

Exploring the role of oral microbiota in head and neck squamous cell carcinoma

BY ANJALI CHANDER AND MIGUEL REIS FERREIRA

Oral microbiota, especially *Fusobacterium nucleatum*, may improve survival and guide personalised treatment in head and neck squamous cell carcinoma.

Head and neck squamous cell carcinoma (HNSCC) is a devastating disease with a low five-year survival rate that has shown little improvement despite aggressive treatment strategies. Recently, research has begun to focus on the role of the microbiome in influencing HNSCC outcomes, particularly the potential impact of oral bacteria on survival and therapeutic responses.

Our study, which used data from two independent cohorts and in vitro models, aimed to assess how the oral microbiota could influence both overall survival (OS) and disease-specific survival (DSS) in patients with mucosal HNSCC. We began by analysing microbiome data from The Cancer Microbiome Atlas, which included 155 patients diagnosed with mucosal HNSCC. The focus was on the relative abundance (RA) of various bacterial genera and their association with patient survival. Statistical analyses revealed a notable finding: the presence of *Fusobacterium*, specifically *F. nucleatum*, was associated with improved survival outcomes. Higher RA of *Fusobacterium* was linked to better OS and DSS, with the detectability of *F. nucleatum* being significantly associated with enhanced OS, with a hazard ratio (HR) of 0.43 and a p-value of 0.042, suggesting a robust correlation with improved survival.

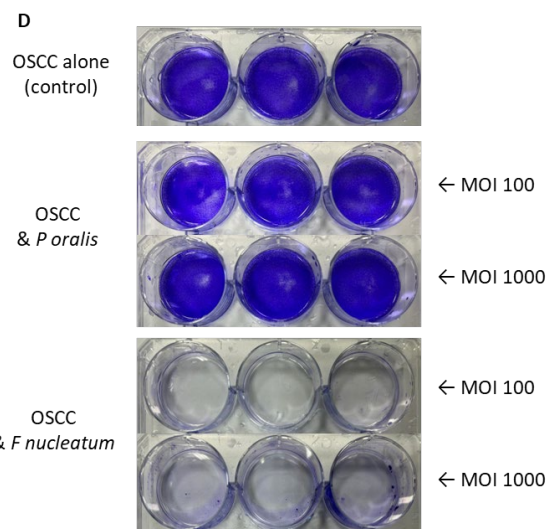
Further validation of these results came from a separate cohort of 175 HNSCC patients in the MicroLearner study, where patients were grouped based on *Fusobacterium* abundance. Those in the high *Fusobacterium* group (FusoHI) demonstrated significantly better progression-free survival (PFS), particularly among HPV-negative patients.

In addition to survival analysis, we explored the mechanistic effects of *F. nucleatum* through in vitro co-culture experiments using oral squamous cell carcinoma (OSCC) cell lines. A series of assays demonstrated that *F. nucleatum* reduced OSCC cell viability in a dose-dependent manner, suggesting that the bacterium may play a role in enhancing treatment efficacy.

Interestingly, when compared to *Prevotella oralis*, another oral commensal bacterium, *F. nucleatum* exhibited a unique effect on OSCC cell viability, highlighting that not all oral bacteria share the same impact on cancer cell behaviour. Further tests using different strains of *F. nucleatum* showed similar cytotoxic effects on OSCC cells, reinforcing the importance of this bacterium in reducing tumour cell viability.

In exploring the mechanisms behind these effects, the study found that *F. nucleatum* could induce OSCC cell death through a contact-independent mechanism, with the bacterial secretome playing a pivotal role. The supernatant from *F. nucleatum* cultures was sufficient to induce cell death, suggesting that factors secreted by the bacteria are key players in this process. Ongoing research is delving deeper into these mechanisms to better understand the underlying pathways.

These findings are promising for the future of HNSCC treatment, particularly in the context of personalised medicine. If confirmed in



larger cohorts, *F. nucleatum* could emerge as a useful prognostic biomarker, indicating better survival outcomes and potentially enhanced responses to treatment. This could lead to more tailored therapeutic approaches, including the possibility of de-escalating treatment in patients who show favourable microbiome profiles. Additionally, understanding how *F. nucleatum* influences HNSCC could open the door to novel microbiome-based therapies, offering new avenues for clinical intervention. As research into the oral microbiome and its impact on cancer progresses, these insights may reshape how clinicians approach HNSCC treatment, providing a more nuanced understanding of the disease and offering hope for improved patient outcomes.

AUTHORS



Anjali Chander,

Senior Clinical Fellow, Centre for Host-Microbiome Interactions, Guys and St Thomas NHS Foundation Trust, London, UK.



Miguel Reis Ferreira, MD, PhD,

Consultant in Head and Neck Cancers, Guys and St Thomas NHS Foundation Trust; Senior Clinical Lecturer, King's College London (Center for Host-Microbiome Interactions), London, UK.

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