Major compulsory comment needed

Question (1): Queried the selection of the tissue for analysis as tumor tissue which is adjacent to the growth border, the critical region for carcinoma characteristics and molecular signature.

The significance of this selection approach is to provide insight into tumor behavior in relation to possible future novel treatment developments.

The response by the investigators of this study was their handling of tissue section selection was at the standard used world-wide. This statement may or may not be accurate but as a reviewer for this study for this journal a high standard for tissue analysis and handling of tissue in consideration of precision and accuracy of data acquisition was the reason for the suggestions.

Forgiving the lack of ability to determine the origin of tissue selected from the original tumor mass or knowledge of grossing and details of sectioning techniques in accessing paraffin or frozen sections there is a persistent concern and lack of attention to histopathology description which is needed to better understand expression of proteins; EGFR and p53.

a. To value EGFR expression we need to know the level of phosphorylated form in comparison to non-phosphorylated form of EGFR. This comparison will permit us to evaluate biologic activation and function of EGFR. Moreover, activated phosphorylated form of EGFR is related to:

1. capability to cross talk to other important receptors and membrane enzymes (IGF-1, TGF-beta, furin convertase)

2. activation of EGFR linked signals to PI3K/AKT/mTor/PTEN pathway resulting in downstream transcription interaction with oncogenes and oxidative regulatory factors such as hypoxia-inducible factors (e.g., 1-3).

3. responsive mediation by redox -ROS substances such as PAH, TSNAs, etc

Furthermore, exposure through tobacco products and chemicals listed above are particularly important to understand the inductive environment which the tissue was exposed and this is specifically notable for this carcinoma type (e.g., OSCC).

In addition there are critical clinical answers that are answered by histopathology descriptions associated with the fore-mentioned proteins, such as why there is a
comparative lack of HPV 16 infection associated with OSCC in comparison with oropharynx carcinoma from a tonsil origin.

b. P53 expression in types of epithelial/keratinocyte cell or region is another feature that is overlooked in this study. Similarly in conjunction with the lack of an EGFR expression pattern discussion the reader is left to wonder the degree of changes related to phenotype and pathology characteristics which comprise grade assessment and this lessens the importance of this study and capability to provide cell biology detail and significance to findings.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'