Looks aren't everything, but neither is microRNA profiling

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Central Message

miRNA profiling may be a beneficial tool in the differentiation of metastatic head and neck from primary LSCC, but not yet.

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For patients with head and neck squamous cell carcinoma (HNSCC), metastasis occurs synchronously in 2% to 17% and metachronously in 10% to 40%; 70% to 85% of the metastases are in the lungs.¹ With similar risk factors and demographics, difficulty in histologic differentiation between primary lung squamous cell cancer (LSCC) and HNSCC metastasis has driven interest in molecular profiling.² Muñoz-Largacha and colleagues³ have asked a clinically relevant question by querying whether a micro (mi)RNA profile can differentiate HNSCC from primary LSCC.

miRNA profiling is a molecular technology under evaluation for biomarkers in multiple cancers.⁴ Regulatory RNA sequences act in both oncogenic and tumor suppressive manners by binding mRNA transcripts and regulating protein expression; they are detectable via liquid biopsy and tumor samples.^{5,6} Examples exist in LSCC, including the report by Chen and colleagues⁷ demonstrating that miR-375 is a tumor suppressor, and the report by Gao and colleagues⁸ identifying a 7-miRNA signature associated with overall survival. Muñoz-Largacha and colleagues³ reported that 3 miRNAs and the ratio of 2 (miR-10a and 10b) differentiated LSCCs from HNSCC. Their analysis benefitted from internal calibration based on the ratio of miR-10a and 10b, which eliminated housekeeping gene normalization. In addition, they reported a correlation to The Cancer Genome Atlas. However, significant limitations exist.

The comparison in this article³ is not between primary LSCC and metastatic HNSCC, rather between primary LSCC and primary HNSCC. The diagnostic dilemma is differentiating metastatic HNSCC with primary LSCC, not differentiating primary tumors. miRNA profiles are associated with the epithelial to mesenchymal transition and metastatic potential; they will be different between primary lesions and metastatic disease from the same tumor.⁹ Muñoz-Largacha and colleagues³ state this limitation. They report that “myo-miRs” associated with striated muscle were found in the primary HNSCC samples versus miRNA associated with multiciliated cells in LSCC samples. These findings suggest that the miRNA profile of

an HNSCC metastasis is unlikely to be synonymous with primary HNSCC. The tumor microenvironment is a limitation of miRNA biomarker discovery. Clearly, the environment is different between the neck and lungs. Ideally, laser microdissection would be performed before miRNA analysis to overcome microenvironmental contamination of the specimens, but analysis between HNSCC lung metastasis and primary LSCC is more achievable. The reproducibility of miRNA is another limitation of this study and the field of miRNA discovery. miRNA profiling of HNSCC has been performed with as many associated miRNA signatures as studies. The heterogeneity is compounded by the differences in diagnoses from the oral cavity to the larynx, which is demonstrated with the differences of miR-10a and miR-34a based on anatomic site.¹⁰

These limitations prevent this technology or the specifically identified miRNAs in this article from being applied to management decisions for patients. However, the attempt to tackle this field by Muñoz-Largacha and colleagues³ is a worthwhile research endeavor that should be continued and hopefully will benefit patients in the future.

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