



Cancer Genomics: Head and Neck Cancer

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Introduction

Head and neck cancer accounts for 4% of all malignancies worldwide, though it constitutes 40% of the cancer burden in India [1,2]. The distinct geographic predilection of head and neck squamous cell carcinoma (HNSCC), a major portion of the burden being laryngopharyngeal cancers, may be due to prevalence of risk factors and genetic susceptibility. Advances in treatment strategies have not been accompanied by a parallel improvement in the survival rates. The major reasons being late presentation, high occurrence rate and the development of multiple primary tumors (10-30%) [1-3]. Detection and identification of patients who are likely to respond to treatment so as to avoid unnecessary toxicity through identifying response/resistant markers are the critical questions that need to be addressed through a comprehensive and systemic approach.

With the advent of improved sequencing technologies such as Next Generation Sequencing (NGS), profiling a tumor to detect therapeutically relevant mutations is becoming an increasingly viable option. NGS based tests can typically profile a few hundred genes causally implicated and clinically relevant in cancer. This deep sequencing technology can detect mutations with far greater sensitivity than other conventional sequencing methods, thus making it ideal to study tumors. According to the COSMIC (database for somatic mutations in cancer, Dated 5 June 2016) database, the most frequently mutated genes in head and neck cancer include TP53, CDKN2A, PIK3CA, MET, HRAS, EGFR, PTEN, BRAF, KRAS, PIK3R1, IL6ST, JAK3, NFE2L2 and FBXW7. In depth assessment of the impact of these mutations such as with the Strand Somatic-48 gene test can yield therapeutically relevant insights and aid in prediction of clinical behaviour of the tumor depending on the mutation pattern. Hence, NGS based multigene testing helps build a larger actionable landscape of mutations thus facilitating minimal loss of time before arriving at the effective therapy option.

Mutation profile of the tumor could indicate poor response to a particular regimen that would be typically considered for the patient. Some mutations may be indicators of overall prognosis or response to certain types of chemotherapy. Chemotherapy and radiotherapy are very important treatment modalities in head and neck cancer patients; mutations in genes such as ATM, FBXW7 and TP53 can provide valuable information regarding responsiveness. It is increasingly being accepted that tumors of different origins can have the same driver mutations and hence can be targeted using the same drug. For example, cetuximab has been approved by FDA for colorectal cancer and more recently for head and neck cancer as well. More than 90% of the head and neck cancer patients overexpress EGFR, either due to amplification of the EGFR gene or polymorphic mutations [4,5], and thus, anti-EGFR drugs provide a therapeutic window. Although the results are promising, there are a few caveats to be considered. Firstly, in tumors treated with cetuximab, presence of an activating mutation in the downstream RAS/RAF/MEK pathway such as codon 12 or 13 mutation in KRAS would make the tumor refractory to anti-EGFR drugs. Such head and neck cancer patients will probably respond better to inhibitors of downstream proteins such as MEK inhibitors, trametinib or selumetinib [6,7]. Secondly, various clinical studies have reported that after the early response to cetuximab, head and neck tumors gradually acquire resistance to treatment [8,9]. In such cases, NGS based mutation profile can help in charting out a second line of

treatment or a more aggressive first line of treatment. Head and neck cancer patients often harbour activating mutations in PIK3C, PTEN or AKT1 resulting in constitutive activation of the PI3K/m TOR/AKT pathway and thus, possibly sensitizing the tumors to mTOR inhibitors such as everolimus or temsirolimus [3].

Strand Somatic 48-gene test based molecular profiling and interpretation gives insight into patient responsiveness to approved treatment, potential treatment regimen inferred from other tumor types and patient prognosis. Treatment regimens aided by such an approach are likely to translate into tailored, less toxic and more cost-effective care.

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Received June 24, 2016; Accepted July 15, 2016; Published August 05, 2016

Citation: Agarwal S (2016) Cancer Genomics: Head and Neck Cancer. *J Mol Histol Med Physiol* 1: 107

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