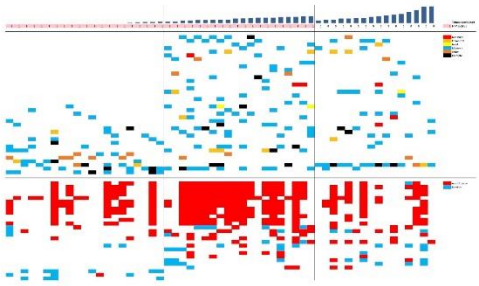
Purpose or Objective
Oropharyngeal squamous cell carcinoma (OPSCC) is now the most common form of head and neck cancer in many western countries due to HPV. Patients with HPV-related (HPV+) OPSCC have clearly better outcomes after treatment. This has led to a strong wish to individualize treatment for these patients, aiming to minimize morbidity as well as to increase survival. However, patients with HPV+ OPSCC and a significant history of former or current tobacco smoking (HPV+ smokers) have increased risk of locoregional failure and increased cancer mortality after radiotherapy-based treatment than HPV+ non-smokers. These observations, recently confirmed in the MARCH-HPV meta-analysis of individual patient data, has led to the hypothesis that HPV+ smokers have altered disease biology, possibly through the additional accumulation of somatic tumor mutations through cumulative carcinogenic exposure.This was a hypothesis-generating study with the aim of characterizing the biology of OPSCC with regards to HPV and tobacco smoking, and to clarify whether HPV+ OPSCC consists of different biological subgroups, and whether these could be related to tobacco smoking.
Material and Methods
We included 64 patients with primary, untreated oropharyngeal squamous cell carcinoma from two prospective protocols. Tumors were comprehensively characterized using targeted sequencing of 409 cancer related genes with regards to mutations and copy-number alterations. Also, we characterized gene expression related to HPV, hypoxia, gene expression subtypes and radiosensitivity.
Results
Fifty-seven patients were available for analysis, of which 41 were HPV-positive. Twenty patients had a history of significant tobacco smoking (≥10 pack-years). Sequencing revealed robust differences between HPV+ and HPV- tumors (*TP53*, p<0.0001). Between HPV+ smokers and HPV+ non-smokers, there was a distinct pattern of amplifications of a number of neighboring genes among smokers (p<0.005).These recurrent amplifications among HPV+ smokers defined a subgroup of patients (n=20) with a distinct mutational profile as well as substantial differences in expression of genes related to stem cells and gene expression subtypes.
Conclusion
HPV+ OPSCC possibly consists of several biologic subgroups, related to tobacco smoking, explaining the diverse outcomes seen among these patients. These subgroups can be characterized by specific DNA copy number alterations and mutations. These differences could explain the poorer prognosis of HPV+ smokers after radiotherapy-based treatment. These findings warrant further large-scale investigation to clarify prognostic value and potential as biomarkers to guide treatment allocation in future clinical trials of intensification or de-escalation.



PO-102 Amplification of genes at 11q13 in relation to HPV status in head and neck squamous cell carcinomas

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Purpose or Objective
Clear differences have been established between head and neck squamous cell carcinomas (HNSCC) depending on human papillomavirus (HPV) infection status. This study investigates the specific role of *CTTN, CCND1* and *ANO1* genes mapping at 11q13 amplicon in relation to HPV status in HNSCC patients
Material and Methods
CTTN, CCND1 and ANO1 protein expression and gene Amplification were respectively analyzed by immunohistochemistry and real-time PCR in a homogeneous cohort of 392 surgically treated HNSCC patients. Results were further confirmed using an independent cohort of 279 TCGA HNSCC patients. The impact on patient survival was also evaluated.
Results
CTTN, CCND1 and *ANO1* gene amplification and protein expression is frequent in HPV-negative tumors, while absent or rare in HPV-positive tumors. Using an independent validation cohort of 279 HNSCC patients, we consistently found that these three genes are frequently co-amplified (28%) and overexpressed (39-46%) in HPV-negative tumors, whereas almost absent in HPV-positive tumors. Remarkably, these alterations (in particular CTTN and ANO1 overexpression) were associated with poor prognosis.
Conclusion
Taken together, distinctive expression/amplification of these genes could cooperatively contribute to the differences on prognosis and clinical outcome between HPV-positive and HPV-negative tumors. These findings could serve as the basis to design more personalized therapeutic strategies for HNSCC patients