ISSN: 0976-822X

Available online on www.ijcpr.com

International Journal of Current Pharmaceutical Review and Research 2022; 14(1); 82-88

Original Research Article

# TONGUE SQUAMOUS CELL CARCINOMA LYMPH NODE METASTASIS PROGNOSTIC FACTORS

**Rohit Kumar Jha[1], Ritesh Kumar Sinha[2], Sumedha Gargy[3], Shalini Jha[4]**

[1]Assistant Professor, Department of Surgical Oncology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India[1]

[2]Senior Resident, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India[2]

[3]Senior Resident, Department of Surgical Oncology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India[3]

[4]MBBS, MS (ENT), Jharkhand, India

**Received: 10-12-2021 / Revised: 14-01-2022 / Accepted: 23-03-2022**

**Corresponding author: Dr. Shalini Kumari**

**Conflict of interest: Nil**

**Objective:** The lingual lymph nodes (LLNs), inconstant nodes that are frequently positioned beyond the regions of basic tongue tumor surgery, are where squamous cell carcinoma of the tongue (SCC of the tongue) most frequently metastasizes. In comparison to cervical lymph node metastasis, the clinicopathological characteristics and prognostic significance of LLN metastasis (LLNM) were examined in the current study in patients with tongue SCC.

**Method:** At Rajendra Institute of Medical Sciences, Ranchi over the course of two years, aggressive surgery was performed on 250 patients with tongue SCC. We examined and resected lateral LLNs during neck dissection when they were present. Twenty individuals had both cervical lymph node metastases and LLNM the 125 patients who had lymph node metastasis. According to a univariate study, LLNM was significantly linked to the negative aspects of cervical lymph node metastases.

**Results:** Patients with LLNMs had significantly poorer 5-year disease-specific survival (5y-DSS) rates than patients without LLNMs (49.1% vs. 88.3%, P<0.02). Additionally, cervical lymph node metastasis at levels IV or V and LLNM were found to be separate prognostic variables for 5y-DSS in Cox proportional hazards model analysis.

**Conclusion:** In individuals with tongue SCC, LLNM has a significant detrimental effect on survival. LLNM may be predicted by the advanced stage of cervical lymph node metastasis.

**Keywords:** lingual lymph nodes, squamous cell carcinoma, Tongue, metastasis



## INTRODUCTION

The most frequent location for head and neck malignancies is the oral cavity [1]. Squamous cell carcinomas (SCCs) make up more than 90% of oral cancers, and more than 50% of primary oral SCCs develop on the tongue and floor of the mouth [Figure 1;1]. Survival in individuals with advanced oral SCC has not significantly increased despite advances in diagnosis and therapy [2]. One of the most reliable prognostic indicators in individuals with oral SCC1 is lymph node metastasis to the cervical region [2]. Compared to SCC that develops at other subsites, SCC that starts in the tongue often spreads to the cervical lymph nodes. However, lingual lymph nodes (LLNs), which block the lymphatic collecting

trunks flowing from the tongue and floor of the mouth to the cervical lymph node, are seldom affected by tongue SCCs [2].

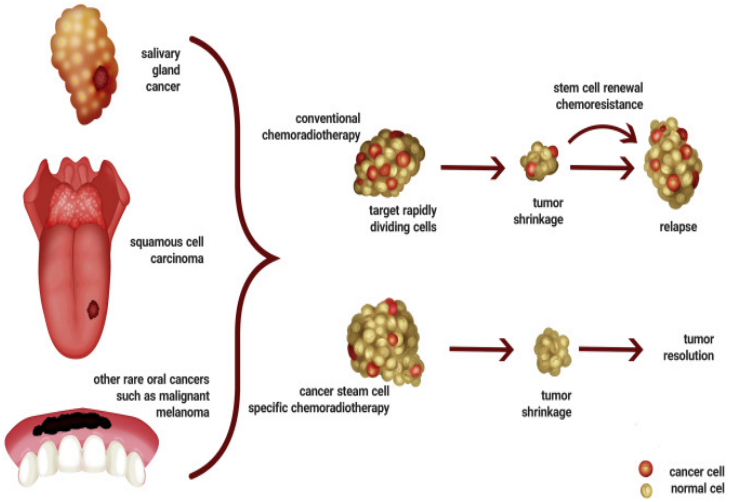


**Figure 1: Oral Cancers**

The two categories of LLNs are median and lateral LLNs7–10. The lateral LLNs are located along the lingual artery's path on the outside of the genioglossus or hyoglossus muscle, whereas the median LLNs are located in the lingual septum between the genioglossus and geniohyoid muscles [4]. Additionally, the lateral LLNs can be split into two groups: the parathyroid nodes, which are situated near the sublingual gland and along the path of the lingual artery at the cornu of the hyoid bone, and the para glandular nodes. Due to their frequent absence or tiny size when present, LLNs are commonly missed during imaging exams [5]. LLNs are frequently located beyond the regions of surgical excision of the original tongue tumor and neck dissection due to their anatomical positions as well [5]. For instance, after a partial glossectomy without the lingual septum, the median LLNs cannot be resected. When doing a partial glossectomy, which commonly excludes the sublingual region, or when performing a discontinuous neck dissection without careful inspection, lateral LLNs in this region cannot be removed. Any sort of neck dissection may miss lateral LLNs in the parathyroid region if not thoroughly examined. According to earlier research, the prevalence of lateral and medial lingual lymph node metastasis (LLNM) ranges from 0.7% to 3.0% [6].

However, because LLNM has gotten little attention up until recently, there isn't enough data on the clinical implications and prognostic usefulness of LLNM in patients with tongue SCC. It was proposed that LLNM, like cervical lymph node metastasis, affected tongue SCC patients' prognosis.

The purpose of the current investigation was to assess the clinicopathological characteristics of LLNM and its influence on survival in patients with tongue SCC when compared to cervical lymph node metastasis.

## METHODS:

***Study Design:*** This retrospective study was carried out at Rajendra Institute of Medical Sciences, Ranchi, within two years.

***Methodology:*** The patient's medical records provided demographic and clinical information, such as age, sex, T stage, pathological differentiation of the main tumor, mechanism of cervical lymph node metastasis, and treatment results. The American Joint Committee on Cancer TNM staging system, 7th edition, was used to clinically stage tumors [7]. The LLNs were divided into three groups: lateral LLNs in the parathyroid area (located along the course of the lingual artery or hypoglossal nerve at the corner of the hyoid bone) and lateral LLNs in the sublingual space (located along the genioglossus or hyoglossus muscle).

Preoperative imaging tests on all patients included computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Physical examination and imaging results were used to evaluate the original tumor and cervical lymph node metastases. Surgical margins larger than 11 mm were used to remove all main tumors. For the treatment of clinically unfavorable cervical lymph node metastases in tongue SCC patients, we used a wait-and-see approach. Supraomohyoid neck dissection (levels I, II, and III) was carried out as an elective neck dissection in patients with cN0 who had removal of the original tumor and reconstruction utilizing a vascularized free fap. Patients who had cervical lymph nodes that were clinically positive received radical neck dissection at levels I through V.

Any time we dissected the neck, we removed the digastric and stylohyoid muscles and examined the lateral LLN at the corner of the hyoid bone along the path of the lingual artery and hypoglossal nerve. When the mylohyoid muscle was still intact, we carefully palpated the lateral LLN in the sublingual region and anteriorly retracted this muscle to examine it. Additionally, where clinically positive LLNM adhered to the surrounding muscles, mandible, hyoid bone, hypoglossal nerve, or lingual artery, extensive resection was carried out.

Patients who had less than three pathologically metastatic lymph nodes or ENE with adhesion to the surrounding tissues had postoperative radiation to the neck or area of the LLNM, ideally in conjunction with the simultaneous administration of platinum-based anticancer medications. next radical therapy, patients were checked on every three weeks for the first year, every month for the next year, and every two months for the following year, with follow-up intervals progressively getting longer after that.

***Sample Size:*** 267 patients were originally enrolled in this study, but, based on inclusion criteria, 250 patients were analyzed in this study.

***Inclusion criteria:*** Data on people with cervical lymph node metastasis, often known as LLNM, that has been confirmed pathologically.

***Exclusion criteria:*** Patients with tongue tumors who have already undergone therapy.

***Statistical analysis:*** The Kaplan-Meier technique was used to analyze survival, and the log-rank test was used to compare survival rates across groups. From the date of surgery until the date of death due to uncontrolled tongue SCC, DSS was calculated. The Cox proportional hazards model was used to undertake a multivariate analysis of variables connected to 5y-DSS. Using Fisher's exact test or Pearson's chi-square test, the relationships between LLNM and categorical factors were evaluated. Statistics were deemed significant at $P<0.04$. Using JMP14, all statistical analyses were carried out.

## RESULTS:

During the research period, 250 patients had therapy for tongue SCC, and 125 (21.0%) of them developed cervical lymph node metastasis or LLNM. 90 males and 35 women, ages 20 to 82 (median 60.4), made up these patients. In the beginning, 88 patients had both a glossectomy and a neck dissection; of them, 81 had a continuous neck dissection using a pull-through technique and nine had a discontinuous neck dissection. 38 individuals had neck dissection for delayed lymph node metastases after the initial excision of the main tumor alone.

Of the 250 patients, 20 had both LLNM and cervical lymph node metastases, while 105 had the former but not the latter. Therefore, 3.2% of tongue SCC patients who underwent radical surgery throughout the research period also had LLNM. Ten of the 20 individuals with LLNM had lateral LLNM in the parathyroid region, seven had lateral LLNM in the sublingual space, and three had median LLNM. 13 patients received excision of the original tumor and neck dissection; 11

underwent continuous neck dissection with a pull-through maneuver, and 2 experienced discontinuous neck dissection. LLNM was confirmed during the first operation in all 13 patients.

To evaluate clinicopathological characteristics between individuals with and without LLNM, univariate analysis was carried out. There was no significant correlation between LLNM and age, sex, cT stage, or pathological differentiation. However, ipsilateral cervical lymph node metastases (I-III vs. IV-V), level (I-III vs. IV-V), ENE (negative vs. positive), and involvement on the contralateral side (absence vs. presence) were all significantly correlated with LLNM.

The variables that affect 5-year disease-specific survival (5y-DSS) were subjected to univariate analysis. According to **Table 1**, there was a significant correlation between 5y-DSS and the quantity of ipsilaterally positive nodes, the degree of ipsilaterally positive nodes, contralateral cervical lymph node metastases, LLNM, and postoperative care.

**Table 1: Clinicopathology traits of patients**

| Clinicopathological factors | 5y-DSS (%) | P-value |
|---|---|---|
| **Gender** | | |
| Male | 79.8 | 0.47 |
| Female | 87.6 | |
| Age | | |
| < 61 years | 84.8 | 0.48 |
| ≥ 61 years | 79.2 | |
| **Pathological differentiation** | | |
| Well | 78.5 | 0.52 |
| Moderate | 87.3 | |
| Poor | 76.5 | |
| Unknown | 99 | |
| cT | | |
| T1 + T2 | 85.2 | 0.09 |
| T3 + T4 | 71.1 | |
| **Number of ipsilateral positive nodes** | | |
| ≤ 2 | 88.7 | <0.02 |
| ≥ 3 | 55.3 | |
| **Contralateral cervical LNM** | | |
| Absence | 86.3 | <0.02 |
| Presence | 46.8 | |
| **Level of ipsilateral positive nodes** | | |
| Level I, II, or III | 86.7 | <0.02 |
| Level IV or V | 12.4 | |
| Post-operative treatments | | |
| No | 89.5 | <0.02 |
| Yes | 71.2 | |
| **LLNM** | | |
| Absence | 88.3 | <0.02 |
| Presence | 49.1 | |
| **ENE of ipsilateral positive nodes** | | |
| Negative | 88.8 | 0.01 |
| Positive | 74.3 | |

Patients with and without LLNM had significantly different 5-year DSS rates (49.1% vs. 88.3%, P<0.02). Pathological differentiation, cT stage, age, and sex were

not significantly linked to 5y-DSS. Level IV or V involvement of the ipsilateral positive nodes was shown to be an independent prognostic factor for 5y-DSS (hazard ratio [HR]: 12.45; 95% confidence interval [CI] 3.16-50.44; P<0.02) as well as the presence of LLNM (HR 5.86; 95% CI 2.08-17.08; P<0.02) [**Table 2**].

**Table 2: Multivariate Analysis of Factors**

| Clinicopathological factors | Hazard ratio | P-value | 95% CI |
|---|---|---|---|
| Level of ipsilateral positive nodes (Level IV or V vs. Level I, II, or III) | 12.45 | < 0.02 | 3.16–50.44 |
| Contralateral cervical LNM (Presence vs. Absence) | 2.18 | 0.18 | 0.66–6.48 |
| Number of ipsilateral positive nodes (≥ 4 vs. ≤ 3) | 1.82 | 0.37 | 0.47–8.21 |
| ENE of ipsilateral positive nodes (Positive vs. Negative) | 1.65 | 0.35 | 0.55–5.22 |
| Postoperative treatment (Positive vs. Negative) | 1.12 | 0.85 | 0.28–4.88 |
| LLNM (Presence vs. Absence) | 5.86 | < 0.02 | 2.08–17.08 |

## DISCUSSION:

The following were the main findings of the present study: (1) Of the 250 patients with tongue SCC, 3.5% had LLNM. (2) Cervical lymph node metastases were present in each patient with LLNM. (3) The 5y-DSS in patients with LLNM was significantly worse than that in patients without LLNM, according to statistical analysis of the link between LLNM and clinicopathological aspects, which showed that pathologic unfavorable features of cervical lymph node metastases may be a reliable predictor of LLNM. In patients with tongue SCC, multivariate analysis showed that LLNM and level IV or V involvement of ipsilateral positive nodes were significant prognostic indicators.

The clinicopathological variables associated with LLNM in individuals with tongue SCC have only been the subject of a few research. According to research, out of 111 patients with tongue SCC, five had cervical lymph node status of pN2 and LLNM [8]. Additionally, in patients with cT1-2N0 tongue SCC, T stage and occult cervical lymph node metastasis were linked to LLNM, whereas in patients with cT2-4 tongue SCC, T stage, tumor differentiation, perineural invasion, lymph vascular invasion, and cervical lymph node metastasis were linked to LLNM [10]. In individuals with cT2-4 tongue SCC19, LLNM was linked to invasion and cervical lymph node metastases.

All of the patients with LLNM also had additional cervical lymph node metastases, we discovered. LLNM was significantly linked with the cervical lymph node metastatic status, including 4 positive nodes, level IV or V involvement, ENE, and spread to the cervical lymph nodes on the opposite side, according to a univariate study. According to these findings, cervical lymph node metastasis, particularly advanced stage, may indicate LLNM in people with tongue SCC. Early T-stage tongue SCC can metastasize to the LLN, however, there was no significant association between the cT stage and LLNM.

Additionally, there isn't much research that has examined the prognostic significance of LLNM in tongue SCC patients. With a 5y-DSS of 51%, one study found that LLNM was an independent prognostic factor for survival only in patients with cT1-2N0 tongue SCC. Another found that recurrent disease in the parathyroid area was a factor in 77 patients' poor disease-specific survival (DSS) due to regional failure of cT1-2 tongue SCC. We studied the effects of cervical lymph node metastasis and LLNM on survival in individuals with tongue SCC. The results showed that patients with LLNM had significantly lower 5-year DSS rates than patients without LLNM (49.1% vs. 88.3%,

P<0.02). Additionally, Cox proportional hazards analysis showed that contralateral cervical lymph node metastases and the number of ipsilateral positive nodes, ENE of ipsilateral positive nodes, were not related to 5y-DSS. However, LLNM and level IV or V participation were significantly linked to a poor 5y-DSS. The findings imply that LLNM, as opposed to other typical unfavourable characteristics of cervical lymph node metastasis, has a stronger detrimental effect on survival in patients with tongue SCC.

This study's findings that the majority of LLNMs were subclinical metastases were in line with those of other studies [11-14].

Glossectomy, including the tongue septum, and continuous neck dissection via a pull-through manoeuvre are necessary to completely dissect asymptomatic median and lateral LLNMs. Due to the low incidence of LLNM (3.4% in the current research), this surgical approach may not be universally advised for all patients with tongue SCC. Therefore, with any form of neck dissection, it may be necessary to thoroughly examine and resect LLNs. We resected the digastric and stylohyoid muscles, which provided an appropriate approach to this area with a clear visual feld, to examine and resect the lateral LLN in the parahyoid area. On the outside of the hypoglossus muscles, we first closely examined the lateral LLN along the hypoglossal nerve. Next, we carefully observed and felt the lingual artery as it travelled from the anterior surface of the external carotid artery to the hyoglossus muscle to examine the lateral LLN. The posterior belly of the digastric muscle and the stylohyoid muscle were spared on one side during bilateral neck dissection to prevent a swallowing problem. Ten, during lateral LLN inspection, we superiorly retracted these muscles. A few papers also suggested that the lateral LLN in the parahyoid region be examined and dissected during neck dissection [15,16]. We anteriorly retracted the mylohyoid muscle to examine the lateral LLN in the sublingual region, carefully palpating the nodes. This treatment for the lateral LLN is consistent with the findings of other investigations [15,16] in that it did not cause any further comorbidity with neck dissection. Additionally, thorough LLNM surveillance should be carried out in patients with tongue SCC.

## LIMITATION:

First, the statistical power to draw conclusions was insufficient because of the small number of tongue SCC patients with cervical lymph node metastases and LLNM that were included. Second, because the study was retrospective in nature, it was unable to assess the survival benefits of closely examining LLNs during neck dissection and hemi glossectomy.

## CONCLUSION:

Patients with tongue SCC are more likely to develop LLNMs, which are linked to worse survival rates. Before surgery, imaging methods cannot identify the majority of metastatic LLNs because they are subclinical. Therefore, during neck dissection, LLNs should be thoroughly examined and removed. LLNM must be carefully monitored in individuals with tongue SCC. The unfavourable characteristics of cervical lymph node metastases may indicate LLNMs. The results of this investigation need to be confirmed by larger prospective studies in order to determine the best course of treatment for LLNMs.

## FUNDING:

No outside funding was used for this study.

## REFERENCES:

1. Speight PM, Takata T. New tumour entities in the 4th edition of the World Health Organization Classification of Head and Neck tumours: odontogenic and maxillofacial bone tumours. Virchows Archiv. 2018 Mar;472:331-9.
2. Brands MT, Brennan PA, Verbeek AL, Merkx MA, Geurts SM. Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature.

European Journal of Surgical Oncology. 2018 May 1;44(5):559-65.
3. Feller L, Lemmer J. Oral squamous cell carcinoma: epidemiology, clinical presentation and treatment.
4. Oikawa Y, Kugimoto T, Kashima Y, Okuyama K, Ohsako T, Kuroshima T, Hirai H, Tomioka H, Shimamoto H, Michi Y, Harada H. Surgical treatment for oral tongue squamous cell carcinoma: A retrospective study of 432 patients. Global Health & Medicine. 2021 Jun 30;3(3):157-62.
5. Sato J, Kitagawa Y, Watanabe S, Asaka T, Ohga N, Hirata K, Shiga T, Satoh A, Tamaki N. Hypoxic volume evaluated by 18F-fluoromisonidazole positron emission tomography (FMISO-PET) may be a prognostic factor in patients with oral squamous cell carcinoma: preliminary analyses. International Journal of Oral and Maxillofacial Surgery. 2018 May 1;47(5):553-60.
6. Sasahira T, Kirita T, Kuniyasu H. Update of molecular pathobiology in oral cancer: a review. International journal of clinical oncology. 2014 Jun;19:431-6.
7. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual 7th edn Springer New York: New York. NY, USA.[Google Scholar]. 2009.
8. Haagensen CD. An Exhibit of Important Books, Papers, and Memorabilia Illustrating the Evolution of the Knowledge of Cancer: For the Graduate Fortnight on Tumors at the New York Academy of Medicine, October 17 to 28, 1932. The American Journal of Cancer. 1933 May;18(1):42-126.
9. Tomblinson CM, Nagel TH, Hu LS, Zarka MA, Hoxworth JM. Median lingual lymph nodes: prevalence on imaging and potential implications for oral cavity cancer staging. Journal of Computer Assisted Tomography. 2017 Jul 1;41(4):528-34.
10. Rouviere H. Lymphatic system of the head and neck. Anatomy of the human lymphatic system. 1938.
11. Ananian SG, Gvetadze SR, Ilkaev KD, Mochalnikova VV, Zayratiants GO, Mkhitarov VA, Yang X, Ciciashvili AM. Anatomic–histologic study of the floor of the mouth: the lingual lymph nodes. Japanese Journal of Clinical Oncology. 2015 Jun 1;45(6):547-54.
12. Ozeki S, Tashiro H, Okamoto M, Matsushima T. Metastasis to the linguallymph node in carcinoma of the tongue. Journal of maxillofacial surgery. 1985 Jan 1;13:277-81.
13. Yang X, Huang X, Hu Q, Wang Z. Metastases to lingual lymph nodes from squamous cell carcinoma of the tongue. British Journal of Oral and Maxillofacial Surgery. 2008 Jul 1;46(5):376-8.
14. Woolgar JA. Histological distribution of cervical lymph node metastases from intraoral/oropharyngeal squamous cell carcinomas. British Journal of Oral and Maxillofacial Surgery. 1999 Jun 1;37(3):175-80.
15. Ando M, Asai M, Asakage T, Oyama W, Saikawa M, Yamazaki M, Miyazaki M, Ugumori T, Daiko H, Hayashi R. Metastatic neck disease beyond the limits of a neck dissection: attention to the 'para-hyoid'area in T1/2 oral tongue cancer. Japanese journal of clinical oncology. 2009 Apr 1;39(4):231-6.
16. Ando M, Asai M, Ono T, Nakanishi Y, Asakage T, Yamasoba T. Metastases to the lingual nodes in tongue cancer: a pitfall in a conventional neck dissection. Auris Nasus Larynx. 2010 Jun 1;37(3):386-9.