

# World Journal of *Clinical Oncology*

*World J Clin Oncol* 2024 April 24; 15(4): 464-575



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yu-Qing Zhao*; Production Department Director: *Xu Guo*; Cover Editor: *Xu Guo*.

**NAME OF JOURNAL**

*World Journal of Clinical Oncology*

**ISSN**

ISSN 2218-4333 (online)

**LAUNCH DATE**

November 10, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2218-4333/editorialboard.htm>

**PUBLICATION DATE**

April 24, 2024

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## Classificatory updates in verrucous and cuniculatum carcinomas: Insights from the 5<sup>th</sup> edition of WHO-IARC head and neck tumor classification

Felipe Martins Silveira, Lauren Frenzel Schuch, Ronell Bologna-Molina

**Specialty type:** Pathology

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Datar UV, India

**Received:** December 9, 2023

**Peer-review started:** December 9, 2023

**First decision:** January 28, 2024

**Revised:** February 2, 2024

**Accepted:** March 20, 2024

**Article in press:** March 20, 2024

**Published online:** April 24, 2024



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### Abstract

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 5<sup>th</sup> 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 categorizing these subtypes into specific sections, the 5<sup>th</sup> edition of the WHO classification aims to provide a more nuanced and detailed account, enhancing our understanding of these specific variants within the broader spectrum of head and neck tumors.

**Key Words:** World Health Organization; Squamous cell carcinoma of head and neck;

Verrucous carcinoma; Mouth neoplasms

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**Core Tip:** 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 5<sup>th</sup> 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.

**Citation:** Silveira FM, Schuch LF, Bologna-Molina R. Classificatory updates in verrucous and cuniculatum carcinomas: Insights from the 5<sup>th</sup> edition of WHO-IARC head and neck tumor classification. *World J Clin Oncol* 2024; 15(4): 464-467

**URL:** <https://www.wjgnet.com/2218-4333/full/v15/i4/464.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v15.i4.464>

## INTRODUCTION

The classification of tumors performed by the International Agency for Research on Cancer (IARC)/World Health Organization (WHO), commonly known as "WHO Blue Books", serves as a tool to standardize the diagnostic process by establishing a consistent nomenclature for human cancers. This classification is based on the application of analytic criteria supported by evidence critically assessed by experts in the field. Regular updates of this classification facilitate the enhancement of tumor classifications and the inclusion of novel entities, driven by advancements in molecular discoveries, progress in immunohistochemical techniques, and evolving clinical insights. Traditionally, cancer classification predominantly relied on histopathological consensus, with minimal consideration for molecular pathology. However, recent technological advancements have significantly accelerated the evolution of pathology. Understanding cancer's molecular intricacies has reached a pivotal stage, underscoring the imperative inclusion of this knowledge for precise diagnostic evaluations. The content of this classification has recently been updated to its 5<sup>th</sup> edition, comprising a total of 14 volumes in the series. In addition, the latest update includes two volumes dedicated to cytopathology, titled WHO Reporting Systems for Cytopathology[1].

In the 5<sup>th</sup> edition of the WHO/IARC classification of head and neck tumors, the 6<sup>th</sup> chapter titled "Oral Cavity and Mobile Tongue" is now divided into non-neoplastic lesions, epithelial tumors, and tumors of uncertain histogenesis[1]. This classification is more concise compared to the previous version, which encompassed categories such as malignant surface epithelial tumors, oral potentially malignant disorders and oral epithelial dysplasia, papillomas, tumors of uncertain histogenesis, soft tissue and neural tumors, oral mucosal melanoma, salivary type tumors, and hematolymphoid tumors[2]. These changes are linked to modifications in this new edition, notably the collective grouping of tumors common to multiple systems. In the previous edition, various soft tissue neoplasms were included in this section, but they now find their place in the soft tissue tumor chapter. The relocation of oral melanoma to the melanocytic tumors chapter and the addressing of intraoral salivary gland lesions in the salivary gland chapter exemplifies the reorganization in this edition.

### Epithelial tumors

Squamous cell carcinomas (SCC), previously collectively described in the 4<sup>th</sup> edition, along with all its histological subtypes under the subsection titled "Malignant Surface Epithelial Tumors"[2], now receive specific attention in the latest edition of the WHO/IARC classification of head and neck tumors. The epithelial tumors section is reorganized based on tumor behavior starting, with squamous papillomas, followed by oral potentially malignant disorders, oral epithelial dysplasia, proliferative verrucous leukoplakia, submucosal fibrosis, and HPV-associated dysplasia. Oral squamous cell carcinoma (OSCC) is now positioned last in this section, following a presentation based on biological behavior. In this classification[1], OSCC is defined as "a malignant neoplasm arising from the mucosal epithelium of the oral cavity and showing variable squamous differentiation" and is identified as the 16<sup>th</sup> most prevalent cancer, registering an annual incidence surpassing 377000 cases, data based on the Global Cancer Statistics/2020[3]. This definition of OSCC is more objective compared to the one presented in the 4<sup>th</sup> 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 oral potentially malignant disorders, and finally, address OSCC, a malignant epithelial neoplasm.

The alterations in the new section on OSCC have been updated to reflect the most recent information regarding the epidemiology, pathogenesis, and histological prognostic factors of this entity. Regarding its clinical features, in the 5<sup>th</sup> 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 pathogenesis of OSCC is characterized by distinguished by most cases arising in regions featuring pre-existing epithelial dysplasia or in correlation with oral potentially malignant disorders. OSCC, for the most part, exhibits genetic instability, marked by notable chromosomal alterations and a heightened burden of somatic mutations. In this latest edition, the described chromosomal losses are observed in 3p, 8p, 9p, and 17p, and the gains in 3q, 5p, 8q, and 11q. The somatic mutations reported are documented in the following genes: *TP53*, *CDKN2A*, *FAT1*, *NOTCH1*, *KMT2D*, *CASP8*, *AJUBA*, *NSD1*, *HLA-A*, *TGFBR2*, *USP9X*, *MLL4*, *HRAS*, *UNC13C*, *ARID2*, and *TRPM3*. It is noteworthy to observe that in the penultimate version of this classification[2], under the Etiology section, several etiological factors of OSCC were well described, including tobacco use, alcohol consumption, smokeless tobacco, HPV, ultraviolet radiation, and the association with poor oral health – this last one being reported as not proved as an independent risk factor. A diet rich in fruits and vegetables was also cited as a protective effect against oral cancer.

### **Histopathology and subtypes of oral squamous cell carcinoma**

In latest WHO classification of head and neck tumors[1], it is specified that the majority of cancers affecting the oral cavity and mobile tongue belong to the category of conventional keratinizing SCC. The classification also recognizes the potential occurrence of rare histological subtypes within this malignant epithelial neoplasia. The histological subtypes of OSCC comprise the following six distinct variants according to the WHO: Spindle cell carcinoma variant manifests as a biphasic tumor, comprising a SCC and a malignant spindle cell component with a mesenchymal appearance. This subtype is recognized for its aggressive behavior and rapid growth[4]. The Basaloid SCC variant is typified by a basaloid cell population and a diminished presence of squamous cells. This type tends to demonstrate a propensity for local relapse and regional lymph node metastasis[5]. The Acantholytic SCC variant is characterized by a disruption of cellular cohesion. This subtype may present with a clinical course marked by increased aggressiveness[6]. Adenosquamous carcinoma variant exhibits dual differentiations-both squamous and glandular. This particular subtype is acknowledged for its heightened aggressiveness[7]. The Papillary SCC variant is identified by finger-like projections or papillae. In contrast to the other subtypes, it may carry a more favorable prognosis[8]. The Lymphoepithelial Carcinoma variant showcases a pronounced lymphoid stroma and is comparatively rare within the oral cavity[9].

As noted, in the 5<sup>th</sup> 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 verrucous carcinoma (VC) and carcinoma cuniculatum (CC) variants are now described in specific sections. VC is often linked to prolonged tobacco use, presents with a well-differentiated, warty appearance, and tends to display a less aggressive nature[10]. CC stands out as a distinct subtype, characterized by a gradual, endophytic growth pattern featuring crypt-like structures[11]. This adjustment recognizes the oral cavity as the primary site in the head and neck for both entities, each with distinct clinical and histologic characteristics that set them apart 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. The current classification[1] defines VC as a well-differentiated, non-metastasizing SCC with a warty keratinized surface and distinctive architecture, lacking significant cytologic features of malignancy. VC is reported as a rare entity, comprising 2%-16% of oral carcinomas, predominantly affecting older individuals. The use of terminology such as “Ackerman tumor” and “verrucous hyperplasia” is not endorsed in the latest classification. The oral mucosa is the primary site, representing 50%-75% of cases in the head and neck. Etiologically linked to the use of chewing tobacco or snuff, VC clinically presents as a slowly growing, slightly exophytic white tumor. Left untreated, VC can lead to bone erosion and extensive destruction. While the pathogenesis is not fully understood, the molecular signature distinguishes VC from other oral SCCs. Morphologically, VC is characterized by a well-differentiated, broad-based squamous epithelial proliferation with marked keratinization. Invasion into the stroma is uniform with well-defined borders, lacking substantial cytologic features of malignancy. VC has an excellent prognosis, with surgery as the preferred treatment; irradiation is considered for select cases.

CC is defined an infrequent, well-differentiated squamous cell carcinoma characterized by local invasiveness without metastatic potential[1]. Typically observed in individuals aged seven to eight decades, CC shows no gender bias, with the gingival-alveolar complex of the mandible being the primary site, followed by the maxilla. Clinical manifestations include pain, swelling, mucosal ulceration, tooth mobility, and induration. The etiology of CC remains undefined in this classification, and its pathogenic mechanisms and potential association with HPV are unknown. Morphologically, CC exhibits an endophytic growth pattern, forming a labyrinthine network of well-differentiated squamous epithelium with interconnecting keratin-filled crypts reaching the surface. Cytological atypia is mild, and the presence of intraepithelial and stromal neutrophils, along with keratin microabscesses, is common. Microsequestra are frequently associated with bone invasion. Prognosis following complete excision is excellent, with local recurrence uncommon following accurate preoperative diagnosis. Notably, metastases do not develop in cases of CC despite multiple interventions.

## CONCLUSION

Recent advances in unraveling the molecular pathogenesis of oral squamous cell carcinoma have significantly enhanced the understanding of the tumor's genesis and evolutionary processes, influencing diagnostic criteria. Due to the dynamic nature of this field, classifications and terminologies undergo continuous refinement. Therefore, keeping abreast of the most up-to-date insights is essential, requiring regular reference to the latest World Health Organization classification edition and contemporary literature. Anticipating future discoveries, ongoing updates, and reclassifications within the Blue Books will be imperative to maintain the precision and relevance of oral cancer diagnostics.

## FOOTNOTES

**Author contributions:** Silveira FM contributed to conceptualization, investigation, writing – original draft; Schuch LF contributed to investigation, writing – original draft; Bologna-Molina R contributed to supervision, writing/review & editing; all authors have read and approved the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**S-Editor:** Gong ZM

**L-Editor:** A

**P-Editor:** Zhao S

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