

# World Journal of *Clinical Cases*

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## Relevance on the diagnosis of malignant lymphoma of the salivary gland

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### Abstract

Malignant lymphoma originates from the lymphohematopoietic system. It can occur in any lymphoid tissue. Malignant lymphoma of the salivary gland is rare, but its incidence has increased in recent years. Its clinical presentations are non-specific, and it is often manifested as a painless mass in a salivary gland, which can be accompanied by multiple swollen cervical lymph nodes. Confirmation of the diagnosis before an invasive procedure is difficult. Clinically, malignant lymphoma of the salivary gland tends to be misdiagnosed, leading to an inappropriate treatment plan and the ultimate delay in the optimal treatment of the disease. This article reviews the pathogenesis, clinical features, imaging findings, diagnosis, treatment and prognosis of malignant lymphoma of the salivary gland.

**Key words:** Salivary gland; Malignant lymphoma; Pathogenic factors; Clinical features; Diagnosis; Treatment

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**Core tip:** Salivary gland lymphoma (SGL) is rare, and it is often manifested as a painless mass in a salivary gland, with or without multiple swollen cervical lymph nodes. Clinically, SGL tends to be misdiagnosed as other epithelial tumors of the salivary gland, leading to an inappropriate surgical excision and delay in the optimal treatment of the disease. This article reviews the pathogenesis, clinical features, imaging findings, diagnosis, treatment and prognosis of SGL.

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## INTRODUCTION

Lymphoma is a malignant tumor originating from the lymphohematopoietic system. It is a group of diseases with extensive clinical and histological features, genetic abnormalities, and immunophenotypes. Lymphomas account for 3% - 4% of malignant tumors and is the most common head and neck malignancy after squamous cell carcinoma and thyroid cancer<sup>[1-4]</sup>. Lymphoma can be divided into two major histopathological entities, Hodgkin lymphoma (HL) and non-HL (NHL), and can be subdivided into intranodal and extranodal types according to its origination inside or outside a lymph node. The majority of oral and maxillofacial lymphomas are extranodal NHLs<sup>[5]</sup>. Head-and-neck NHLs can originate in any lymphoid tissue, most commonly in Waldeyer's ring, the nasal cavity, nasal sinuses, oral cavity, and salivary glands<sup>[6,7]</sup>. An NHL originating from a salivary gland is rare, accounting for only 1.7% - 3.1% of all salivary gland malignant tumors<sup>[8,9]</sup>. Most NHLs involving the salivary glands originate from B cells, with the most common location being the parotid glands, followed by the submandibular glands, minor salivary glands, and sublingual glands, in descending order<sup>[8-11]</sup>. Salivary gland lymphoma (SGL) is a diverse tumor with nonspecific clinical features and imaging manifestations. Therefore, differentiating it from other epithelial tumors of the salivary gland is difficult.

Because of the complicated histopathological classification of NHLs, the gold standard for the diagnosis and determination of the subtype of this disease is an incisional biopsy of the deep portion of tumor<sup>[12]</sup>. The complexity of the diagnostic process can lead to a misdiagnosis or a delayed diagnosis<sup>[10]</sup>. Because the treatment for SGL is different from the treatment for an epithelial tumor of the salivary gland and lymphomas in other parts, a misdiagnosis or delayed diagnosis may lead to an inappropriate treatment plan, affecting the outcome of the patients.

A primary SGL is thought to involve the parenchyma of the salivary gland, rather than being confined to soft tissue or a regional lymph node, and no lymphomatous lesion was detected in other parts of the body before diagnosis<sup>[13]</sup>. In view of the diagnostic difficulties for primary salivary gland lymphomas, we researched 944 articles about malignant lymphoma of the salivary gland published in PubMed from 2000 to December 2019 in English. Some of the articles were excluded because they were not primarily originated from the salivary gland tissue. Among them, 344 articles involved the research on the primary salivary gland lymphoma, including 102 case reports. In addition, the data from articles other than case reports was not concrete concerning the clinical information, so we finally selected 16 case reports, and the detailed data are listed in Table 1<sup>[13-28]</sup>. This article analyzes the pathogenesis, clinical features, imaging findings, diagnosis, treatment, and prognosis of primary SGL.

## PATHOGENIC FACTORS

The incidence of SGL has recently shown an upward trend. Epidemiological investigations show that the main causative factors of malignant lymphoma include infection and changes in immune function. Genetic factors, occupational and environmental factors, diet, smoking, alcohol, and socioeconomic status are also involved.

### Viral infections

The prevalence of NHL in human immunodeficiency virus (HIV)-infected people is almost twice that in the general population<sup>[12,29,30]</sup>. HIV infection is believed to be associated with lymphomagenesis primarily due to the immunosuppressed state of the patient rather than mechanisms involving the virus *per se*<sup>[31]</sup>. The development of AIDS-related NHL is caused by long-term administration of HIV-related immunostimulant leading to the proliferation of B lymphocytes<sup>[12,32]</sup>. The parotid gland is the most common location of SGL in HIV patients<sup>[33]</sup>.

Epstein-Barr virus (EBV) is associated with a variety of malignant lymphomas, including Burkitt lymphoma, HL, and BHL<sup>[34]</sup>. EBV is a herpes virus that can infect B and T lymphocytes, natural killer cells, epithelial cells, and myocytes<sup>[35,36]</sup>. Antibodies

Table 1 Clinical features of cases with lymphoma of the salivary gland

Ref.	Age/sex	Location	Size(mm)	Pathogenic type	Treatment	Response	Follow-up
Andola <i>et al</i> <sup>[13]</sup>	55/M	Bilateral parotid	50 × 40	DLBCL	Radiation therapy + chemotherapy	CR	1 yr
Hwang <i>et al</i> <sup>[14]</sup>	56/F	Parotid	25 × 8	MALT	Chemotherapy	CR	6 mo
Shum <i>et al</i> <sup>[15]</sup>	53/F	Parotid	15 × 12	MALT	Radiation therapy	CR	5 yr
	53/F	Parotid	21 × 9	FL	Chemotherapy	CR	2 yr
	63/F	Parotid	20 × 80	FL	Chemotherapy + radiation therapy	CR	1 yr
Choi <i>et al</i> <sup>[16]</sup>	16/M	Parotid	35 × 20	FL	Radiation therapy	CR	6 mo
Alnoor <i>et al</i> <sup>[17]</sup>	69/M	Bilateral parotid	Oct-40	FL	Excision	CR	3 mo
Romero <i>et al</i> <sup>[18]</sup>	82/F	Parotid	NA	FL	Radiation therapy + chemotherapy	CR	NA
Park <i>et al</i> <sup>[19]</sup>	68/F	Parotid	NA	FL	Radiation therapy	RD	54 mo
	55/M	Parotid	NA	FL	NA	NA	NA
Yang <i>et al</i> <sup>[20]</sup>	41/M	Parotid	NA	MALT	Radiation therapy + chemotherapy	RD	12 mo
Yonal-Hindilerden <i>et al</i> <sup>[21]</sup>	61/F	Ulcerated palate + parotid	20 × 25/25 × 35	MALT	Chemotherapy (R-CHOP)	CR	44 mo
Shashidara <i>et al</i> <sup>[22]</sup>	40/F	Submandibular	90 × 40	FL	NA	NA	NA
Faur <i>et al</i> <sup>[23]</sup>	71/F	Parotid	50 × 35	DLBCL	NA	NA	NA
	49/F	Parotid	65 × 63	MALT	NA	NA	NA
Alves <i>et al</i> <sup>[24]</sup>	32/M	Parotid	30	NLPHL	Radiation therapy	CR	1 yr
Revanappa <i>et al</i> <sup>[25]</sup>	73/F	Parotid + submandibula	NA	DLBCL	Radiation therapy + chemotherapy	NA	NA
Titsinides <i>et al</i> <sup>[26]</sup>	64/F	Ulcerated palate	10	MALT	Chemotherapy	CR	2 yr
Van Mello <i>et al</i> <sup>[27]</sup>	53/F	Labial	NA	MALT	Chemotherapy	NA	NA
	53/F	Labial + parotid	NA	MALT	Chemotherapy	NA	NA
	55/F	Labial + parotid	NA	MALT	Chemotherapy	NA	NA
Hew <i>et al</i> <sup>[28]</sup>	55/F	Parotid	20 × 8	T cell lymphoma	Radiation therapy + chemotherapy	NA	NA

MALT: Mucosa associated lymphoid tissue lymphoma; DLBCL: Diffuse large B cell lymphoma; FL: Follicular lymphoma; CR: Complete remission; NA: Not available; RD: Relapsed disease; R-CHOP: Rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; NLPHL: Nodular lymphocyte predominance hodgkin lymphoma.

to EBV are detectable in more than 90% of the normal adult population. Because the immune system can be unsuccessful in controlling EBV-induced cellular proliferation, the infected cells can transform into malignant cells<sup>[37]</sup>. Therefore, EBV-related NHLs are more common in immunosuppressed populations, especially those infected with HIV<sup>[36,38]</sup>.

Many epidemiological studies have provided evidence that hepatitis C virus (HCV) infection is associated with the development of indolent and aggressive B-cell lymphomas<sup>[39-41]</sup>. HCV-infected patients may develop lymphomas that are either independent of viral infection or result from indirect activation of B cells by the virus<sup>[42]</sup>. Investigators have proposed several mechanisms for HCV-induced lymphomagenesis. These mainly include the chronic viral stimulation of lymphocytes and HCV replication in B cells, which is mediated by the interaction of HCV envelope proteins with lymphocyte-specific glycoproteins<sup>[42-44]</sup>.

### *Helicobacter pylori* infection

Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal marginal-

zone B-cell lymphoma<sup>[45]</sup>, and is the third most common subtype of NHL after diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). It exhibits an indolent behavior<sup>[46,47]</sup>. Although gastric MALT is most common, it can develop in almost every organ and tissue, including the salivary gland, thyroid gland, thymus, skin, and orbital adnexa<sup>[47-49]</sup>. *Helicobacter pylori* (*H. pylori*) infection is thought to play a key role in the development of gastric MALT lymphoma<sup>[50]</sup>. Normal gastric mucosa and salivary glands do not contain lymphoid tissue, but the long-term exposure to microbial antigens in a chronic inflammatory disease can lead to increased lymphoid tissue<sup>[51,52]</sup>. Similar to gastric MALT, chronic gastritis associated with *H. pylori* infection confers a significantly increased risk of SGL<sup>[49,50,53]</sup>.

### Immunosuppression

Factors associated with immunosuppression are linked with an increased risk of lymphoid malignancies<sup>[7,31]</sup>. Primary or secondary immunosuppression and autoimmunity are associated with NHLs<sup>[54,55]</sup>. Autoimmune conditions have attracted substantial attention; Sjögren syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and immunosuppressive therapy for solid organ or stem cell transplantation are frequently associated with increased risk of NHL<sup>[31,54,56]</sup>.

SS is characterized by lymphocytic infiltration and destruction primarily of salivary and lacrimal glands, which leads to xerostomia and xerophthalmia, respectively. Among the salivary glands, the parotid and submandibular glands are primarily affected<sup>[26,57]</sup>. According to a meta-analysis of 20 studies, SS presents a higher risk factor for development of NHL than SLE and RA<sup>[57]</sup>. The main risk factor for death in patients with SS is thought to be lymphoma<sup>[58]</sup>. There is evidence that the occurrence of lymphoma in SS patients is related to ectopic germinal center-like structures in salivary gland biopsy tissue<sup>[56]</sup>. Moreover, the structures are connected with elevated levels of numerous chemokines, including C-X-C motif chemokine ligand 13 and C-C motif chemokine ligand 11, the levels of which were significantly elevated in patients with SS-associated SGL<sup>[56,59-61]</sup>.

## CLINICAL FEATURES AND PRESENTATIONS

Clinical presentations of SGL are nonspecific<sup>[1-3]</sup>, so that a routine clinical examination cannot differentiate them from other benign or malignant salivary gland tumors<sup>[15]</sup>. The disease affects both genders equally. The mean age of patients is generally older than 50 years<sup>[62]</sup>. Patients with primary lymphoma of the parotid gland generally present with a unilateral asymptomatic mass that enlarges over a period of time. Other manifestations include bilateral swelling of the parotids, cervical lymphadenopathy, pain, and facial nerve paralysis<sup>[15,63-65]</sup>. The tumor appears as a border-clear, medium-texture mass, and even presents with superficial ulcers when inflammation is present<sup>[65]</sup>. Lymphomas occasionally cause diffuse swelling of parotid gland region similar to mumps<sup>[64]</sup>. Unilateral or bilateral glands may present enlargement if lymphomas occur in the submandibular glands, with hypoglossal nerve and mandibular margin branches of the facial nerve being rarely involved<sup>[66,67]</sup>. The most frequent location of lymphomas of the minor salivary glands is the hard palate<sup>[68]</sup>. They can initially appear as a nontender diffuse mass protruding from the mucosal surface, and are sometimes accompanied by ulceration and pain<sup>[21,68]</sup>. NHL occurring in the sublingual glands is extremely rare. It can be manifested as a diffuse swelling of the floor of the mouth with indistinct boundaries, and is easily misdiagnosed as a cyst of the sublingual gland<sup>[69]</sup>.

## IMAGING MANIFESTATIONS

Lymphomas of the parotid glands are more common than SGL. Therefore, we reviewed the imaging characteristics of lymphomas of the parotid glands and synthesized information from the literature. The initial evaluation for a mass involving the parotid gland should include ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) to determine the location, shape, size, and intensity of the mass. The literature indicates that the CT and MRI findings of MALT lymphoma of the parotid gland include variations in the contours and internal structures of the masses, as follows: Solitary solid mass, solitary solid-cystic mass, diffusely solid-cystic lesion, and multiple solid nodules or masses, in which solitary and diffusely solid-cystic



changes are more common<sup>[70,71]</sup>. Non-MALT lymphomas of the parotid gland are characterized mainly as solitary lesions, usually accompanied by enlarged and fused cervical lymph nodes. They are also characterized as well-defined masses of uniform density with necrotic areas within the tumor matrix<sup>[1,70,71]</sup>. MRI features of lymphomas of the parotid gland generally include masses with homogeneous intermediate-signal intensity and an enhancing rim on the postcontrast T<sub>1</sub>-weighted images and low-signal intensity on the T<sub>2</sub>-weighted images without obvious enhancement effects<sup>[64,71]</sup>.

## HISTOPATHOLOGY AND CLINICAL STAGES OF SGL

The definitive histopathological diagnosis and final classification of malignant lymphomas depend on histopathological examinations combined with immunohistochemical staining. B cell non-Hodgkin's SGL is predominant, it can be of any histopathological classification, though<sup>[10,45]</sup>. The common subtypes of lymphomas of the salivary glands include MALT lymphoma, DLBCL, and FL. T-cell types and HL are rare<sup>[11]</sup>. Based on the natural course of the disease, SGL can also be divided into aggressive and indolent types, among which DLBCL is aggressive and MALT lymphoma and FL are indolent<sup>[46,47]</sup>. Clinical staging is generally determined according to the Ann Arbor staging system, and is aided by Positron emission tomography-CT (PET-CT) and the evaluation of a bone marrow biopsy<sup>[15,72]</sup>.

## DIAGNOSTIC APPROACHES

Attention should be paid to the differential diagnosis of a SGL when the rapidly growing, painless mass occurs in a salivary gland, and especially if multiple cervical lymph nodes are involved. Imaging studies can indicate whether or not the mass involves a salivary gland but do not aid in the histological classification<sup>[13]</sup>. The gold standard for diagnosis is histopathological examination of a specimen combined with immunohistochemical staining<sup>[12,73]</sup>.

Fine needle aspiration cytology (FNAC) has recently become the method of choice for salivary gland tumors, because an FNA is safe, easy-to-perform, quick, repeatable, and without risk of seeding tumors along the needle tract. Data from the literature indicates that the overall sensitivity, specificity, and accuracy of FNAC for lesions of the oral cavity and salivary glands are 89.5%, 100% and 85%, respectively<sup>[73]</sup>. Since FNAC provides morphological findings on individual and small group of cells aspirated by a fine needle<sup>[74]</sup>, it can lead to a false-negative diagnosis of lymphoma. Fakhry *et al*<sup>[75]</sup> studied the diagnostic value of FNAC for 249 parotid tumors and obtained false-negative results for 11 cases (7.7%), among which lymphoma was the most common histological type. The high false-negative diagnostic rate of FNAC for lymphoma is due to the low sensitivity of FNAC, particularly for cystic tumors and/or tumors situated deep in salivary gland parenchyma. The review of the literature revealed that the diagnostic accuracy of FNA is affected by both the inadequate cellularity of the smears and inadequate sampling of the lesions<sup>[76]</sup>. In addition, morphological analysis is a difficult method for accurate identification of the histological subtypes of NHL of the salivary gland<sup>[13,73,74]</sup>. In conclusion, an excisional biopsy of the lesion is the most important approach for the diagnosis of SGL.

In addition, <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET/CT is an important noninvasive means for the diagnosis and staging of NHLs<sup>[77]</sup>. It provides both structural and functional metabolic information while localizing and estimating the tumor burden<sup>[78]</sup>. The diagnostic accuracy of <sup>18</sup>F-FDG PET/CT depends on the avidity of tumors for <sup>18</sup>F-FDG, which varies for different histological subtypes, regardless of grade<sup>[77,79]</sup>. The literature review revealed that invasive lymphoma subtypes have high <sup>18</sup>F-FDG avidity; therefore, <sup>18</sup>F-FDG PET/CT is the current reference standard for the staging of invasive lymphomas<sup>[77,79]</sup>. By contrast, the sensitivity of <sup>18</sup>F-FDG PET/CT for indolent lymphomas is not high<sup>[77,78,80]</sup>. Since <sup>18</sup>F-FDG PET/CT leads to a substantial dose of ionizing radiation, whole-body (WB)-MRI has been proposed as the radiation-free imaging technique of choice for the staging of indolent lymphomas with low <sup>18</sup>F-FDG avidity<sup>[78]</sup>. Even so, <sup>18</sup>F-FDG PET/CT remains the reference standard for the staging of HL and invasive NHL. WB-MRI tends to underestimate the response of the tumor to treatment. Multicenter prospective studies are needed to further confirm the role of WB-MRI in staging SGL<sup>[78,79]</sup>.

Small clonal B-cell populations, which is also known as monoclonal B-cell lymphocytosis, has been found to be associated with occult SGL. However, the

evaluation of monoclonal B-cell lymphocytosis in bone marrow has been mainly used for staging the lymphoma or monitoring the response to treatment<sup>[80]</sup>.

## TREATMENT AND PROGNOSIS

The treatment of SGL depends on the histopathological classification of the lesion, which leads to an individualized treatment plan. The treatment is generally nonsurgical, depending mainly on chemotherapy, radiation, or both<sup>[15]</sup>. Aggressive lymphomas such as DLBCL of the salivary gland are presumed to be disseminated disease. The suggested treatment is systemic chemotherapy and rituximab<sup>[15]</sup>. The standard treatment of DLBCL is rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)<sup>[81]</sup>. However, there remains room for improvement, particularly for elderly patients and patients with advanced or recurrent DLBCL<sup>[82]</sup>. Wilson *et al*<sup>[83]</sup> studied the regimen consisting of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (R-DA-EPOCH), which might be better than R-CHOP.

FL and MALT are two common subtypes of indolent NHL of the salivary glands. Radiotherapy is often applied for the treatment for indolent NHL of the salivary glands, and the standard dose range is normally between 20 and 30 Gy<sup>[84]</sup>. 24 Gy is the curative dose for early stages of MALT, which could minimize toxicity<sup>[85]</sup>. But anti-infection treatment is required if the MALT is associated with *H. pylori* infection<sup>[86,87]</sup>. A watch-and-wait approach is often recommended by the treatment guidelines for patients with low-grade FL of the salivary glands who are asymptomatic at the time of diagnosis<sup>[88]</sup>. In patients with advanced indolent lymphomas including MALT and FL, bendamustine plus rituximab (BR) can be considered as a preferred first-line treatment regimen over R-CHOP<sup>[86,89]</sup>. However, FL can transform into DLBCL, and is expected to behave more like DLBCL. Therefore, the World Health Organization classification recommends that FL should be treated with the same regimen that is used for DLBCL<sup>[86]</sup>. For recurrent and refractory indolent or aggressive lymphomas, autologous hematopoietic stem-cell transplantation is usually used in combination with high-dose chemotherapy<sup>[90]</sup>.

The evaluations of response include complete remission (CR), partial remission (PR), and progression of disease (PD). CR has been defined as the complete disappearance of signs and symptoms due to lymphoma for at least 6 wk. PR has been defined as a reduction of at least 50% of the product of the largest perpendicular diameters of all measurable lesions for a duration of at least 6 wk. PD has been defined as clear evidence of advancing disease, despite continuation of the treatment<sup>[91]</sup>. WB metabolic tumor volume (MTV) is a new metric derived from <sup>18</sup>F-FDG PET/CT to predict response to therapy and outcomes in patients with lymphomas, especially aggressive NHL. MTV is a volume parameter that can be quantitatively measured. The most common method to measure MTV is the fixed threshold method, where the optimal threshold is standard uptake value (SUV) 3 or SUV 6. The risk of disease progression increases with higher value of MTV<sup>[92]</sup>.

## CONCLUSION

Primary SGL with or without cervical masses is an uncommon tumor. Most lymphomas of the salivary gland are B-cell NHLs, including mainly MALT, DLBCL, and FL. The gold standard for diagnosis is the excisional biopsy combined with histopathological examination and immunohistochemical staining. The optimal treatment is chemotherapy or radiotherapy instead of complete surgical excision. At present, R-DA-EPOCH and BR have been widely recommended. The overall survival rate for patients with NHL of the salivary gland is usually higher than for patients with lymphomas originating from other extranodal sites. The prognosis of patients with lymphomas involving the salivary glands depends on the pathological subtypes and staging. Generally, patients with MALT and FL have a much better prognosis than patients with DLBCL. <sup>18</sup>F-FDG PET/CT is frequently used for monitoring the patients during the post-treatment period. Regular follow-ups could improve the survival rates of patients with SGL.

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