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Original Research

Targeted next-generation sequencing of locally advanced squamous cell carcinomas of the head and neck reveals druggable targets for improving adjuvant chemoradiation☆,☆☆

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Abstract ***Background:*** Despite clear differences in clinical presentation and outcome, squamous cell carcinomas of the head and neck (SCCHN) arising from human papilloma virus (HPV) infection or heavy tobacco/alcohol consumption are treated equally. Next-generation sequencing is expected to reveal novel targets for more individualised treatment.
Patients and methods: Tumour specimens from 208 patients with locally advanced squamous cell carcinoma of the hypopharynx, oropharynx or oral cavity, all uniformly treated with adjuvant cisplatin-based chemoradiation, were included. A customised panel covering 211 exons from 45 genes frequently altered in SCCHN was used for detection of non-synonymous point and frameshift mutations. Mutations were correlated with HPV status and treatment outcome.
Results: Mutational profiles and HPV status were successfully established for 179 cases. HPV− tumours showed an increased frequency of alterations in tumour suppressor genes compared to HPV+ cases (*TP53* 67% versus 4%, *CDKN2A* 18% versus 0%). Conversely, HPV+ carcinomas were enriched for activating mutations in driver genes compared to HPV− cases (*PIK3CA* 30% versus 12%, *KRAS* 6% versus 1%, and *NRAS* 4% versus 0%). Hotspot *TP53* missense mutations in HPV− carcinomas correlated with an increased risk of locoregional recurrence (hazard ratio [HR] 4.3, 95% confidence interval [CI] 1.5–12.1, $P = 0.006$) and death (HR 2.2, 95% CI 1.1–4.4, $P = 0.021$). In HPV+ SCCHN, driver gene mutations were associated per trend with a higher risk of death (HR 3.9, 95% CI 0.7–21.1, $P = 0.11$).
Conclusions: Distinct mutation profiles in HPV− and HPV+ SCCHN identify subgroups with poor outcome after adjuvant chemoradiation. Mutant p53 and the phosphoinositide 3-kinase pathway were identified as potential druggable targets for subgroup-specific treatment optimisation.

1. Introduction

It is generally acknowledged that human papilloma virus-negative (HPV−) and HPV+ squamous cell carcinomas of the head and neck (SCCHN) represent two distinct subgroups with significant differences in treatment outcome [1]. The dissimilarities are thought to result from distinct molecular patterns which have evolved during the pathogenesis of HPV− and HPV+ SCCHN. Recent studies designed to unravel the genomic landscape of SCCHN by next-generation sequencing (NGS) have discovered large differences between HPV− and HPV+ tumours [2–6]. Smoking-related patterns which mainly comprised loss-of-function mutations in tumour suppressor genes were predominantly detected in HPV− carcinomas. In