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Diagnostic Tumor Markers in Neck and Head Squamous Cell Carcinoma (HNSCC) in the Clinical Setting

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Head and neck epithelial cell carcinoma (HNSCC) represents a gaggle of tumors arising within the mouth, oropharynx, and larynx. Although HNSCC is traditionally related to tobacco and alcohol consumption, a growing proportion of head and neck tumors, mainly of the oropharynx, are related to Human Papilloma Virus (HPV). Recurrent/metastatic disease is characterized by dismal prognosis and there is an unmet need for the development of biomarkers for detection of early disease, accurate prediction of prognosis, and appropriate selection of therapy. Based on the REMARK guidelines, a spread of diagnostic and prognostic biomarkers is being evaluated in clinical trials but their clinical significance is doubtful. Herein, we'll specialize in biomarkers in HNSCC utilized in the clinical setting and that we will illustrate their clinical relevance [1].

Head and neck epithelial cell carcinoma (HNSCC) encompasses a heterogeneous group of malignancies that arise within the mouth, larynx and pharynx and are mainly related to tobacco and alcohol consumption. In addition, epidemiological, molecular pathology and cell line data indicate that a considerable proportion of oropharyngeal cancers represents a sexually transmitted disease and is causally related to high-risk human papillomaviruses (HPV), especially type 16. HPV-associated oropharyngeal cancers (HPV-OSCCs) represent a definite biological and clinical entity, have a definite mutation landscape, and are characterized by markedly improved survival. The majority of HNSCC patients present with loco regionally advanced (LA) disease that multimodality therapeutic approach is used. Despite advances in diagnostics, treatment and surveillance, the 5-year progression-free survival (PFS) of HPV negative patients with LA disease is 40-50% and survival rates for recurrent/metastatic (R/M) disease have not significantly changed over the past years [2].

Low survival rates associated with HNSCC are partly due to failure in early diagnosis. Indeed, only one third of HNSCC patients are diagnosed at an early stage; early diagnosis is mainly attributed to lack of appropriate screening and diagnostic biomarkers. Biomarkers are defined, consistent with the National Cancer Institute (NCI), as "a biological molecule found in blood, other body fluids, or tissues that's a symbol of a traditional or abnormal process, or of a condition or disease. A biomarker could also be wont to see how well the body responds to a treatment for a disease or condition". Basically, biomarkers represent important tools that contribute to diagnosis, assess the likely course of the disease and predict response to treatment; thus, they're categorized as diagnostic, prognostic or predictive, respectively. Regarding HNSCC, although many biomarkers are suggested to significantly impact diagnosis and prognosis, few of them are validated to be used in clinical practice. Indeed, a big proportion of biomarkers in development aren't introduced into clinical practice because they lack important features, like high specificity and sensitivity, low cost, high positive predictive value, clinical relevance, and short turnaround time. The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) initiative, which has been developed with the joint effort of clinicians, statisticians, epidemiologists, and journal editors, has recommended a suggestion for the reporting of studies developing, validating, or updating a prediction model, whether for diagnostic or prognostic purposes. Based on the remark criteria, a handful of biomarkers are validated for clinical use in HNSCC. In this review, we'll specialize in established diagnostic biomarkers that are in clinical use in HNSCC, and that we will discuss emerging biomarkers that are in development [3].

Validated Biomarker

HPV

A growing proportion of oropharyngeal cancers are related to HPV infection. More than 130 HPV types are known and classified as low-risk or high-risk based on their oncogenic potential; HPV16 is the most commonly found and is present in ~90% of HPV-OSCCs. Two meta-analyses of case-control studies have provided epidemiological evidence of the causative role of HPV in OSCC supported strong correlation between HPV16 exposure and HNSCC in certain anatomical sites. Indeed, a strong correlation has been described between HPV-16 detection at the time of diagnosis with tonsillar cancer. Biologically, the integration of high-risk HPV DNA into the host genome can lead to the expression of oncogenes E6 and E7 in the host cell; however, 60% of HPV-positive OSCC can contain extrachromosomal (episomal) virus. The E6 oncogene provokes the degradation of TP53. The E7 oncogene is implicated in binding and destabilizing of the tumor suppressor retinoblastoma (pRb).

HPV-OSCC differs from HPV-driven cervical cancer, during which cervical smear and HPV DNA are widely used for screening in clinical practice; in HPV-OSCC there's no identified oropharyngeal premalignant lesion and the presence of HPV DNA in the oral cavity or oropharynx is not directly linked to subsequent development of HNSCC. Although detection of HPV16 DNA by Polymerase Chain Reaction (PCR) in both salivary oral rinses and plasma has demonstrated marked sensitivity and specificity, it has not been incorporated into clinical practice as a screening tool [4].

Detection of HPV DNA in saliva samples has been shown be a predictive tool for recurrence in HPV-associated OSCC. More specifically oral rinse samples were collected from patients with HPV-OSCC at diagnosis and at several timepoints after diagnosis and evaluated for HPV DNA. HPV DNA was detected in 54% of patients at diagnosis, but only in 5% of patients post-treatment. Importantly, all patients with HPV DNA positive samples post-treatment relapsed

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and persistent oral HPV infection correlated with disease free survival (DFS) and overall survival (OS). Two additional smaller cohort studies have reported a correlation of HPV16 DNA detection in post-treatment oral rinses with survival. These findings support the potential utility of HPV DNA detection in post-treatment oral rinses as a clinical trial for the prediction of relapse.

Identification of appropriate biomarkers can cause early detection of HNSCC. It is commonly accepted that a tumor biomarker may be a molecular signal or process-based change that reflects the status of an underlying malignant disease and may be detected by one or more assays or tests. However, a tumor biomarker must be characterized by accuracy, reproducibility and reliability in order to be clinically useful and guide management [5].

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Conflict if interest

None

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