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BRIEF REVIEW

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Regional Lymphatic Status in Oral Squamous Cell Carcinoma: A Brief Review

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Abstract

Oral squamous cell carcinoma (OSCC) is a common type of head and neck malignancy, leading to high morbidity and mortality rates. This brief review focuses on the regional lymphatic status in patients with OSCC. The lymphatic system plays a key role in the dissemination of malignant cells from the primary tumor. Tumor cell migration into the lymphatic system is a complex process involving multiple mechanisms and interactions within the tumor microenvironment. This multistep process is associated with the complex role of lymphatic endothelial cells in the tumor microenvironment, lymphangiogenesis, lymphatic invasion, and the modulation of the immune response. Despite recent advances, the precise role of the regional lymphatic system in the progression of OSCC remains unclear, highlighting the need for further in-depth study.(**International Journal of Biomedicine. 2025;15(4):639-644.**)

Keywords: oral cancer • lymph node • lymphangiogenesis • lymphovascular invasion • metastases

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Abbreviations

CT, computed tomography; **DWI**, diffusion-weighted imaging; **DCE-PWI**, dynamic contrast-enhanced perfusion-weighted imaging; **DKI**, diffusion kurtosis imaging; **DTI**, diffusion tensor imaging; **FGF**, fibroblast growth factor; **LVI**, lymphovascular invasion; **LN**, lymph node; **LEC**, lymphatic endothelial cell; **LLNs**, lingual lymph nodes; **LYVE-1**, lymphatic vessel endothelial hyaluronic acid receptor 1; **MRS**, magnetic resonance spectroscopy; **MRI**, magnetic resonance imaging; **OSCC**, oral squamous cell carcinoma; **RLS**, regional lymphatic status; **VEGF,** vascular endothelial growth factor.

Oral squamous cell carcinoma (OSCC), originating from the flat squamous cells that line the mouth, lips, and tongue, accounts for more than 90% of all oral malignancies.[1] OSCC dramatically impacts patients' quality of life, resulting in high morbidity and mortality rates. Early diagnosis and complete tumor removal are considered the mainstays of treatment for OSCC.[2,3] Despite improvements in diagnosis and treatment over the past 30 years, the five-year survival rate for OSCC remains only 50%.[4,5] Cervical lymph node (LN) involvement (N-status) is one of the most important independent prognostic factors in OSCC.[6,7]

This review focuses on the regional lymphatic status (RLS) of patients with OSCC.

Regional lymphatic status in patients with oral cavity carcinoma is crucial for determining the stage of the disease, prognosis, and treatment strategy. The drainage and transport functions of the lymphatic system are essential to oral cancer, as they serve as the primary pathway for metastasis.

Lymphatic endothelial cells (LECs), a specialized subset of endothelial cells, play multiple roles in the tumor microenvironment in addition to lining lymphatic vessels.[8,9] Lymphatic endothelial cells interact with innate and adaptive immune cells in both tissues and lymph nodes. These cells produce chemokines to attract immune cells to lymph nodes; specifically, CCL21 is involved in recruiting dendritic cells, which, in turn, promotes lymph node enlargement.[10-12]

Lymphatic endothelial cells play a crucial role in the formation of new lymphatic vessels observed in highly active tumors, a process known as tumor-associated lymphangiogenesis.[13] Tumor-associated lymphangiogenesis also involves various lymphangiogenic factors secreted by tumor cells or host cells present in the tumor microenvironment. These include vascular endothelial growth factor (VEGF) C and D, known primarily for stimulating lymphatic vessel growth, angiopoietin-2, fibroblast growth factor (FGF), and others.[14]

Importantly, the discovery of specific markers for LEC, such as the lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE-1) and podoplanin (D2-40), has enabled the distinction between lymphatic and blood vessels.[15-17] LYVE-1 exhibits a high degree of lymphatic vessel specificity and has been an essential component in numerous studies on tumor-induced lymphangiogenesis.[17,18] Furthermore, LYVE-1 is closely associated with lymph node metastasis in OSCC.[19]

The complex role of lymphatic endothelial cells in the tumor microenvironment and recent advances in this field require in-depth study.

The lingual, sublingual, and submental nodes provide lymphatic drainage from the tongue and surrounding tissues, playing a crucial role in local immunity. Lymphatic metastases in oral cavity carcinoma are a sign of a more aggressive course of the disease and make the prognosis less favorable.

Lymphovascular invasion (LVI), in which cancer cells invade the lumen of endothelial-lined lymphatic and blood vessels, is considered an important step in lymph node metastasis.[8,20] Lymphatic invasion is the main mechanism by which cancer cells in oral squamous cell carcinoma disseminate to regional lymph nodes.[21] Blood vessel invasion is considered a secondary route of distant metastasis, although it does not appear to be associated with lymph node metastasis.[22]

Michikawa et al.[23] reported a multivariate analysis of 63 patients with oral tongue squamous cell carcinoma, which showed that lymphatic vessel invasion was an independent risk factor for the presence of lymph node metastasis, although blood vessel invasion was not.

Several retrospective studies have also reported a significant positive association between LVI and lymph node metastasis.[24,25] A meta-analysis by Huang et al.[21] included 36 studies involving 17,109 patients with squamous cell carcinoma. It concluded that LVI can serve as a prognostic indicator of metastasis and prognosis in OSCC.

In oral carcinoma, due to its location and the characteristics of the vessels and lymphatic pathways that pass through the glossopharyngeal neuromuscular complex, metastasis and lymphatic drainage occur under high pressure, which can influence the rate of tumor growth and dissemination.[26] Recently, numerous studies have shown that abnormal tumor vasculature can create significant pressure on the tumor microenvironment, collectively referred to as hydrostatic stress.[27] Typically, fluid stress is generated by blood flow and interstitial blood flow, which includes microvascular fluid pressure, interstitial fluid pressure, and shear stress.[28] Due to increased interstitial fluid pressure in the central regions of the tumor, interstitial fluid flows from the center to the periphery and carries proangiogenic factors such as VEGF, promoting tumor hemangiogenesis. These proangiogenic factors also lead to increased lymph node metastasis by promoting lymphangiogenesis.[29] Shear stress in lymphatic vessels has also been shown to activate YAP1 (Yes-associated protein 1), thereby stimulating cancer cell migration.[30]

In oral carcinoma, lymphatic pathways lead to metastasis to regional lymph nodes, including the submandibular and cervical nodes, located outside the muscular structures in the subcutaneous tissue.[31,32] Lymph node metastasis is the most adverse prognostic factor of OSCC, with an incidence rate of approximately 40%.[33,34]

Having precise knowledge of the regional spread can be highly beneficial before initiating any definitive treatment. There are approximately 300 lymph nodes in the head and neck region, which are classified according to various criteria, such as superficial and deep or medial and lateral.[35-37]

Lymph from the tongue drains along a specific pathway: the anterior third to the submental lymph nodes (level IA), the middle third to the submandibular lymph nodes (level IB), and the posterior third and root of the tongue to the deep lymph nodes of the neck located along the internal jugular vein (levels IIB and III, less commonly IV).[38,39]

The intraoral areas have a rich lymphatic supply and are a typical site of metastasis in oral cancer.[40] There is a predictable pattern of spread from upper to lower lymph node levels: submental (IA), submandibular (IB), superior jugular (II), middle jugular (III), inferior jugular (IV), and posterior cervical (V).

In oral cavity carcinomas, the submandibular lymph nodes (level IB) and the superior deep jugular lymph nodes (level II) are the most frequent sentinel lymph nodes. Metastasis to the lateral lingual lymph nodes (LLNs), located lateral to the hyoglossus muscle behind the submandibular gland, has not been frequently reported in English literature. This group of LLNs was illustrated by Rouvière.[41] Lingual lymph nodes are intervening lymph nodes that appear inconstantly within the fascial/intermuscular spaces of the floor of the mouth.[42,43] Rouvière classified LLNs into median LLNs located between the genioglossus muscles and lateral LLNs located lateral to the genioglossus muscle or the hyoglossus muscle.[41]

Ozeki et al.[44] first reported a case of LLN metastasis in 1985, and subsequent cases have been reported since then.[45-48] According to studies, the incidence of metastases to the medial and lateral LLNs in patients with squamous cell carcinoma of the tongue was 0.7-3.0%[45,49,50] and 1.4-14.3% [44,49-52], respectively.

Suzuki et al.[42] presented the first case of metastasis to the lateral LLN located behind the submandibular gland from squamous cell carcinoma of the tongue. Eguchi et al.[53] presented a clinical case of a 55-year-old man with squamous cell carcinoma of the tongue (stage T4aN0M0) who underwent hemiglossectomy with cervical dissection and free flap reconstruction. An 8-mm lesion was present in the lingual septum, which, upon histopathological examination, was diagnosed as a metastasis to the medial lingual lymph node. The patient developed multiple distant metastases and died of the disease 18 months after the initial surgery. The presence of metastases to the medial lymph node could have led to metastases to the contralateral neck and worsened the prognosis.

In a study by Kuroshima et al.,[54] a 5-year disease-specific survival was significantly lower in patients with squamous cell carcinoma of the tongue and LLN metastasis than in patients without LLN metastasis (49.0% vs. 88.4%, $P< 0.01$). Cox proportional hazards analysis revealed that cervical lymph node metastases at levels IV or V and LLN metastasis were independent prognostic factors for 5-year survival. LLN metastasis had a strong negative impact on survival in patients with squamous cell carcinoma of the tongue.

In a letter to the editors, Calabrese et al.[55] stated that LLN metastases may worsen prognosis and may have the same effect as level I lymph node metastases.

However, data on the clinical significance and prognostic value of LLNs in patients with squamous cell carcinoma of the tongue are insufficient, as LLNs have received little attention until recently.

Median LLNs, located in the muscularis propria of the tongue, are a rare anatomical structure, and their presence can be variable. Their unique location, directly within the muscularis propria of the tongue rather than in the submandibular glands, may serve as a site for metastasis in tongue cancer, a poorly understood issue. A study by Tomblinson et al.[48] estimated the prevalence of median LLN metastases from oral cavity squamous cell carcinoma. In the study group, a solitary metastasis to the median LLN from a tumor on the lateral surface of the tongue (T4aN2c) was detected in 1 of 105 cases of OSCC (0.95%).

Assessment of regional lymphatic status in oral carcinoma includes a clinical examination to palpate the nodes, a combination of instrumental methods (ultrasound, CT, MRI, PET-CT) to detect metastases in deep lymph nodes, and a biopsy of an enlarged lymph node for histological verification of the diagnosis.

Magnetic resonance imaging (MRI) has a high degree of soft tissue discrimination, making it the preferred method for assessing oral soft tissue conditions. The use of advanced MRI techniques, such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced perfusion-weighted imaging (DCE-PWI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and diffusion kurtosis imaging (DKI) (an advanced DWI technique that focuses on the non-Gaussian diffusion of water molecules in heterogeneous tissue microstructures), can improve diagnostic accuracy. These advanced functional MRI techniques enable noninvasive assessment of the biochemical, structural, and metabolic characteristics of tissues, which is crucial for the diagnosis, staging, and monitoring of oral cancer treatment.

For example, Shaukat et al.[56] investigated the accuracy of DWI for diagnosing oral cancer metastases to cervical lymph nodes. Magnetic resonance imaging, including a DWI sequence, in a 1.5-T scanner with a phased-array head and neck coil, was performed in 150 patients diagnosed with oral cancer. In the DWI sequence, the area scanned included the lymph nodes from the suprasternal notch to the base of the skull. Histopathological examination of the lymph nodes was used as the gold standard. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of DWI for diagnosing oral cancer metastasis to cervical lymph nodes, using histopathology as the gold standard, were 90.57%, 91.75%, 94.68%, 90.57% and 91.33%, respectively.

Innovative lymphography methods, such as radionuclide and fluorescence, have made it possible to visualize the process of lymph movement. Fluorescence lymphography, which visualizes the lymphatic system using a fluorescent dye such as indocyanine green, enables the assessment of the condition of lymphatic vessels and nodes, which is particularly important in oncological diseases.[57] Fluorescence imaging visualizes biological processes occurring during the early stages of carcinogenesis and can facilitate the detection of small tumors at early stages. Due to its high sensitivity and spatial resolution, fluorescence imaging can aid in assessing resection margins during surgery.[58]

Recently, near-infrared (NIR) fluorescence has been introduced intraoperatively to detect lymph nodes, tumors, and vital structures.[59] A study by van der Vorst et al.[36] demonstrated the feasibility of detecting draining lymph nodes in patients with head and neck cancer using NIR fluorescence imaging.

Yang et al.[35] evaluated the capability of indirect computed tomography and magnetic resonance lymphography (CT/MR-LG) with gadolinium-loaded gold nanoprobes embedded in polyethyleneimine (Gd-Au PENP) to assess sentinel lymph node metastasis in the VX2 tongue carcinoma model. They found that indirect CT/MR-LG with Gd-Au PENP can be used to diagnose sentinel lymph node metastasis in tongue cancer.

Conclusion

The lymphatic system plays a key role in the dissemination of malignant cells from the primary tumor. Tumor cell migration into the lymphatic system is a complex process involving multiple mechanisms and interactions within the tumor microenvironment. This multistep process is associated with the complex role of lymphatic endothelial cells in the tumor microenvironment, lymphangiogenesis, characterized by the expression of MMPs, VEGF, FGF, and PDGF, promoted by adhesion molecules and cytokines, including CCR7, CCL21, MMPs, and VCAM-1.[60,61] A key step in cancer cell invasion and metastasis is the destruction of the basement membrane. Basement membrane destruction through targeted secretion of matrix metalloproteinases can lead to increased adhesion of migrating cells, as well as the release and activation of various growth factors necessary for angiogenesis, tumor growth, and metastasis. Lymphatic invasion and lymphatic metastasis are significant prognostic factors determining tumor survival and progression. Despite recent advances, the exact role of the regional lymphatic system in the progression of oral squamous cell carcinoma remains unclear, underscoring the need for further in-depth study.

Competing Interests

The author declares that there are no conflicts of interest regarding the publication of this paper.

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