

February 2024

*To Editorial Office,
World Journal of Clinical Oncology,*

Please find enclosed the revised Editorial entitled “*Classificatory Updates in Verrucous and Cuniculatum Carcinomas: Insights from the 5th Edition of WHO-IARC Head and Neck Tumor Classification*” (NO: 90627) for evaluation by the Editorial Council of the prestigious *World Journal of Clinical Oncology*. The Editorial was authored and approved by Felipe Martins Silveira, Lauren Frenzel Schuch, and Ronell Eduardo Bologna-Molina.

We express our gratitude for the insightful comments, significantly enhancing our Editorial. Below, we present our point-by-point response and changes made to address all the concerns. All alterations are highlighted in yellow color in the new version of Editorial.

Thank you for providing us the opportunity to address the comments. We trust the revised Editorial meets the high standards of the *World Journal of Clinical Oncology*. We appreciate your time in reconsidering our submission and look forward to your earliest response.

Best regards,

A handwritten signature in black ink, appearing to read 'Ronell Bologna-Molina', with a stylized flourish at the end.

Ronell Bologna-Molina

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Response letter

Reviewer #1:

Specific Comments to Authors:

1) The manuscripts provides insights about the changes in the recent WHO book and is quite engaging 2) Although the manuscript is current and relevant, if the authors explain the reasons for the changes made or recommendations the readers would be benefitted.

Response: The authors express their gratitude for your valuable consideration of our manuscript. Indeed, elucidating the reasons behind the modifications in the categorizations of the entities discussed is a significant goal of this editorial. We would like to clarify that some of these explanations are already referenced in the text and, in reality, they are predominantly of a classificatory nature. In this context, we delve into the concepts that explain the main modifications in the latest edition of the World Health Organization Classification for Head and Neck Tumors (Oral Cavity and Mobile Tongue). Changes related to this issue are highlighted in yellow in the revised version of the editorial, as follows:

“This definition of OSCC is more objective when compared to the definition presented in the 4th edition of the WHO Blue Book, which also included demographic characteristics and the presentation of associated risk factors. These alterations involve a classification reorganization. Considering the behavior of pathological entities, it is logical to begin with the presentation of squamous papilloma, a benign epithelial neoplastic lesion, then progress to potentially malignant oral disorders, and finally, address OSCC, a malignant epithelial neoplasm. The alterations on the new section on OSCC has been updated to reflect the most recent information regarding epidemiology, pathogenesis, and histological prognostic

factors of this entity. Regarding its clinical features, in the 5th Edition of the Blue Book the occurrence of OSCC is reported to predominantly affects male individuals with the potential to manifest at any location within the oral mucosa, presenting as lesions characterized by diverse colorations (white, red, or mixed) and varied configurations (flat, nodular, or mass) in terms of size.”

“The classification also acknowledges the possible occurrence of rare histological subtypes of this malignant epithelial neoplasia. The histological subtypes of OSCC comprises the following six distinct variants according to the WHO: (...)”

“As noted, in the 5th edition of the WHO Blue Book, the histological subtypes of OSCC remain unchanged being specified in the Subtype(s) section as: Spindle Cell, Basaloid, Acantholytic, Adenosquamous, Papillary, and Lymphoepithelial. Notably, an alteration from the previous classification is here observed, wherein VC and CC variants are now described in specific sections. Verrucous Carcinoma (VC) is often linked to prolonged tobacco use, presents with a well-differentiated, warty appearance and tends to display a less aggressive nature^[10]. Carcinoma Cuniculatum (CC) stands out as a distinct subtype, characterized by a gradual, endophytic growth pattern featuring crypt-like structures^[11]. This adjustment acknowledges the oral cavity as the predominant site in the head and neck for both entities, each possessing distinct clinical and histologic characteristics that differentiate them from the conventional type. The choice to designate specific sections for these entities likely originates from the imperative to provide comprehensive and focused information about these particular subtypes. This involves elucidating their unique clinical features,

distinct histological characteristics, prevalence and significance, as well as their clinical relevance.”

“Verrucous Carcinoma and Carcinoma Cuniculatum

In the previous edition, VC was discussed in the chapter covering the Hypopharynx, Larynx, Trachea, and Parapharyngeal Space. Given the distinctive manifestation of VC in the oral cavity, accounting for more than half of all VC cases in the head and neck, a specialized section has been included in the most recent edition.”

Editorial Office’s comments

(1) Science editor:

Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. **Classification: Grade B; Language Quality: Grade B.** The manuscripts provide insights about the changes in the recent WHO book and is quite engaging. Although the manuscript is current and relevant, if the authors explain the reasons for the changes made or recommendations the readers would be benefitted.

Response: The authors appreciate your feedback. The requested revisions have been completed as per the suggestions from Reviewer 1. The responses are detailed above, and all the modifications pertaining to this issue have been highlighted in yellow in the revised version of the editorial.

Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjnet.com/bpg/gerinfo/240>.

Response: The authors would like to emphasize that the text has been thoroughly reviewed, and minor changes have been made to enhance its flow and comprehensibility. All modifications related to the text's writing are highlighted in green in this revised version of the editorial.

Specific comments:

Please add the author's contribution section. The format of this section will be as follows: Author contributions: Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; Wang CL, Liang L and Fu JF wrote the paper.

Response: The author's contribution section was included in the revised version of the manuscript, as follows:

“Author's contribution: Silveira FM – Conceptualization, Investigation, Writing – original draft; Schuch LF – Investigation, writing – original draft; Bologna Molina R – Supervision, Writing / review & editing.”

Please add the Core tip section. The number of words should be controlled between 50-100 words.

Response: An Core tip section was included in the revised version of the manuscript, as follows:

“The collaboration between the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) has produced indispensable 'WHO Blue Books,' crucial for standardizing cancer diagnostics. In the 5th edition of the WHO/IARC Classification of Head and Neck Tumors, the 'Oral Cavity and Mobile Tongue' chapter refines its structure, introducing sections for non-neoplastic lesions, epithelial tumors, and tumors with uncertain histogenesis. Notable adjustments in the Epithelial Tumors section highlight a reorganization based on tumor behavior, offering comprehensive insights into distinct subtypes.”

Please add the content of the abstract section. An informative, unstructured abstract of no less than 200 words should accompany each manuscript. Abbreviations must be defined upon first appearance in the Abstract. Do not use

non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition.

Response: An Abstract section was included in the revised version of the manuscript, as follows:

“The International Agency for Research on Cancer (IARC) and World Health Organization (WHO) collaboratively produce the 'WHO Blue Books,' essential tools standardizing the diagnostic process for human cancers. Regular updates in this classification accommodate emerging molecular discoveries, advances in immunohistochemical techniques, and evolving clinical insights. The 5th edition of the WHO/IARC Classification of Head and Neck Tumors refines the 'Oral Cavity and Mobile Tongue' chapter, including sections for non-neoplastic lesions, epithelial tumors, and tumors of uncertain histogenesis. Notably, the Epithelial Tumors section is rearranged by tumor behavior, starting with benign squamous papillomas and progressing through potentially malignant oral disorders to Oral Squamous Cell Carcinoma (OSCC). The section on OSCC reflects recent information on epidemiology, pathogenesis, and histological prognostic factors. Noteworthy is the specific categorization of Verrucous Carcinoma (VC) and Carcinoma Cuniculatum (CC), both associated with the oral cavity and distinct in clinical and histologic characteristics. This classification adjustment emphasizes the oral cavity as their predominant site in the head and neck. Designating specific sections for VC and CC aims to provide comprehensive insights into these unique subtypes, elucidating their clinical features, distinct histological characteristics, prevalence, significance, and clinical relevance. By segregating these subtypes into distinct sections, the 5th edition of the WHO classification aims to offer a more nuanced and detailed account, facilitating a better understanding of these specific variants within the broader spectrum of head and neck tumors.”

Please provide 4-10 keywords.

Response: The keywords was included in the revised version of the manuscript, as follows:

“Keywords

World Health Organization; Squamous Cell Carcinoma of Head and Neck; Verrucous Carcinoma; Mouth Neoplasms”

Please provide the PMID and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

Response: The reference list has been thoroughly revised as requested, as follows:

“References

1. WHO Classification of Tumours Editorial Board. Head and neck tumours (WHO classification of tumours series, 5th ed. vol. 9). Lyon (France): International Agency for Research on Cancer 2022.
2. WHO Classification of Tumours Editorial Board. Head and neck tumours (WHO classification of tumours series, 4th ed. vol. 9). Lyon (France): International Agency for Research on Cancer 2022.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; 71: 209-249. doi: 10.3322/caac.21660. PMID: 33538338.
4. Yamazaki M, Maruyama S, Abé T, Sumita Y, Katsumi Y, Nikkuni Y, Hayashi T, Tanuma JI. Spindle cell squamous cell carcinoma exhibiting prominent neutrophil phagocytosis: a case report. *J Med Case Rep* 2021; 15: 438. doi: 10.1186/s13256-021-03066-z. PMID: 34452644.
5. Chicrala GM, Caminha RG, Filho SAJF, Oliveira DT, Santos PSS. A rare case of basaloid squamous cell

- carcinoma in the labial commissure region with literature review. *Oral Oncology Reports* 2023; 6: 100027. doi: 10.1016/j.oor.2023.100027.
6. Sharma G, Devi A, Kamboj M, Narwal A. Acantholytic oral squamous cell carcinoma with clear cell change - a rare amalgamated variant. *Autops Case Rep* 2023; 13: e2023450. doi: 10.4322/acr.2023.450. PMID: 38034517.
 7. Abé T, Yamazaki M, Maruyama S, Ikeda N, Sumita Y, Tomihara K, Tanuma JI. Adenosquamous Carcinoma with the Acantholytic Feature in the Oral Cavity: A Case Report and Comprehensive Literature Review. *Diagnostics (Basel)* 2022; 12: 2398. doi: 10.3390/diagnostics12102398. PMID: 36292088.
 8. Fitzpatrick SG, Neuman AN, Cohen DM, Bhattacharyya I. Papillary variant of squamous cell carcinoma arising on the gingiva: 61 cases reported from within a larger series of gingival squamous cell carcinoma. *Head Neck Pathol* 2013; 7: 320-6. doi: 10.1007/s12105-013-0444-1. PMID: 23620148
 9. Emfietzoglou R, Pettas E, Georgaki M, Papadopoulou E, Theofilou VI, Papadogeorgakis N, Piperi E, Lopes MA, Nikitakis NG. Lymphoepithelial Subtype of Oral Squamous Cell Carcinoma: Report of an EBV-Negative Case and Literature Review. *Dent J (Basel)* 2022; 10: 165. doi: 10.3390/dj10090165. PMID: 36135160.
 10. Kristofelc N, Zidar N, Strojanc P. Oral verrucous carcinoma: a diagnostic and therapeutic challenge. *Radiol Oncol* 2023; 57 :1-11. doi: 10.2478/raon-2023-0015. PMID: 36942907
 11. Baz S, Amer HW, Wahed AA. Oral carcinoma cuniculatum: an unacquainted entity with diagnostic challenges-a case report. *J Egypt Natl Canc Inst* 2022; 34: 3. doi: 10.1186/s43046-021-00101-4. PMID: 35037108.”

The article title cannot exceed 18 words.

Response: The title was updated according to this request, as follows:

“Classificatory Updates in Verrucous and Cuniculatum Carcinomas: Insights from the 5th Edition of WHO-IARC Head and Neck Tumor Classification.”

Please provide the filled conflict-of-interest disclosure form.

Response: It was included a Conflict of Interest statement in the title page and the conflict of interest disclosure forms were sent.

5 Recommendation: Conditional acceptance.

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|------------|----------|-------|---|--------|----------|------------|
| Language | Quality: | Grade | B | (Minor | language | polishing) |
| Scientific | Quality: | Grade | B | (Very | good) | |

(2) Company editor-in-chief:

The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

I have reviewed the Peer-Review Report, full text of the manuscript, all of which have met the basic publishing requirements of the *World Journal of Clinical Oncology*, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.

Response: The authors appreciate your feedback. The requested revisions have been completed and the responses are detailed above.