Dear reviewers

Thank you very much for your important contributions.

Reviewer 1

The manuscript is clear and presented in a well structured manner. The topic is relevant. Squamous cell carcinoma is a frequent tumor, not only in the oral cavity. Immunotherapy has recently changed the approach in the head and neck area, so tools for biomarker assessment are needed. Specifically, the CPS (combined positive score) has a whole series of evaluation rules (in the infiltrating component, it must necrosis ..) which needs training and competence. Just minors: - please explain if other tecniques (immunoistochemistry) can be relevant or not –

We consider that in cases of poorly differentiated carcinomas, complementary immunohistochemical studies (cytokeratins) would be very useful to confirm the epithelial origin of the neoplasm.

Discuss the differential diagnosis and isssues in oral cavity (e.g. pseudoepiteliomatous hyperplasia, verrucous histotype (the issue of infiltration is crucial..) - discuss the role of immunotherapy and the needing of tools to implement reproduibility or make simple easy biomarker assessement (quote Prevalence of PD-L1 expression in head and neck squamous precancerous lesions: a systematic review and meta-analysis. Girolami I et al. Head Neck. 2020 Oct;42(10):3018-3030. doi: 10.1002/hed.26339, PD-L1 in oral squamous cell carcinoma: A key biomarker

from the laboratory to the bedside. Nocini R et al. Clin Exp Dent Res. 2022 Jun;8(3):690-698. doi: 10.1002/cre2.590)

Currently, there are other efforts focused on elucidating the prognosis in oral SCC. Some of these have been reported by Nocini et al. 7 and Girolami et al. 8 who studied the expression of programmed death-ligand 1 (PD-L1) both in precancerous lesions of the head and neck, and in oral SCC. There are contrasting results for PD-L1 in the world literature; the authors suggest that if an adequate standardization is carried out both in the performance and the evaluation of the marker, more reliable results can be obtained.7,8 As shown here, this work is aimed at standardizing both histopathological characteristics and molecular biology techniques, with the sole purpose of facilitating the clinical management of oral SCC patients in a correct, precise, and timely manner.

Reviewer 2

As you article is mainly focused on histopathology, you have to try to explain with more details in the legend the histopathological features and to add explanative arrows... 2. In the manuscript, you stated that your working group has evaluated the histopathological parameters of for example 10 cases.... You have to give clear details about the origin of these cases evaluated....

We analyzed 10 cases diagnosed in the Oral Pathology Laboratory of the Stomatology Department of the Universidad Autonoma de Ciudad Juarez in Mexico; 9 corresponded to well-differentiated SCC and 1 was poorly differentiated.

The other modifications were also made.

Company Editor-in-Chief

If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

We make this change

Comment on at least one related article published in the World Journal of Clinical Cases.

When the origin of the primary tumor is unknown in head and neck SCC, the 5-year survival rate is only 5% to 15%.

Große-Thie C, Maletzki C, Junghanss K, Schmidt K. Long-term survivor of metastatic squamous-cell head and neck carcinoma with occult primary after cetuximab-based chemotherapy: A case report. World J Clin Cases. 2021; 9(24):7092-98.