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The University of Osaka

## Abstract of Thesis

Name ( Hani Al-Shareef )

Title

Lymphangiogenesis Mechanism Predicts the Correlation between Metastatic Oral Squamous Cell Carcinoma and Prognosis  
(リンパ管新生は口腔扁平上皮癌におけるリンパ節転移と生命予後に関連する)

## Abstract of Thesis

Lymph node (LN) metastasis was suggested as a major prognostic factor for oral cancer, which also determines prognosis after treatment. Knocking down growth factor, neuropilin, chemokine and semaphorin receptors involved in these mechanisms could significantly reduce LN metastasis and improve survival of oral cancer patients after treatment.

Therefore, the aim of this study was to evaluate the expression levels of vascular endothelial growth factors (i.e. VEGF-C, VEGF-D) that bind to tyrosine kinase receptors (i.e. vascular endothelial growth factor receptor 3 (VEGFR-3)) on cell surfaces, chemokine receptor 7 (CCR7), neuropilins (i.e. NRP1, NRP2), and semaphorin 3E in SCC of the tongue. Moreover, microvessel density (MVD) and lymphatic vessel density (LVD), were assessed in order to demonstrate the correlation between regional LN metastasis and these factors with respect to clinical and pathological features. Finally, the correlation of overall survival and disease-free survival, with related proteins was analyzed in order to demonstrate the prognostic value of these proteins.

The expression of NRP1, NRP2, VEGF-C, VEGF-D, VEGFR-3, CCR7, SEMA3E proteins and MVD, LVD were assessed by immunohistochemistry.

Univariate analysis on the staining intensity of SCC cells revealed a significant association between LN metastasis and expression levels of NRP1, VEGF-C, VEGFR-3, CCR7, SEMA3E and LVD.

In multivariate analysis, associations between NRP1 expression and LN, and LVD and LN metastasis were identified, whereas no correlations were identified between expression levels of other proteins and LN metastasis.

Overall and disease-free survival times in patients with metastatic cancers were more likely to be less, compared to patients with non-metastatic cancers. Expression of NRP1, VEGF-C, VEGFR-3, and SEMA3E were correlated with disease-free survival time, and LVD was correlated with disease-free survival time. These results showed that LN metastasis is associated with poor survival in SCC.

This study suggests VEGF-C, VEGFR-3, CCR7, and SEMA3E expression are non-independent factors; and LVD and NRP1 are independent factors more likely to predict the risk of LN metastasis.

## 論文審査の結果の要旨及び担当者

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## 論文審査の結果の要旨

本研究は、舌扁平上皮癌の切除組織におけるリンパ管新生関連因子の発現と頸部リンパ節転移との関連を検討したものである。免疫染色において、VEGF-C、VEGFR-3、CCR7、SEMA3E、NRP1 の発現増生と LVD の上昇がみられ、LVD、NRP1 が独立した因子であった。本研究により、舌扁平上皮癌におけるリンパ管新生関連因子の発現が、頸部リンパ節転移の予測因子として有用であり、ひいては生命予後因子となる可能性を示唆するものである。よって、博士（歯学）の学位論文として価値のあるものと認める。