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# Investigation of the relationship of lysyl oxidases on neck metastasis and prognosis in early stage oral cavity cancers

## *Erken evre ağız boşluğu kanserlerinde lizil oksidazların boyun metastazı ve prognoz ile ilişkisinin araştırılması*

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**ABSTRACT**

Oral cavity cancers (OCC) remain a significant global health challenge, particularly in regions where tobacco use, alcohol consumption, and HPV-independent carcinogenic pathways drive rising incidence rates. In this context, we highlighted the promising yet underexplored role of post-translationally modified (PTM) proteoforms of lysyl oxidase (LOX) and its paralog LOX-like 2 (LOX-2) as potential biomarkers for both primary tumor aggressiveness and propensity for neck metastasis. As proteoform science evolves, prioritizing these molecular targets should become a key focus for the OCC research community. Their integration into diagnostic and prognostic frameworks may significantly enhance our ability to detect aggressive disease early and tailor treatments more effectively, ultimately improving patient survival and quality of life.

**Keywords:** LOX, LOX-2, proteoforms, post translational modification, oral cavity cancers, metastasis

**ÖZ**

*Ağız boşluğu kanserleri (AK), özellikle tütün kullanımı, alkol tüketimi ve HPV'den bağımsız karsinojenik yolların görülme sıklığını artırdığı bölgelerde önemli bir küresel sağlık sorunu olmaya devam etmektedir. Bu bağlamda, hem primer tümör agresifliği hem de boyun metastazı eğilimi için potansiyel biyobelirteçler olarak lizil oksidazın (LOX) ve onun paralogu LOX benzeri 2'nin (LOX-2) post translasyonel modifiye (PTM) proteoformlarının umut verici ancak yeterince keşfedilmemiş rolünü vurguladık.*

*Proteoform bilimi geliştikçe, bu moleküler hedeflere öncelik vermek AK araştırma topluluğunun temel odak noktası haline gelmelidir. Bunların tanı ve prognoz çerçevelerine entegre edilmesi, agresif hastalığı erken saptama ve tedavileri daha etkili bir şekilde uyarlama becerimizi önemli ölçüde geliştirebilir ve sonuç olarak hasta sağ kalımını ve yaşam kalitesini iyileştirebilir.*

***Anahtar Sözcükler:*** *LOX, LOX-2, proteoform, post translasyonel modifikasyon, oral kavite kanserleri, metastaz*

Dear Editor,

Oral cavity cancers (OCC) remain a significant global health challenge, particularly in regions where tobacco use, alcohol consumption, and HPV-independent carcinogenic pathways drive rising incidence rates (1). Despite advances in imaging and molecular characterization, early detection and reliable risk stratification for cervical lymph node metastases—the most powerful prognostic determinant in OCC—continue to lag behind clinical need (2). In this context, we would like to highlight the promising yet underexplored role of post-translationally modified (PTM) proteoforms of lysyl oxidase (LOX) and its paralog LOX-like 2 (LOX-2) as potential biomarkers for both primary tumor aggressiveness and propensity for neck metastasis.

The LOX family of proteins are copper-dependent extracellular amine oxidases required for

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collagen and elastin crosslinking. While traditionally related to their structural functions, increasing evidence suggests that these enzymes are important components that actively influence the tumor microenvironment. In OCC particularly, the overexpression of LOX and LOX-2 has been associated with extracellular matrix stiffening and tumor invasion (2). However, it is becoming increasingly apparent that the biological activity of LOX proteins cannot be fully reflected by transcript or total protein expression alone.

Protein function is strongly affected by post-translational modifications such as glycosylation, proteolytic processing, copper loading, and oxidative changes, which generate distinct proteoforms. These PTM-defined proteoforms can more specifically reflect tumor phenotype than total protein measurements (3). For instance, certain glycosylated isoforms of LOX exhibit enhanced enzymatic stability, while specific proteolytically cleaved LOX fragments have been implicated in intracellular signalling pathways independent of matrix remodelling. Similarly, LOX-2 undergoes PTMs that alter its nuclear localization, enabling transcriptional regulation of metastasis-related gene networks. The presence, abundance, or absence of these specific proteoforms may therefore act as a molecular fingerprint of a tumor's invasive potential (4).

The dense vascular-lymphatic network and constant mechanical movement of oral cancers may enhance the importance of LOX-mediated tissue remodelling. In this context, it is suggested that tumors' production of highly active or aberrantly modified LOX/LOX-2 proteoforms may contribute to the formation of a pre-metastatic niche in cervical lymph nodes that is more conducive to metastasis. It is also a potential possibility that detecting these proteoforms in tumor tissue, saliva, or serum could provide a non-invasive approach to predict metastatic propensity before radiographic or clinical findings appear.

Recent advancements in top-down proteomics, high-resolution mass spectrometry (5), and PTM-specific antibodies now make it feasible to characterize LOX family proteoforms with a level of detail previously unattainable. Integrating these technologies into translational research for OCC could lead to the development of PTM-aware biomarker assays that outperform standard immunohistochemistry or transcript quantification. A panel of LOX/LOX-2 proteoforms—rather than a single bulk measurement—may serve as a highly discriminatory molecular signature for identifying patients at higher risk of occult nodal metastasis, treatment resistance, or recurrence. Furthermore, LOX-mediated extracellular matrix alterations can modulate drug penetration, radiotherapy sensitivity, and immune response. Therefore, PTM-specific proteoform profiles can provide important guidance for clinical treatment decisions. Patients with tumors enriched in highly crosslinking proteoforms might benefit from LOX-targeted inhibitors, matrix-modifying agents, or adjusted radiotherapy dosing strategies. Such precision oncology applications highlight the significant clinical value of understanding LOX biology beyond gene or total protein expression levels.

In conclusion, the exploration of PTM proteoforms of LOX and LOX-2 represents a promising frontier in biomarker research for OCC and their neck metastases. As proteoform science evolves, prioritizing these molecular targets should become a key focus for the OCC research community. Their integration into diagnostic and prognostic frameworks may significantly enhance our ability to detect aggressive disease early and tailor treatments more effectively, ultimately improving patient survival and quality of life.

Sincerely.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Declaration of Competing Interest**

The authors declare to have no competing interests.

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