific mutant-allele fractions. For comparison with previous work, we limited analysis to mutant-allele fractions no less than 0.075 and used the high-MATH cutoff value of 32 previously found to distinguish outcome classes. Cox proportional hazards analysis was used to evaluate the relations of MATH and HPV to overall survival. Both clinical and NGS data were available for 302 patients, 35 with tumors positive for HPV. Median follow-up of the 173 surviving patients was 22 months.

Results: We verified that high tumor MATH at time of surgery is a poor prognostic sign (high-MATH hazard ratio, HR, 2.1; 95% CI, 1.4 to 3.2; \( p = 0.0002 \), logrank test) and that HPV-positive HNSCC have lower average MATH values than HPV-negative HNSCC (34.2 ± 2.3 SEM vs. 39.8 ± 0.7; \( p = 0.007 \)). In bivariate analysis both MATH and HPV were significantly associated with survival (high-MATH HR, 1.8; 95% CI, 1.2 to 2.8; HPV-positive HR, 0.36; 95% CI, 0.18 to 0.75; \( p = 0.0002 \), logrank test). In analyses stratified by HPV status, MATH was similarly related to outcome in clinically defined subsets of patients, whether the patient subsets had favorable or unfavorable clinical characteristics (negative tumor margins: high-MATH HR, 2.2; nodal classification N0: high-MATH HR, 2.0; AJCC Stage III-IV: high-MATH HR, 1.7).

Conclusions: In the multi-institutional HNSCC data set provided by TCGA, including MATH as a biomarker of intratumor heterogeneity improved outcome prognostication based on HPV status. These results support the evaluation of MATH as a prognostic biomarker to be added to HPV status in the design of clinical trials and, ultimately, in treatment choices.

Author Disclosure Block: J.W. Rocco: None. A.D. Tward: None. Y. Ren: None. R.J. Hammon: None. E.A. Mroz: None.