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# Is Salivary Gland Lymphoepithelioma a Surgical Disease?

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## Abstract

**Background:** Lymphoepithelioma-Like Carcinoma (LELC) is best known to occur in the nasopharynx, but can arise in other sites, such as the lung, thymus, stomach, and skin. Primary LELC of the salivary gland is rare, and is characterized by poor differentiation and high-grade histological appearance. There is unclarity regarding the optimal treatment of this rare disease. Based on the limited available data, surgery, radiation or a combination of them are accepted treatments for LELC. However the extent of surgery and radiation is controversial.

**Aim of Study:** The aim of our study was to evaluate the clinicopathologic characteristics and disease outcome in patients with LELC of salivary glands.

**Methods:** Retrospective study.

**Results:** Five patients with LELC of a salivary gland were included. The tumor was located in the parotid in 4 patients and in the sublingual gland in 1 patient. Four were women, and the mean age at diagnosis was 60.4 years (range 19 years to 78 years). One had a history of tobacco abuse, and none used alcohol. Four patients underwent tumor resection and ipsilateral neck dissection, the other patient was treated only by radiotherapy. Two patients had positive surgical margins and 3 had involvement of regional lymph nodes. All patients underwent nasopharyngeal biopsy and a nasopharyngeal primary tumor was excluded. All patients received radiotherapy (66 Gy). Radiation field included the primary tumor site and ipsilateral neck, sparing the nasopharynx and the contralateral neck. PET-CT that was performed 3 months after the end of radiotherapy, demonstrated a complete response in all cases. During a mean follow-up period of 37 months (range 7 months to 72 months) none of the patients recurred.

**Conclusion:** Lymphoepithelioma-like carcinoma of the salivary gland is a rare entity, but despite its poor histological appearance, its clinical course is better than other poorly differentiated tumors. Our experience suggests that LELC of salivary glands is radiosensitive as a primary treatment, and good clinical results were also obtained in cases with positive surgical margins. LELC can be treated successfully with surgery and radiotherapy limited to the primary site and ipsilateral neck after exclusion of nasopharyngeal origin.

**Keywords: Lymphoepithelioma-like carcinoma; Salivary gland; Radiotherapy salivary gland**

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## Introduction

Lymphoepithelioma-Like Carcinoma (LELC) of the salivary gland is a rare tumor. LELC is characterized by undifferentiated non-keratinizing squamous-cell carcinoma, featuring syncytial cytoplasm, vesicular nuclei, and large central nucleoli and lymphoid tissue with germinal centers. The tumor occurs mainly in the nasopharynx, but is also found in other tissues such as lung, thymus, stomach, and skin; as well as in salivary glands [1].

Lymphoepithelial carcinomas have been described as arising from a gland where a Benign Lymphoepithelial Lesion (BLEL) was previously diagnosed in biopsy [2]. This suggests malignant transformation of the epithelial elements of the BLEL. Since most LELCs are not diagnosed after discovering a BLEL, the tumor probably develops *de novo*.

Undifferentiated carcinoma of the lymphoepithelial type is a well-defined epithelial malignancy of the nasopharynx. It is equivalent to a type 3 nasopharyngeal carcinoma according to the World Health Organization (WHO) classification. Histologically, LELCS is composed of a neoplastic epithelial component associated with a reactive lymphoid infiltrate. The epithelial component of the tumor is represented by atypical polygonal cells with vesicular nuclei and prominent nucleoli.

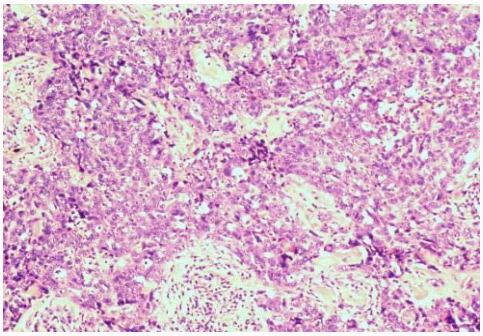

**Figure 1:** Dense inflammatory infiltrate surrounding nests of poorly differentiated carcinoma cells.

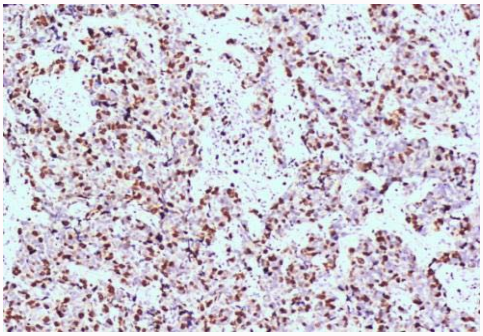

**Figure 2:** Immunohistochemical stain anti-Ki-67 Monoclonal Antibody.

The histologic diagnosis of LELCS may be complicated by the variable architectural of the epithelial cells and the dense lymphoplasmacytic infiltrate. In contrast to other high-grade salivary gland carcinomas in which the primary treatment is surgery, LELCs are considered.

Radiosensitive, though the clinical data concerning salivary glands LELC is inadequate compared with other common histological types [3,4]. Moreover, the clinical course and prognosis of this disease after treatments has not been thoroughly studied in the medical literature and optimal treatment strategies not yet established. Specifically should the tumor be treated surgically, by radiation or with both modalities?

The aim of our study was to evaluate treatment result and failure patterns in patients with salivary gland LELC.

## Patients and Methods

A retrospective chart review was conducted for all patients diagnosed with LELCs between 2006 and 2015. Cases of LELC metastatic to the neck from unknown primary were excluded. Data collection focused on treatment, results and failure patterns of LELC of the salivary glands.

Between 2006 and 2015, 5 patients were initially diagnosed with LELC of the head and neck whose primary tumor site was located outside the nasopharynx and treated with a curative intent. All patients underwent nasopharyngeal biopsy and a nasopharyngeal primary tumor was excluded. Four patients were female and the mean age at diagnosis was 60.4 years (range 19 years to 78 years). One patient is a smoker, and none used alcohol. The patient's medical records were reviewed and their pathological specimens were re-evaluated and confirmed as LELC.

The clinical presentation in all cases was a painless swelling of variable duration (2, 3 months and 1 year); the tumor was located in the parotid in 4 patients and in the sublingual gland in 1 patient.

CT imaging of the head and neck were performed routinely using PET-CT (4 patients) and MRI (1 patient). PET-FDG scans were performed in all cases and showed pathological uptake in the parotid glands in four cases and in the sublingual gland in the fifth case. No distant pathological uptake was demonstrated. Pathologic specimens from all patients were reviewed and confirmed as salivary gland LELC. Staging was classified in accordance with the American Joint Committee against Cancer TNM staging system (Table 1).

## Histopathological View

Pathological specimens had two characteristics, lymphoid-dense stroma with germinal centers and irregular shaped aggregates of large epithelial cells within lymphocyte-rich stroma (Figure 1). Epithelial spindled cells with amphophilic to eosinophilic cytoplasm and one or more prominent nucleoli were variably arranged in small nests, cords, syncytial masses with cell borders, or isolated cells. Mitotic figures presented. The malignant tissues stained positively for cytokeratin, CD3, CD20, p53, and Ki67, but negatively for CK20 (Figures 2 and 3). No Benign Lymphoepithelial Lesions (BLEL) was noted in the proximity of any of the malignant tumors [2-5].

## Treatment

Two treatment strategies were followed. Three patients with LELC of the parotid gland and the one patient with a sublingual gland LELC were initially treated with surgery than received post-operative radiation. One patient with LELC of the parotid gland was treated only with radiation.

Three of the patients with LELC of the parotid gland underwent an ipsilateral neck dissection; two underwent superficial parotidectomy and the third a radical parotidectomy. All patients presented positive surgical margins and involvement of regional lymph nodes, some with Extra Capsular Extension (ECE). One patient, who had a sublingual gland LELC, underwent a resection of the sublingual salivary gland, marginal mandibulectomy from teeth 33 to 47, partial glossectomy and bilateral neck dissection, then reconstruction of the jaw with titanium plate, prosthetic dental implants, and a myocutaneous free-flap from her arm. The margins were microscopically involved by the

**Table 1:** AJCC staging at presentation.

| | Age (years) | Sex | Primary Site | Stage (c) | Treatment | Stage (p) | F/U |
|---|---|---|---|---|---|---|---|
| Patient 1 | 78 | female | Parotid | T1N0M0 | S + Rx | T1N1M0 | 3 yr |
| Patient 2 | 65 | male | Parotid | T4aN1M0 | S + Rx | T4aN1M0 | 3 Yr |
| Patient 3 | 78 | female | Parotid | T1N0M0 | S + Rx | T1N1M0 | 3 Yr |
| Patient 4 | 19 | Female | Sublingual | T2N0M0 | S + Rx | T2N0M0 | 7 yr |
| Patient 5 | 62 | female | Parotid | T2N1M0 | Rx | T2N1M0 | 8 yr |

S: Surgery; Rx: Radiotherapy

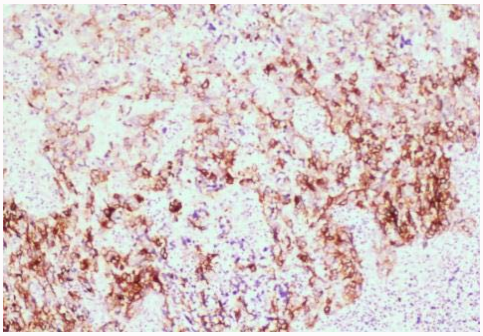

**Figure 3:** Epithelial nature of the tumor cells is highlighted by positive cytokeratin immuno reactivity.

tumor.

All surgically treated patients subsequently received post-operative radiotherapy (66 Gy). The radiation field for the patients with LELC of the parotid gland encompassed the primary tumor site and ipsilateral neck, sparing the nasopharynx and contralateral neck.

The fourth patient with LELC of the parotid gland was given a cycle of chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF); followed by radiotherapy (50 Gy for the left parotid and bilateral neck and a boost of 16 Gy to the left parotid gland).

The PET-CT performed 3 months following radiotherapy treatment indicated a complete response for all five patients. During a mean follow-up period of 4.7 years (range 35 months to 100 months) none of the patients recurred. PET-CT performed 3 months after the end of radiotherapy, for all five patients, demonstrated a complete response in all cases.

## Discussion

LELC of the salivary gland was first described in 1962 by Hilderman et al., [6], who presented a case of a 40-year-old man with a "malignant epithelial lesion with carcinomatous component" in the parotid gland, which was defined by the authors as a "malignant counterpart of benign lymphoepithelial lesions". One year later, Wallace et al., [7] described 14 cases of common and unusual salivary gland tumors in Canadian Eskimos, among which were 9 cases of "malignant lymphoepithelioma". From 1977 to 2008, there were 28 reports of LELC in the literature; only 2 were in the submandibular gland. In 2003, Saku et al., [8] reviewed 160 cases from Asian countries and Russia. The incidence of LELC was highest in Guanzhou, followed by Shanghai and Chengdu; and lowest in northern parts of China, Seoul, Niigata, and Moscow [5-7].

More recently, 2 cases of Mexican-Mestizo women were described by Saqui-Salces et al., [9], 3 cases in Thailand were described by Larbcharoensub et al., [10], and another case reported by Manganaris et al., [11] of a Caucasian female.

It is evident from the literature that this neoplasm has a mysteriously strong racial prevalence, with approximately 75% of published cases in Mongolian populations. Less than 15% of cases were found in Caucasians, mostly North Americans, and 10% were Japanese or Indian [12].

Regarding treatment, some of the studies suggest the necessity of aggressive surgery plus radiation, whilst there is controversy regarding the extent of considered surgery, specifically the extent of surgical neck treatment and the importance of negative margin. The width of normal tissue cuff around the resected tumor is of significant importance in cases where the facial nerve may be affected. In our study, the nerve was not sacrificed in any patient.

Regarding radiation, one may question the necessity for surgery. In the vast majority of reported cases, patients were treated either surgical or with bimodal treatment. Therefore the role of radiation alone is unclear. In our series, one patient was treated solely with radiation and in the other cases patients underwent radiation after incomplete resection.

All cases achieved complete response and patients were free of disease at the end of follow up (3 years to 8 years). However, more cases and long-term data are needed to verify this conclusion.

## Conclusion

Lymphoepithelioma-like carcinoma of the salivary gland is a rare entity, but despite its poor histological appearance, its clinical course is better than other poorly differentiated tumors. Our experience suggests that LELC of salivary glands is radiosensitive as a primary treatment, and good clinical results can also be obtained in cases with positive surgical margins. Patients were shown to have favorable prognoses as no local or regional failure occurred.

LELC can be treated successfully with limited surgery and adjuvant radiotherapy limited to the primary site and ipsilateral neck after exclusion of nasopharyngeal origin. Future studies are recommended to explore the role of and criteria for surgery alone.

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