Molecular Imaging and Precision Medicine in Head and Neck Cancer

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KEYWORDS

• Head and neck cancer • Tumor genetic profiling • Molecular imaging • Targeted therapy

KEY POINTS

- Human papillomavirus (HPV) in head and neck squamous cell carcinoma (HNSCC), Epstein-Barr virus in nasopharyngeal carcinoma (EBV), and PET imaging features provide robust prognostic biomarkers that are being incorporated into clinical trials.
- Patients with HPV-positive HNSCCs have a better prognosis than patients with HPV-negative tumors; the HPV-positive status has facilitated efforts to de-intensify therapy in a subset of patients with a more favorable prognosis; FDG-PET/CT plays a role in safely de-intensifying therapy.
- Understanding the molecular and genetic alterations in the pathogenesis of head and neck cancer will help elucidate the mechanisms involved in tumor growth as well as identify potential targets for improved treatment.
- Novel drug developments focused on molecular targeting therapeutic agents for patients with genomically defined head and neck cancer have brought a new, exciting approach in the response assessment of head and neck cancer; this may open new strategies for using PET imaging to identify treatment response, and manage secondary resistances.
- Development of prognostic biomarkers using PET imaging could potentially predict early identification of responders/nonresponders, leading to improvement in clinical management and individualizing therapy decisions.

INTRODUCTION

Head and neck (HN) cancer is a heterogeneous malignancy that involves multiple sites and cellular origins, commonly arising from the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract, and nasopharynx.[1] HN cancer accounts for 650,000 cases annually worldwide and is the sixth most common neoplasm.[2,3]

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According to American Cancer Society, 47,000 new cases of HN cancers are diagnosed every year in the United States, constituting 3% of all cancers.[4] Squamous cell carcinoma (SCC) is the commonest type of HN cancer, accounting for 95% of cancers, and the remaining 5% includes non-SCC.[5] The most important risk factors for developing HN cancer include carcinogens (tobacco and alcohol) and human papillomavirus (HPV). Although the prevalence of traditional carcinogen risk factors–related HN cancers have reduced, there is an increased incidence of HPV-related HN cancers.[6] Despite the advances in management of HN cancer, the prognosis of patients with locally advanced HNSCC is poor, with 5-year survival rate of 40% to 50%,[7] without much change in the survival rates over the past decades, mainly due to the inability to control locoregional recurrences and distant metastases. Currently the treatment decisions are based on clinical and imaging diagnostics. Understanding the molecular carcinogenesis, individual genetic differences, and pharmaco-genetics may help in formulating new tailored therapeutic approaches; hence, improving the disease outcome. Identification of biological markers predictive of treatment failure also allows the use of more targeted therapies. This is illustrated in the use of novel targeted therapies focusing on epidermal growth factor receptor (EGFR). EGFR is overexpressed in nearly 80% to 90% of the HNSCC and correlates with poor prognosis and resistance to radiation therapy.[8] Evidence showed that treatment with inhibitors of EFGR offers better survival benefits when compared with standard therapies.[9]

The use of molecular imaging using PET offers unique insights in the field of oncology, helping early disease detection, localization, monitoring treatment responses, and identification of tumor recurrence. This review summarizes the recent genomic discoveries in HN cancer and their implications in imaging, highlighting the evolving role of PET imaging in HN cancer, with the use of ^{18}F-Fluorodeoxy-glucose (FDG) and other novel PET tracers designed to characterize the specific biological behavior of the cancer, and follow-up response assessment to a specific therapy.

MOLECULAR GENETICS IN HEAD AND NECK CANCER: VALUE OF PET IMAGING

The molecular origins of HN cancer lie on the interaction between environmental factors and host genetic susceptibility. Classically, HN cancer was driven by habitual exposure to tobacco and alcohol; however, in the past decades, there has been an alarming rise in the number of HN cancer cases arising from the oropharynx (tonsil and base of the tongue) as a result of oral infection with human papillomavirus (HPV), especially serotype 16. Tumor HPV status has been shown to be the single strongest predictor factor for oropharyngeal squamous cell cancer (OPSCC) (**Fig. 1**). HPV-positive tumors have a favorable prognosis, responding better to chemotherapy, radiation, and chemoradiation. Although currently HPV status does not influence treatment choices, increasingly clinical trials are exploring whether HPV-positive tumors may require less therapy in the goal of reducing long-term side-effects in a younger patient population. Emerging insights into the genetic differences between HPV-positive and HPV-negative HN cancers may eventually guide treatment choices; that is, HPV-negative tumors consistently show lower expression levels of EGFR and other kinase amplifications, whereas HPV-positive tumors have higher rates of PI3K-pathway alterations.[10] Genetic abnormalities have been extensively studied in HN cancer, suggesting the existence of several different molecular types of HNSCC based on the biological characteristics of differentially expressed genes.[11,12] Among others, the most reported genes and their molecular pathways involved in the development and progression of HNSCC are TP53, PI3K, EGFR, p16, and NOTCH1.[13] Recently, Chung and colleagues[14] investigated the genomic profile among HPV-positive and HPV-negative tumors including DNA samples from 252 HNSCCs, concluding that the most common genes with genomic alterations were PIK3CA and phosphatase and tensin homolog (PTEN) for HPV-positive tumors and TP53 and CDKN2A/B for HPV-negative tumors. In the pathway analysis, the PI3K pathway in HPV-positive tumors and DNA repair-p53 and cell cycle pathways in HPV-negative tumors were frequently altered. Moreover, the HPV-positive oropharynx and HPV-positive nasal cavity/paranasal sinus carcinoma shared similar mutational profiles.

Understanding the role of viral mechanisms, epigenetics, and genetics in HN cancer could play a role in developing a robust personalized medicine approach by identifying individuals whose tumors harbor specific characteristics that can guide more appropriate treatment selection; and as a direct result, developing new strategies for tumor imaging, using PET imaging as an early biomarker to identify responders/nonresponders and ultimately to accelerate personalized drug development for patients with HN cancer.