23 September 2021

Dear Prof. Robert Ferris,

Please find enclosed the submission package for our manuscript **“**RAS mutations in Head and Neck Cancer: A Systemic Review and Meta-Analysis**”** to be considered for publication as a Systemic review and meta-analysis in *Oral Oncology*.

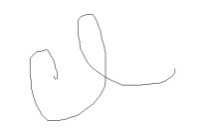
In this study, we conducted the first comprehensive systematic review and meta-analysis assessing the prevalence of RAS gene mutations in head and neck cancer (HNC). Specifically, we analyzed 149 studies, integrating data from 8500 HNC patients to shed light on the differences in the prevalence of HRAS, KRAS, and NRAS gene mutations. We further analyzed patient data and studied RAS mutations distributions according to geographical region, anatomical site, and other clinical features. We found that the estimated global prevalence of HRAS mutations is 7%, but this rate was more than double the global average in South Asia (15.28%). Estimated KRAS and NRAS mutation prevalence rates were 2.89% and 2.20%, respectively. HRAS mutations were more prevalent in tumors of the oral cavity and salivary glands. In contrast, KRAS mutations were more frequently detected in sinonasal tumors, and NRAS mutations were found chiefly in tumors of the nasopharynx. Odds ratio analyses revealed a significant association between HRAS mutations and high tumor stage or grade, and a significant association was found between Human Papillomavirus (HPV) positivity and KRAS mutations. In addition, we present data on the distribution of HRAS, KRAS, and NRAS codon substitutions in each of the HNC sites

In summary, this meta-analysis integrates data from the past 20 years and provides updated insights into the worldwide prevalence of RAS family mutations and the characterization of mutated RAS genes in the seven major HNC sites. This work fits the scope of *Oral Oncology* because the findings presented in our analysis provide a simplified overview of the complexity and heterogeneity of RAS mutations for the oral oncology community and reinforce the potential of targeting RAS and the RAS pathway in HNC patients.

The work described in the manuscript has not been discussed with a specific *Oral Cancer* editor before submission, and has not been published previously. All authors have approved the manuscript for submission and declare no conflict of interest.

We hope that you will find the article suitable for peer review in *Oral Oncology.*

Sincerely,



Prof. Moshe Elkabets

