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Diagnostic and Prognostic Utility of Salivary MicroRNAs Combined with Radiological Imaging Across Human Cancers: A Systematic Review and Radiomics-Biomarker Synthesis

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Abstract: Background: Salivary microRNAs (miRNAs) and quantitative radiological features (radiomics) derived from Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Ultrasound (US) represent promising non-invasive tools for cancer detection and risk stratification. Salivary miRNAs provide liquid biopsy insights into systemic and local tumor biology, whereas radiological imaging captures macroscopic spatial heterogeneity, organ invasion and anatomical burden. Combining salivary miRNA profiles with quantitative imaging phenotypic traits (radiomicroRNA multi-modal models) offers enhanced diagnostic accuracy and prognostic stratification. However, variations in imaging acquisition parameters, saliva handling, assay platforms and tumor histology contribute to inconsistent performance metrics across individual studies. **Objective:** To systematically evaluate and synthesize the diagnostic accuracy and prognostic utility of salivary miRNAs alone and in combination with radiological imaging modalities across human malignancies, identifying methodological factors driving inter-study heterogeneity. **Methods:** A systematic review will be conducted adhering to PRISMA and PRISMA-DTA guidelines across PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library and IEEE Xplore from database inception. Eligible studies include human investigations evaluating salivary miRNAs, radiological features or multi-modal biofluid-imaging diagnostic/prognostic models in cancer using clinically defined reference standards. Risk of bias will be evaluated using QUADAS-2 for diagnostic test accuracy and MEALIT/RQS (Radiomics Quality Score) for quantitative imaging studies. Bivariate random-effects and Hierarchical Summary Receiver Operating Characteristic (HSROC) models will synthesize diagnostic performance metrics. Prognostic associations will be synthesized using pooled Hazard Ratios (HRs). Subgroup analyses and meta-regression will assess cancer site, imaging modality, radiomic feature category, exosomal vs. free miRNA and multi-modal integration strategies. **Results:** The review will synthesize evidence across oncological sites, contrasting single-modal (salivary miRNA or radiomics alone) against multi-modal (salivary miRNA+radiological imaging) diagnostic and prognostic outcomes. Standardized summary metrics (pooled sensitivity, specificity, Diagnostic Odds Ratios [DOR], HSROC AUC) will be generated alongside radiomic feature stability indices. Meta-regression will isolate sources of inter-study variance stemming from scanner models, reconstruction algorithms, biofluid collection protocols and biomarker normalization methods. **Conclusions:** Integrating salivary miRNAs with advanced radiological imaging provides a robust multi-modal approach for precision oncology. Defining standardized biofluid-imaging workflows and identifying key methodological sources of variance will guide future prospective clinical validation.

Key Words: Salivary microRNA, Radiomics, Radiology, Computed Tomography, Magnetic Resonance Imaging, Liquid Biopsy, Cancer Diagnosis, Prognostic Biomarker, Diagnostic Test Accuracy, Systematic Review, Multi-Modal Biomarkers

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INTRODUCTION

Early diagnosis and robust risk stratification remain essential for improving survival rates and treatment response in human oncology. Traditional diagnosis relies heavily on tissue biopsy, which is invasive, subject to spatial sampling errors and difficult to repeat

sequentially during therapy monitoring [1-3]. Liquid biopsies-including cell-free DNA, circulating tumor cells and non-coding RNA-have emerged as valuable non-invasive adjuncts. Among non-coding RNAs, microRNAs (miRNAs) are short (18-25 nucleotides), single-stranded RNA molecules that regulate post-transcriptional gene expression and play key roles in oncogenesis, metastasis and therapy resistance [4-8].

Saliva has gained attention as an accessible biofluid for liquid biopsy. Salivary miRNAs originate from direct shedding by head and neck lesions or through passive transudation from microvasculature into salivary glands, enabling the detection of both local and systemic malignancies [9,10]. Salivary miRNAs exhibit high stability in biofluids due to protection by extracellular vesicles (EVs/exosomes) or binding with ribonucleoprotein complexes. Despite these advantages, clinical implementation of salivary miRNA biomarkers faces challenges, including inconsistent sample collection protocols, platform-dependent quantification variability, low yield and overlap in miRNA dysregulation profiles across different inflammatory conditions [11-13].

Concurrently, diagnostic radiology has evolved beyond qualitative anatomical visual assessment into quantitative imaging phenotyping (radiomics). Radiomics extracts high-dimensional, mineable quantitative features (e.g., texture, shape, intensity histograms, wavelets) from routine CT, MRI, PET and Ultrasound scans. These features capture macroscopic spatial heterogeneity, tumor microenvironment traits and invasive margins across the entire tumor volume. However, radiomics alone can be susceptible to image acquisition protocol variations, reconstruction kernel disparities and motion artifacts, while lacking fine-grained cellular and molecular context [14-18].

Combining salivary miRNA profiling with quantitative radiomic features (radiomicroRNA multi-modal models) bridges macroscopic tumor architecture with microscopic molecular signatures. While multi-modal integration shows potential for improving diagnostic sensitivity, specificity and prognostic accuracy, reported performance metrics across individual studies remain variable. This systematic review protocol and meta-analysis framework aims to evaluate the diagnostic accuracy and prognostic power of combined salivary miRNA and radiological imaging signatures across human cancers while evaluating underlying methodological sources of heterogeneity [19-21].

LITERATURE REVIEW

Biological Mechanics and Stability of Salivary MicroRNAs

Salivary miRNAs exist in two primary states: packaged within extracellular vesicles (EVs/exosomes) or complexed with proteins such as Argonaute-2 (Ago2). Exosomal packaging protects miRNAs from endogenous salivary RNases, ensuring stability across temperature fluctuations and freeze-thaw cycles. In Head and Neck Squamous Cell Carcinomas (HNSCC) and Oral Squamous Cell Carcinomas (OSCC), miRNAs are shed directly into the oral cavity, producing localized expression changes. For systemic cancers (e.g., pancreatic, breast, lung, gastrointestinal), tumor-derived exosomes pass into the systemic circulation and traverse the acinar cells and ductal epithelium of the salivary glands into saliva. Key dysregulated miRNAs repeatedly reported in literature include miR-21, miR-1246, miR-200a and miR-155, which regulate cellular proliferation, Epithelial-to-Mesenchymal Transition (EMT) and angiogenesis.

Quantitative Radiology and Radiomics in Cancer Management

Diagnostic imaging modalities provide distinct, non-invasive insights into tumor biology:

- **Computed Tomography (CT):** Evaluates tissue density, structural distortion, lymph node enlargement and vascular involvement. Radiomic CT metrics (e.g., gray-level co-occurrence matrix [GLCM] entropy, run-length matrix non-uniformity) capture heterogeneity related to tumor necrosis and microvascular density
- **Magnetic Resonance Imaging (MRI):** Provides soft-tissue contrast. Advanced sequences like Diffusion-Weighted Imaging (DWI/ADC mapping) and Dynamic Contrast-Enhanced (DCE) MRI reflect cellular density, membrane integrity and microvascular permeability
- **Positron Emission Tomography (PET):** Molecular PET imaging (e.g., ^{18}F-FDG) quantifies metabolic activity (Standardized Uptake Value [SUVmax], Metabolic Tumor Volume [MTV], Total Lesion Glycolysis [TLG]), which correlates with aggressive tumor biology and cell proliferation
- **Ultrasound (US):** Offers real-time evaluation of lesion echogenicity, vascularity (Doppler) and tissue stiffness (elastography), particularly useful in thyroid, breast and head-and-neck imaging

Rationale for Multi-Modal Integration: RadiomicroRNA Signatures

Single-source biomarkers face inherent limitations. A biofluid miRNA measurement provides a global molecular snapshot without indicating anatomical localization, multi-focal presence or spatial variations within a tumor. Conversely, radiological imaging delineates tumor volume, structural invasion and spatial heterogeneity but may lack molecular specificity to distinguish benign inflammatory tissue from malignant lesions.

Integrating quantitative imaging features with salivary miRNA expression profiles helps overcome these individual limitations. RadiomicroRNA frameworks combine high-dimensional imaging data with molecular

biofluid signatures using machine learning classifiers (e.g., Random Forests, Support Vector Machines, Gradient Boosting, Deep Neural Networks). Preliminary studies indicate that multi-modal models achieve superior Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) metrics compared to standalone biofluid assays or single-modality imaging.

Sources of Heterogeneity and Methodological Standardizations

Literature reveals significant heterogeneity in reported sensitivity (ranging from 55-95%) and specificity across published studies. Primary sources of variance include:

- **Pre-analytical Biofluid Factors:** Unstimulated vs. stimulated saliva collection, time of collection, storage temperature (-80 vs. -20°C), centrifuge speeds and exosome isolation methods (ultracentrifugation vs. precipitation reagents)
- **Analytical Assay Variations:** Differences between RT-qPCR, microarray profiling and Next-Generation Sequencing (NGS), along with variations in reference normalization genes (e.g., U6, miR-16, global mean)
- **Radiological Protocol Variations:** Multi-vendor scanner variations, slice thickness, tube current, contrast timing, slice reconstruction algorithms and variations in manual vs. automated Region-of-Interest (ROI) segmentation
- **Study Cohort Constraints:** Retrospective designs, small sample sizes, lack of external validation cohorts and inconsistencies in patient reference standards (histopathology vs. clinical follow-up)

DISCUSSION

The synthesis of salivary miRNAs and radiological imaging highlights an evolving shift toward multi-modal diagnostic and prognostic frameworks in oncology [22-25]. This integrative approach leverages both molecular and macroscopic tumor characteristics to address clinical challenges across the diagnostic continuum.

Diagnostic Complementarity

A persistent diagnostic challenge in cross-sectional radiology is distinguishing malignant lesions from benign, inflammatory or post-radiation changes (e.g., radiation necrosis vs. tumor recurrence in neuro-oncology and head and neck cancer; indeterminate solitary pulmonary nodules on chest CT). While inflammatory tissue often displays high tracer uptake on ^{18}F-FDG PET or contrast enhancement on MRI, the co-assessment of tumor-specific salivary miRNA upregulation (e.g., exosomal miR-21 or miR-155) can significantly reduce false-positive rates. Conversely, when salivary miRNA yields are low or equivocal due to systemic factors (e.g., dry mouth, systemic inflammation), high-resolution radiomic imaging features (e.g., GLCM contrast, non-spherical shape metrics) provide essential structural evidence to maintain overall diagnostic accuracy [26-28].

Prognostic Risk Stratification and Biological Mapping

Beyond initial diagnosis, the combination of salivary miRNAs and quantitative imaging provides actionable prognostic information:

- **Lymph Node Metastasis:** In HNSCC and OSCC, occult cervical lymph node metastasis is difficult to detect using anatomical CT or MRI alone. Integrating salivary miRNA profiles associated with aggressive invasion (e.g., miR-200 family down-regulation) with radiomic features extracted from primary tumor imaging improves pre-operative nodal staging
- **Systemic Disease Burden:** For distant tumors, such as pancreatic ductal adenocarcinoma or lung adenocarcinoma, elevated levels of specific salivary miRNAs combined with high PET Metabolic Tumor Volume (MTV) or MRI diffusion restriction correlate with poor Overall Survival (OS) and higher risk of early recurrence

Methodological Heterogeneity and Standardization Needs

For radiomicroRNA multi-modal models to transition from research into clinical practice, standardized workflows must be established across both biofluid and imaging pipelines. In radiomics, compliance with the Image Biomarker Standardization Initiative (IBSI) guidelines and reporting against the Radiomics Quality Score (RQS) are essential to ensure reproducible feature extraction across different imaging platforms. In salivary biomarker workflows, standardization must address biofluid collection time, exosome enrichment protocols and consensus internal reference controls for miRNA normalization. Addressing these methodological factors in future research will be critical to establishing reliable, reproducible clinical assays [29,30].

CONCLUSIONS

Integrating salivary microRNA expression profiles with quantitative radiological imaging modalities represents a viable multi-modal approach for non-invasive cancer diagnosis, staging and prognostic evaluation. While salivary miRNAs provide molecular insights into tumor biology, radiological imaging (CT, MRI, PET, US) captures macroscopic anatomical structures, spatial heterogeneity and volumetric lesion burden. Multi-modal radiomicroRNA models demonstrate improved diagnostic performance metrics compared to single-modality approaches. Realizing the full clinical potential of these signatures will require standardizing biofluid handling, harmonizing quantitative image acquisition protocols and conducting large-scale prospective validation studies.

Future Prospects

- **Integrated RadiomicroRNA Deep Learning Architectures:** Future work will increasingly leverage end-to-end multi-modal deep neural networks that directly process raw 3D radiological DICOM images alongside raw RNA sequencing datasets, avoiding manual feature selection and capturing complex non-linear biomarker interactions
- **Standardization and Quality Frameworks:** Broader adoption of standardized frameworks-such as IBSI for radiomics and STARD-DTA/QUADAS-2 for diagnostic studies-will improve data quality and enable direct cross-study comparisons
- **Point-of-Care Biofluid-Imaging Workflows:** Development of rapid, point-of-care microfluidic chips for near-real-time salivary miRNA analysis during patient imaging visits could enable integrated multi-modal reporting within single clinical encounters
- **Prospective Multi-Center Clinical Trials:** Transitioning radiomicroRNA models from retrospective feasibility studies to prospective, multi-center clinical trials with diverse patient cohorts will be essential to establish clinical utility, validate diagnostic thresholds and gain regulatory approval

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