Editorial Commentary

Utility of miRNA biomarkers for detection of early head and neck squamous cell carcinoma

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cause of cancer worldwide (1). Major risk factors for HNSCC include lifestyle factors such as tobacco and alcohol consumption, in addition to the infectious causes such as carcinogenic subtypes of human papilloma virus (HPV), with most common being HPV-16 (2). Therefore, HNSCC is usually subclassified into HPV-negative and HPV-positive subgroups. According to the latest global cancer statistics, the incidence of HNSCC is expected to rise and increase by 30% in the coming decade (3). Although variable across anatomical sites, the average 5-year survival of HNSCC is estimated to be anywhere around 66–56% (4,5) with worse prognosis when diagnosed at late stages. Poor survival outcomes among this patient population may be attributed to later detection and diagnosis (6), with some estimates suggesting only a third of cases being diagnosed at an early stage [American Joint Committee on Cancer (AJCC) stages I and II] (4,7). This has resulted in increasing efforts in enhancing current diagnostic methods and the development of new, innovative diagnostic modalities that could expedite treatment and improve patient outcomes.

The use of liquid biopsies could provide a cost-effective, non-invasive means to detect HNSCC at earlier stages with high levels of fidelity through the detection of various biomarkers (8,9). Studies have documented the utility of various analytes as biomarkers for head and neck cancers (HNCs). Circulating tumor DNA (ctDNA), exosome (EXO), and circulating tumor cells (CTCs) have been some of the identified biomarkers effective in detecting HNCs to various degrees, in addition to their utility in screening and response to treatment (9) (*Table 1*). In addition to these biomarkers, recent studies have shed light on utility of microRNAs (miRNAs) in HNC. The role of miRNAs in early detection of other malignancies have been extensively studied. miRNA play an important role in controlling tissue homeostasis and coordinating various functions including cellular proliferation and cellular differentiation. Given their role, in addition to being tissue specific and stable for detection within serum, miRNA have attracted high interest in their potential to be used as early tumor markers (10). Lawrie *et al.* (11) first reported them to be potential screening tool for diffuse large B-cell lymphoma in 2008. Since then, miRNAs have been found to be found to be effective for early detection of breast (12), lung (13), and prostate cancer (14). The use of such biomarkers in detecting HNSCC is still a developing field. Previous studies have reported up/down-regulation of various salivary miRNAs in HNSCC at various stages of disease (15), with sensitivity and specificity of different miRNAs ranging anywhere 14–100% and 38–100% respectively in detecting HNSCC (16). However, there is still not much known about the expression of miRNA by HNSCC *in vitro* nor miRNA expression difference dependence on HPV status.

In their paper published in 2017, Langevin *et al.* reported patterns of specific, differentially secreted exosomal

Table 1 Various properties among HNC biomarkers

Properties	Biomarker			
	ctDNA	miRNA	CTC	EXO
Source	Blood, saliva	Blood, saliva	Blood	Blood, saliva
Concentration	Moderate	High	Low	High
Sensitivity	Moderate	Higher	Lower	Higher
Specificity	Moderate	Variable	Variable	Lower
Applications	Screening, prognosis, post treatment surveillance	Screening, prognosis	Prognosis, treatment selection	Prognosis, post-treatment surveillance

Table adapted and modified from Aulakh *et al*. (9). HNC, head and neck cancer; ctDNA, circulating tumor DNA; miRNA, micro-RNA; CTC, circulating tumor cell; EXO, exosome.

miRNA (exo-miRNA) by HPV-negative HNSCC cells that distinguished them from healthy primary oral epithelial cells *in vitro* (17). This study highlighted the potential of specific patterns of miRNA for detection of early HNSCC, but the translational capability of miRNA in HNSCC remained a question. In their follow-up study, the authors sought out to determine the patterns of exo-miRNA secretion in HPV-positive cell lines and assess the translational capability of these patterns of biomarkers in patient with confirmed early stage HNSCC.

In the initial part of their study, Galiveti *et al.* (18) analyzed the differential secretion of exo-miRNA between HPV-positive and negative cell lines *in vitro*. Given the high degree of differentiation among HPV-positive cell lines, there was a total higher number of unique exo-miRNA detected from HPV-positive cells (143 total) as compared to HPV-negative [32] with 25 being commonly secreted by both. This analysis supports the possible use of miRNA as a HNSCC biomarker for detection of malignancy regardless of the HPV status of the SCC cells. Furthermore, it poses a potential capability of miRNA in differentially detecting malignant cells regardless of their HPV status, which could be useful in patients with synchronous HPV-positive and negative HNSCC.

To better evaluate translational potential of miRNA in detecting early HNSCC, the authors isolated and analyzed pretreatment sample serums from cases diagnosed with early HNSCC with both HPV-positive and negative biopsies represented. Serum analysis revealed the presence of differentially unique miRNA patterns relative to the benign neoplasia samples with ranging degree of quantities anywhere 0.18 to 51.72-fold-changes. Notably, the majority of miRNAs detected in specimens collected from patients had higher than 2-fold-change difference when compared to control; additionally, the top four most oversecreted miRNA had higher median levels when compared control samples. Furthermore, two of the four most over-secreted miRNAs in serum were also detected in the *in vitro* analysis of HNSCC cell lines. These results lend strength to the translational capability of miRNA in detecting early stage HNSCC regardless of the HPV status.

Overall, Galiveti *et al.* present promising findings with potential for detection of HPV-positive and negative HNSCC at an early stage, and potential for translational capability of miRNA in HNSCC in patients at an early stage through blood-based biomarkers. Furthermore, the clinical findings of the study present potential in distinguishing in detection early malignancy by HPV-specific miRNA biomarkers. Due to the limitations of the study to a small population, further studies should focus on externally validating the results, in addition to expanding the number of included subjects and including multicenter trials. Additionally, future studies should expand to different tumor sites, and explore differential secretion of miRNA between non-malignant HPV-positive epithelial cells, in addition to specifying the carcinogenic strain of HPV-positive cells to determine whether there are any differences.

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Footnote

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