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PROGNOSTIC BENEFITS OF GENOMIC TESTING IN HEAD AND NECK CANCERS

Otorhinolaryngology

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ABSTRACT

Aim: To evaluate the cancer related mortality and morbidity based of the elucidation of the genomic basis of head and neck cancers and to see the prognosis in customizing the treatment based of the genomic study. **Materials and Methods:** This is a prospective study were the patients of head and neck cancers, presenting to the Head and Neck clinic of Sree Mookambika cancer centre, in kanyakumari, Tamil Nadu, from August, 2021 to February, 2023, were chosen for this study. **Results:** The age distribution of the patients ranged from 18 to 74 years, with a median age of 45.94 years. There were 15 males and 3 females in the group. Family history was obtained patients of whom 6 had a family history of other cancers. There were 11 patients with a history of exposure to tobacco, 3 with alcohol consumption history while the others did not report any risk factors. The study identified somatic mutations in 9 out of 18 cases using a 48-gene panel of targetable mutations and 2 germline mutations. The genomic study revealed germline mutations in BRCA – 5.5% in a patient with carcinoma nasopharynx and AIP- 5.5 %, somatic mutations in P53 in 3 patients-16.6% and HRAS in 3 patients -16.6, while the other mutations detected were STK11 in a patient with mucoepidermoid carcinoma of the hard palate, GNA11 -5.5% in metastatic alveolar sarcoma of the tongue, phosphatase and tensin homolog PTEN, and RB1 in a case of SCC involving the gingivobuccal sulcus and the base of the tongue. **Conclusion:** Early genomic testing in head and neck cancers cases helps in customizing a modifying the treatment protocol which in turn demonstrate potential prognostic benefits compared to treatment protocol without genomic testing.

KEYWORDS

Genomic testing, Head and Neck cancers, Head and Neck squamous cell carcinoma.

INTRODUCTION

A significant portion of cancer related mortality and morbidity worldwide are contributed by head and neck malignancies [1]. Even though there are recent advances in multimodality treatments, the overall survival has not improved significantly over time [2]. Genomic profiling and testing of Head and Neck Cancers can give a biological basis of the individual tumor pathogenesis and helps in identifying potential carcinogens and in turn contributes in dentification of diagnostic and prognostic markers and choice of targeted treatment protocol hence having an impact on the clinical outcome.[3]

AIM:

To evaluate the cancer related mortality and morbidity based of the elucidation of the genomic basis of head and neck cancers and to see the prognosis in customizing the treatment based of the genomic study.

MATERIALS AND METHODS:

This is a prospective study conducted in patients with Head and Neck cancers, presenting to the Head and Neck clinic of Sree Mookambika cancer centre, in kanyakumari, Tamil Nadu, from August, 2021 to February, 2023, were chosen for this study. The approval of the scientific research committee and Institutional Ethics Review Board (IERB) was obtained. Informed consent about the limited applicability to current treatment protocols, though with a possibility of future benefits but was obtained from patients. The clinical data of the patients including details of family history of cancers were obtained from the referring oncologist and, whenever possible through pretest genetic counseling by a genetic counselor. The tissue samples (paraffin-embedded tissue/fresh frozen tissue) were obtained from 18 patients diagnosed with tumors of the head and neck. To assess tumor tissue quality, a small section of each biopsy (3–5 mm3) was cut, fixed in formalin, and stained with hematoxylin and eosin for scoring by an onco-pathologist. These slides were scored for the percentage volume of the tumor. The methodology for sequencing has been outlined below in Fig 1.

Chromosome number	Genes affected
1	MPL, NRAS
2	ALK, ERBB4, IDH1
3	PIK3CA, MLH1, PDGFRA, VHL
4	FGFR3, KDR, KIT
5	CDH1, APC, CSF1R, NPM1
7	EGFR, BRAF, MET, SMO
8	FGFR1
9	NOTCH1, CDKN2A/B, ABL1, GNAQ, JAK2
10	FGFR2, PTEN, RET
11	HRAS, ATM
12	HNF1A, KRAS, PTPN11
13	FLT3, RB1
14	AKT1
18	SMAD4
19	GNA11, JAK3, STK11
20	SRC, GNAS
22	SMARCB1

Fig 1: Genomic sequencing of the collected tissue.

RESULTS AND OBSERVATIONS:

The age distribution of the patients in our ranged from 18 to 74 years, with a median age of 45.94 years. There were 15 males and 3 females in the group. Family history was obtained patients of whom 6 had a family history of other cancers where 2 patients had siblings with a history of other cancers and 4 had parents with a history of other cancers. There were 11 patients with a history of exposure to tobacco, 3 with alcohol consumption history while the others did not report any risk factors. The study identified somatic mutations in 9 out of 18 cases using a 48-gene panel of targetable mutations and 2 germline mutations. The genomic study revealed germline mutations in BRCA – 5.5% in a patient with carcinoma nasopharynx and AIP- 5.5 % in a patient with adenoid cystic carcinoma of the right submandibular gland, somatic mutations in P53 in 3 patients-16.6% with squamous cell carcinoma one case of SCC of the tongue, one with SCC of the

gingivobuccal sulcus, and the third involving the oropharynx and base of the tongue and HRAS in 3 patients -16.6% in a case of metastatic papillary thyroid cancer, a case of malignancy of unknown origin, and a case of SCC of the tongue, while the other mutations detected were STK11 in a patient with mucoepidermoid carcinoma of the hard palate, GNA11 -5.5% in metastatic alveolar sarcoma of the tongue, phosphatase and tensin homolog (PTEN), and RB1 in a case of SCC involving the gingivobuccal sulcus and the base of the tongue.

The remaining samples 4 cases of SCC, one involving the pyriform sinus, one involving both the oropharynx and pyriform sinus, one of the tongue, and the fourth, SCC of the buccal mucosa. Two cases of mucoepidermoid carcinoma of the right parotid and one patient with carcinoma of the base of tongue showed no mutation as seen by the 48-gene panel, while one sample belonging to a patient of papillary carcinoma thyroid failed quality control testing. The Genes detected are shown in Fig2.

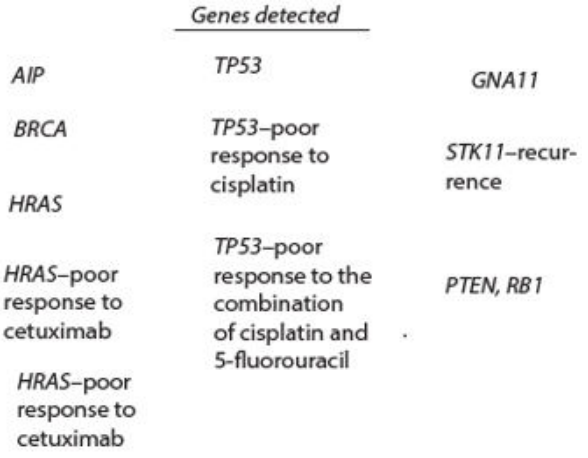

Fig 2: Genes detected in the study.

DISCUSSION:

TP53 is the most commonly mutated gene in HNC patients in studies conducted by Agrawal et al. and Stransky et al. on 32 and 74 samples, respectively. HPV-positive cancers were 100% positive for E6 and E7 oncogenes. The other mutations that were picked up in significant numbers were SYNE1, NOTCH1, and HRAS. [4,5]

Pickering et al. conducted two studies on oral squamous cell cancer and on carcinoma tongue specimens in the years 2013 and 2014, respectively. Among the samples in both the studies, CDKN2A and TP53 were the common mutations picked up. [6,7] In a study conducted by Lin et al. on 128 samples of nasopharyngeal carcinoma, a mutation in TP53 was seen in 17%, CDKN2A in 13%, and ARID1A in 11% samples. Less than 10% of tissue samples showed the presence of mutations in SYNE1, ATG13, MLL2, PIK3CA, CCND1, NOTCH3, and FGFR2. [8]

In 2015, Seiwert et al. and The Cancer Genome Atlas (TCGA) conducted genomic studies on both HPV-positive and -negative tumor tissue samples separately and found that in the HPV-negative group, the most commonly mutated gene was TP53 followed by CDKN2A, while in the HPV-positive group, E6/E7 were positive in 100% samples and the second most commonly mutated gene was PIK3CA. [9]

In 2018, a targeted sequencing conducted by Perdomo et al. on 180-paired diagnosed samples of head and neck squamous cell carcinoma (HNSCC) revealed the most frequently mutated genes to be TP53, PIK3CA, NOTCH1, TP63 and CDKN2A.[10]

The mutations detected commonly in the above studies conducted from 2011 to 2015 were TP53, EGFR, HRAS, NOTCH1/2/3, CDKN3A, CCND1, PIK3CA, and ATM. E6 and E7 oncogenes were seen to be expressed in HPV-positive cancers.

In our study, germline mutations were detected in two patients—AIP and BRCA, while somatic mutations were detected in nine patients. These were TP53, PTEN, RB, STK11, GNA11, and HRAS. TP53 and HRAS were seen in 16.67% of patients each while the other mutations were detected in 5.5% of patients each.

CONCLUSION:

Early genomic testing in head and neck cancers cases helps in customizing a modifying the treatment protocol which in turn demonstrate potential prognostic benefits compared to treatment protocol without genomic testing. Although this is a preliminary study, early genomic testing do help in better prognosis.

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