

Predicting Outcome in Head and Neck Cancer: miRNAs with Potentially Big Effects

David A. Clump¹, Curtis R. Pickering², and Heath D. Skinner¹



A five-miRNA signature for human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) identifies patients at risk for inferior outcomes. Combining established clinical variables with this novel

miRNA signature affords an opportunity to personalize and intensify treatment strategies in this high-risk patient population.

See related article by Hess et al., p. 1505

In this issue of *Clinical Cancer Research*, Hess and colleagues (1) report on a prognostication strategy for patients with human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC), where a five-miRNA signature was associated with disease recurrence and inferior survival. In this study, pretreatment specimens were obtained from patients with HPV-negative HNSCC treated with surgery and postoperative radiotherapy (\pm cytotoxic chemotherapy). In an initial training set of 162 tumors, slightly over 1,000 miRNAs were identified and examined for association with recurrence following treatment, leading to the identification of an optimized five-miRNA expression signature (hsa-let-7g-3p, hsa-miR-6508-5p, hsa-miR-210-5p, hsa-miR-4306, and hsa-miR-7161-3p) associated with recurrence. This five-miRNA signature was then refined in a second cohort of patients using a threshold defined from the training cohort. In both cohorts of patients, the signature could be used to define high- and low-risk groups, with dramatically different rates of recurrence, disease-specific survival, and most importantly overall survival. Specifically, in both patient cohorts, the low-risk group demonstrated a survival of approximately 70% while that in the high-risk group was 30%. Combining this signature with clinical parameters including tumor stage, nodal stage, and extranodal extension facilitated the stratification of patients into four risk groups based upon freedom from recurrence. Although this latter analysis is limited by numbers per risk group, the separation between groups is quite impressive.

miRNAs are small noncoding RNAs of approximately 22 nucleotides that are generated in the nucleus and transported into the cytoplasm for processing. A series of processing steps generates a sequence capable of negatively regulating gene expression and disrupting oncologic signaling pathways. Since their initial discovery, a variety of miRNAs have been linked to tumorigenesis and outcome in multiple disease sites. Indeed, as pointed out by the authors, two of the miRNAs identified in the signature

(hsa-mir-210-5p and hsa-let-7g-3p), have been previously linked to outcome in HNSCC (2, 3). However, despite a wealth of literature examining miRNAs associated with outcome in a variety of different malignancies, there are no miRNAs currently used for prognostic or predictive purposes in clinical practice.

At present, the clinical and translational landscape of HNSCC is dominated by the HPV-positive versus negative distinction. Indeed, these two types of HNSCC can really be thought of as two distinct malignancies. HPV-positive HNSCC presents in younger patients, has an indirect association with smoking and alcohol, and a better prognosis. Conversely, HPV-negative HNSCC presents in older patients, is usually directly linked to smoking and alcohol exposure, and has comparatively worse outcomes. On the basis of the increasing incidence of HPV-positive HNSCC (specifically in the oropharynx), there has been a seismic shift in the study of HNSCC toward identifying the mechanisms of this virally mediated disease and away from the more classic form of HNSCC. Although the responsiveness of the community to the HPV epidemic is laudatory, the fact remains that the outcomes for locally advanced HPV-negative HNSCC (the kind of patient represented in this study) remain far, far poorer than their HPV-positive counterparts. Indeed, patients with locally advanced HPV-positive HNSCC can generally expect a survival rate of approximately 85%, compared with 50%–60% in a similarly staged HPV-negative patient (4). Moreover, in HPV-negative patients, we lack validated biomarkers to either identify groups of patients who will do worse with the current standard-of-care or identify targetable drivers of resistance to current therapy.

Thus, this study is a welcome addition to several previously identified biomarkers in HPV-negative HNSCC (Fig. 1). These biomarkers have been identified in the context of HPV-negative HNSCC treated with radiation, usually following surgery and sometimes with concurrent chemotherapy. As HPV-negative HNSCC leads to death largely via local and regional recurrence of disease, these biomarkers have, by and large, been associated specifically with resistance to radiation. Indeed, several of these biomarkers have been directly targeted to increase sensitivity to radiation in preclinical models and may provide mechanistic insight to pathways of innate radioresistance in HPV-negative HNSCC (5, 6). In examining the current five-miRNA signature a broad variety of pathways may be affected, including several important for response to radiation such as DNA damage repair, apoptosis, hypoxia response, and even immune signaling (Hess and colleagues, Supplementary Fig. S12). However, one of the challenges of identifying pathways associated with any miRNA is

¹Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. ²Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Corresponding Author: Heath D. Skinner, UPMC Hillman Cancer Center, Research Pavilion Suite 2.6a, 5117 Centre Avenue, Pittsburgh, PA 15213-1863. Phone: 412-623-3275; Fax: 412-623-7761; E-mail: skinnerh@upmc.edu

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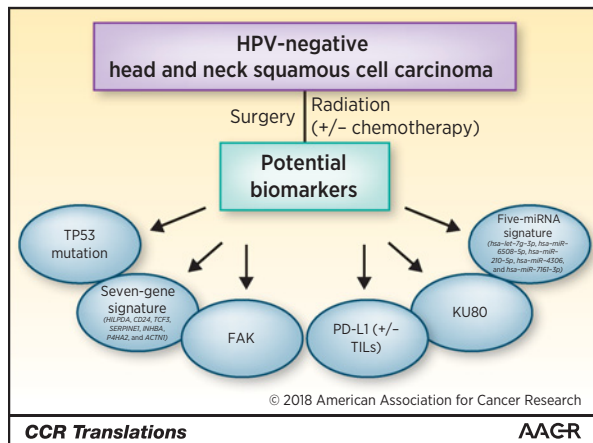


Figure 1.

Graphical representation of biomarkers of outcome and potential radioresistance in HPV-negative HNSCC. TILs, tumor-infiltrating lymphocytes.

the sheer number of canonical pathways modulated by each individual miRNA, let alone a signature of five. Moreover, the five-miRNA signature in this study appears to be more associated with distant than locoregional failure (Hess and colleagues, Supplementary Fig. S4A and S4B). Thus, the biological effect associated with one or several miRNAs in the signature may be related more to invasion and motility than intrinsic resistance to radiation. Additional preclinical studies are necessary to integrate this clinical finding into a framework of pathways that may be driving each type of recurrence (distant and locoregional) as opposed to those just along for the ride.

Perhaps the more important question, however, is how best to move forward clinically with this signature as well as other

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biomarkers of outcome in HPV-negative HNSCC. The answer to this question is far from clear. Quite rightly, the authors point out that prospective validation is necessary. However, this is often easier said than done. Proceeding from an interesting novel prognostic or predictive biomarker to broad clinical applicability is exceedingly challenging. This process presents multiple hurdles, not the least of which are prospective validation in a uniformly treated group of patients, a highly reproducible assay, ability to perform the assay beyond a centralized laboratory, and the logistics of integrating a given assay into routine clinical use (7). Although these difficulties are certainly surmountable, they require both patience as well as collaboration between multiple groups of stakeholders to reach fruition. Means of streamlining and consolidating this process must be identified, if novel biomarkers such as those identified here and others, are to be fully utilized to improve patient care.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H.D. Skinner
 Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.D. Skinner
 Writing, review, and/or revision of the manuscript: D.A. Clump, C.R. Pickering, H.D. Skinner

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