

Clinical Paper
Head and Neck Oncology

The influence of lymph node ratio on survival and disease recurrence in squamous cell carcinoma of the tongue

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Abstract. This study was performed to report the outcomes of patients with oral squamous cell carcinoma (OSCC) of the tongue over a 10-year period with the aim of testing the hypothesis that the lymph node ratio (LNR) has a significant influence on loco-regional recurrence. The charts of 227 patients with OSCC of the mobile tongue treated at the University Hospital of Zurich from 2003 to 2012 were screened. Following the application of the exclusion criteria (prior chemotherapy, radiotherapy, or surgery, perioperative death, N3 disease, unresectable disease, synchronous second primary, no signed informed consent, and follow-up <3 years), prospective data were collected and a retrospective analysis performed for 88 of these patients who were treated with selective neck dissection. During a mean follow-up period of 78 months (standard deviation 37 months), loco-regional recurrence was diagnosed in 25 patients (28%). The overall and disease-specific survival rates for the study population were 72% and 80%, respectively. Perineural invasion was identified as an independent risk factor for decreased disease-specific survival, whereas LNR was not. LNR did not show an influence on disease recurrence. Thus, its prognostic value in patients with tongue cancer remains uncertain and the decision regarding adjuvant therapy should not be made solely on the basis of LNR.

Key words: head and neck cancer; tongue cancer; survival rate; neck dissection.

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Oral squamous cell carcinoma (OSCC) is the sixth most common type of cancer worldwide, and with approximately 200,000 newly diagnosed cases and around 128,000 deaths per year, the bur-

den of disease is considered high^{1,2}. In patients with OSCC, the tongue is the most commonly affected anatomical location^{3–5}. Tongue cancer spreads to draining lymph nodes, and lymph node

metastasis is already present at diagnosis in around 50% of patients, as this form of cancer is much more likely to metastasize than other cancers^{6,7}. Metastatic involvement of cervical lymph nodes is the major

adverse prognostic factor and dramatically decreases the 5-year survival of patients with tongue cancer⁶.

The American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) staging classification for oral cavity cancer quantifies nodal disease by the number, size, and laterality of positive cervical lymph nodes⁸. Pathological nodal status (pN) is divided into pN1 (metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension), pN2 (metastasis in a single ipsilateral lymph node of 3–6 cm in greatest dimension, or in multiple ipsilateral nodes < 6 cm in dimension, or in the bilateral nodes or contralateral nodes < 6 cm in dimension), and pN3 (metastasis in a lymph node > 6 cm in dimension)⁸.

Whereas the presence of one or more metastatic cervical lymph nodes significantly predicts poor survival, the nodal stage by itself seems to be insufficient for the prediction of the prognosis among patients with positive cervical lymph nodes, especially after adjuvant radiotherapy^{9–13}. It seems obvious that the identification of metastatic lymph nodes relies on the surgical quality of neck dissection and the accuracy of histopathological evaluation, and it has been shown that the number of excised lymph nodes corresponds to the likelihood of identifying metastatic disease^{14–16}.

As the dissection of too few lymph nodes may lead to pathological understaging, the total number of dissected lymph nodes has been taken into consideration. The concept of lymph node density (LND) or lymph node ratio (LNR) was introduced primarily for carcinoma of the bladder and oesophageal cancer, and this was found to be superior to the traditional TNM nodal staging classification in predicting survival after surgery^{17–19}.

The principle of the LNR is that both the number of positive nodes (regional disease spread) and the total number of nodes excised during surgery (surgical technique) are considered to compensate for the potential bias of the sampling method²⁰. The LNR is defined as the ratio of positive lymph nodes to the total number of dissected lymph nodes, and this has also been found to be an independent prognostic factor for OSCC^{21,22}. Several studies have shown that the LNR is suitable as a prognostic marker for OSCC and is superior to the conventional nodal staging classification for the prognosis of loco-regional and distant recurrence^{20,21}.

However, data on the anatomical subtypes of OSCC and the role of the LNR in tongue cancer are very limited and these remain under investigation. Two studies

with different inclusion criteria concluded that the LNR is a suitable prognostic parameter for squamous cell carcinoma of the oral tongue^{23,24}, and Safi et al. recently reported its usefulness in predicting loco-regional recurrence²⁵.

The aim of this study was to contribute to the proposed findings and to evaluate the role of the LNR as a prognostic predictor in patients with OSCC of the oral tongue on a long-term basis.

Materials and methods

Ethical approval was obtained from the local ethics committee and the study followed the guidelines of the Declaration of Helsinki. Data were collected prospectively and a retrospective analysis was performed for 227 patients diagnosed with OSCC of the tongue between 2003 and 2012 at the University Hospital of Zurich. Patients were enrolled in the study according to predefined exclusion and inclusion criteria. The inclusion criteria were (1) patients operated on at the University Hospital of Zurich, (2) OSCC of the mobile tongue, and (3) surgery with curative intent, indicated by microscopically negative resection margins > 5 mm (R0). Exclusion criteria were (1) simultaneous second primary at the time of diagnosis, (2) prior treatment including surgery, radiotherapy, and/or chemotherapy, (3) N3 disease, (4) unresectable disease, (5) no informed consent for the use of data, and (6) follow-up < 3 years if not censored.

All patients were staged and graded according to the seventh edition of the AJCC TNM classification system⁸.

Pre- and postoperative treatment plans were discussed by an interdisciplinary tumour board involving specialists in otorhinolaryngology, maxillofacial surgery, oncology, and radiology as well as radio-oncology, and were based on the latest recommendations of the National Comprehensive Cancer Network (NCCN).

The primary treatment for all patients included radical tumour resection and unilateral or bilateral selective neck dissection of levels I–III, depending on whether the tumour approximated or exceeded the midline. Patients identified with adverse features, including extracapsular spread, perineural invasion, or locally advanced disease ($> pT3$), underwent postoperative radiotherapy or radio-chemotherapy. Local disease recurrence was defined as a tumour of similar histology appearing after 6 weeks of treatment and within the first 3 years of follow-up^{25,26}. Regional recurrence was defined as recurrence within the neck lymph nodes and distant re-

currence as metastasis outside the head and neck region.

Statistical analysis

The aim of the study was to test the null hypothesis that the LNR has a significant influence on loco-regional recurrence of the disease against the alternative hypothesis that it has not. All statistical analyses were performed using GraphPad Prism 6.0 software (GraphPad Software Inc., La Jolla, CA, USA). The patient profiles were compared by χ^2 test, Fisher's exact test, or Mann–Whitney *U*-test to identify associations between clinicopathological features and disease recurrence or progression. A *P*-value of < 0.05 was considered statistically significant. Overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) were analyzed by Kaplan–Meier statistics. The log-rank test was used to compare survival rates between subgroups. Univariate analysis was used to determine the influence of patient and tumour-specific characteristics, as well as postoperative treatment protocols, on OS, DSS, and DFS rates. The non-parametric Spearman correlation test was used to determine the correlation coefficient (*r*) and the *P*-value for non-normally distributed, non-linear values. Correlation coefficients were interpreted as follows: 0.8 to 1.0 (or -0.8 to -1.0) = very strong correlation, 0.6 to 0.8 = strong correlation, 0.4 to 0.6 = moderate correlation, 0.2 to 0.4 = weak correlation, and 0.0 to 0.2 = negligible correlation.

Results

The prospective data collection was performed for 227 patients diagnosed with and treated for OSCC of the tongue at the University Hospital of Zurich between 2003 and 2012. Following the application of the study inclusion and exclusion criteria, a retrospective analysis of 88 patients was performed, in accordance with the guidelines of the Declaration of Helsinki. The characteristics of the patients and tumour-related data are presented in Table 1. At the time of diagnosis, the patients had a median age of 57 years (range 26–95) and the male-to-female ratio was 1.4:1 (52 male and 36 female). The mean duration of follow-up for the study population was 78 months (SD 37 months, range 3–177 months) after treatment with curative intent.

Local or regional recurrence was diagnosed in 25 patients (28%) at a mean of 28 months (SD 31 months) following surgical treatment. Ten patients suffered from local

Table 1. Demographic characteristics of the patients and tumour-related data.

Characteristic	Patients, <i>n</i> (%)
Total population	88 (100%)
Sex	
Male	52 (59%)
Female	36 (41%)
Age (years)	
Median (range)	57 (26–95)
Smoker	43 (49%)
Alcohol consumer	63 (72%)
T-classification	
pT1	37 (41%)
pT2	49 (56%)
pT3	2 (2%)
N-classification	
pN0	43 (49%)
pN1	25 (28%)
pN2a	2 (2%)
pN2b	18 (20%)

recurrence, seven from regional recurrence, and eight from both local and regional recurrence of the disease. Ten of these patients were also diagnosed with distant metastasis. At 5 years, 25 patients presented with a recurrence of the disease and one with a second primary, thus the DFS rate for the study population was 69% (Fig. 1). Thirty-one patients (35% of the study population) died during the follow-up, with 24 (77%) of these patients dying within 5 years, revealing an overall survival rate of 72% at 5 years. For 18 patients, all suffering from a distant recurrence of the disease, the tongue cancer and its associated consequences were identi-

fied as the cause of death. Distant recurrence was diagnosed at a mean follow-up time of 17 months (SD 17 months). There was a direct correlation between DSS and distant recurrence ($r = 1.0$). At 5 years, 17 patients had already died following a progression or recurrence of the disease, resulting in a DSS of 80%. The OS, DSS, and DFS rates at 5 years are illustrated in Fig. 1. Sixty percent of patients suffering from a recurrence of the disease died within 1 year.

On univariate analysis, the LNR, number of positive lymph nodes, tumour grading, and perineural invasion showed a weak relationship with distant recurrence

and DSS. The size of the lymph node metastasis showed a significant moderate correlation with distant recurrence and DSS (Table 2). Other parameters including the number of resected lymph nodes, tumour size, and extranodal spread did not correlate with distant recurrence or DSS.

In the analysis of the potential influence of postoperative treatment protocols on the OS, DSS, and DFS rates, no significant influence could be detected, as indicated by P -values of $P = 0.306$, $P = 0.100$, and $P = 0.137$, respectively. Twenty-one of 64 cases (33%) classified with a cN0 lymph node status showed pathological cervical lymph nodes after elective neck dissection. Their mean LNR was 4%. The median value of the LNR for lymph node patients was 6%, with a maximum of 27%. Setting a threshold at the median of 6% for subgroup analysis, no significant difference in DFS, DSS, or loco-regional recurrence was found between patients with a LNR of $\geq 6\%$ and patients with a LNR of $< 6\%$. The rate of loco-regional recurrence was 66% for patients with a LNR $\geq 6\%$ and 71% for those with a LNR $< 6\%$ ($P = 0.766$, Fig. 2). Thus, the null hypothesis must be rejected.

On multivariate analysis, perineural invasion was identified as an independent risk factor for decreased DSS ($P = 0.012$) and the number of positive lymph nodes as an independent risk factor for increased loco-regional recurrence ($P = 0.033$). Other parameters including the LNR, tumour

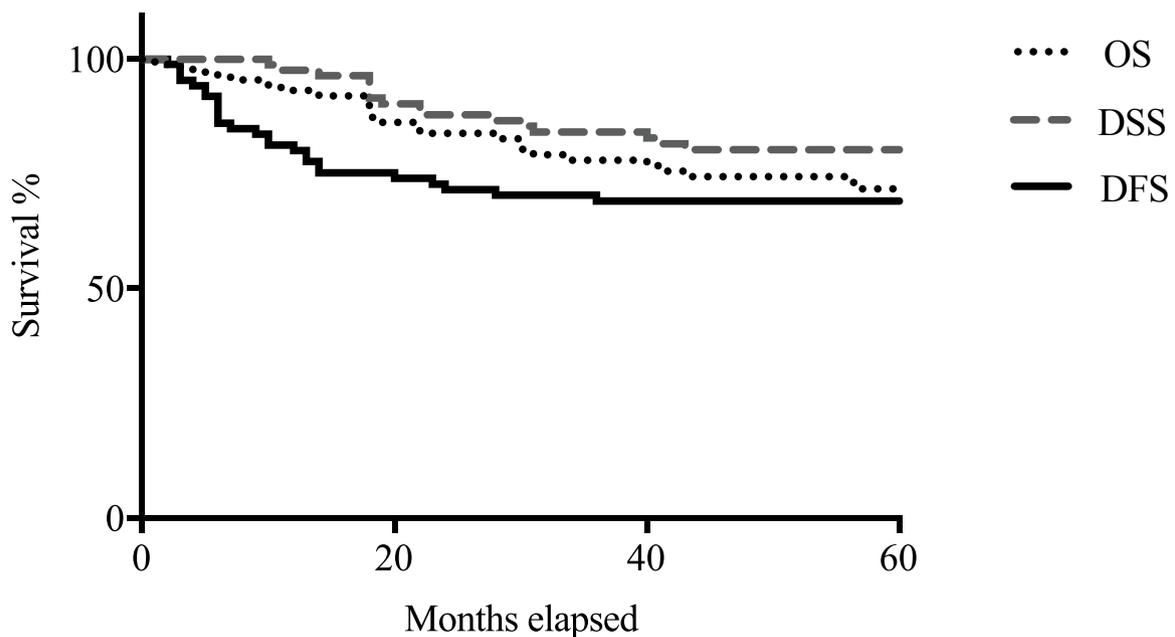


Fig. 1. Kaplan-Meier curve showing the overall survival (OS; 72%), disease-specific survival (DSS; 80%), and disease-free survival (DFS; 69%) of the study population at 5 years of follow-up.

Table 2. Univariate analysis of correlations between tumour-related parameters and disease specific survival.

Parameter	Correlation coefficient (<i>r</i>)	<i>P</i> -value ^a
Distant recurrence	1.0	<0.001*
Lymph node ratio	0.26	0.013*
Number of positive lymph nodes	0.28	0.008*
Size of lymph node metastasis	0.40	0.006*
Perineural invasion	0.37	<0.001*
Tumour grading	0.23	0.034*
Tumour size	0.11	0.328
Number of resected lymph nodes	0.14	0.194
Extranodal spread	0.15	0.166

^a Asterisks (*) indicate statistical significance.

grading, tumour size, and size of lymph node metastasis were not found to be independent risk factors.

Discussion

The prognosis of OSCC of the tongue is often uncertain and therefore difficult to predict^{23,27}. Long-term survival and a good response to treatment, as well as aggressive recurrence of the disease following curative treatment of the early stages are possible²⁸. Thus it is of great clinical importance to analyze patient and disease-specific factors in patient cohorts to identify possible risk factors allowing more precise prediction and prognosis of the disease. In the present study, 31% of patients suffered from a recurrence of the disease and more than half of them died within the first year after the recurrence was diagnosed. This is in line with the findings of other studies; however, a mor-

tality rate of up to 90% has been reported for patients experiencing a relapse^{4,29}.

Furthermore, this study supports the findings of a previous study in which it was found that the differentiation grade of OSCC could not be related to the presence of nodal metastasis or survival³⁰. A poor differentiation grade was found not to show any prognostic value concerning the outcome of OSCC of the tongue, floor of the mouth, or cheek³⁰. Thus, the predictive value of the differentiation grade determined by biopsy is considered to be poor.

Without a doubt, the presence of lymph node metastases is an important prognostic factor for head and neck cancer, as even the presence of one positive lymph node is considered to reduce OS by 50%^{6,31,32}.

Besides the number of positive lymph nodes, the LNR or LND has been shown to have prognostic value in a variety of cancer types, including head and neck

cancer^{17,20,21,33–35}. The benefit of calculating the LNR in cancer patients is seen in the fact that it accounts for the number of positive lymph nodes and the number of excised lymph nodes³⁶. The clinical significance of the LNR in patients with OSCC has been evaluated in a large collaborative study of 11 cancer centres across the globe²⁰. Patients with a higher LNR were identified as having worse OS and DSS, as well as a higher rate of loco-regional and distant disease recurrence compared to patients with a lower ratio, even when they had a similar N classification²⁰. Thus, it is concluded that the predictive value of the LNR is superior to the conventional N staging system²⁰.

Furthermore, the LNR has been reported as an independent risk factor for loco-regional recurrence and has been suggested to improve the diagnosis and therapy of affected patients^{23–25}. However, the methods differed between these studies. Safi et al. and Ong et al. included patients with negative cervical lymph nodes^{23,25}, whereas Lieng et al. did not²⁴. Against these findings, the present study, which included patients with negative lymph nodes, did not identify LNR as having an influence on loco-regional recurrence, but revealed an influence on distant recurrence, also reflecting DSS. From these data, the predictive value of LNR is not superior to the established N-classification. These data are in line with those of Roberts et al., who reported no prognostic significance of LNR, whereas the prognostic value of pN and AJCC

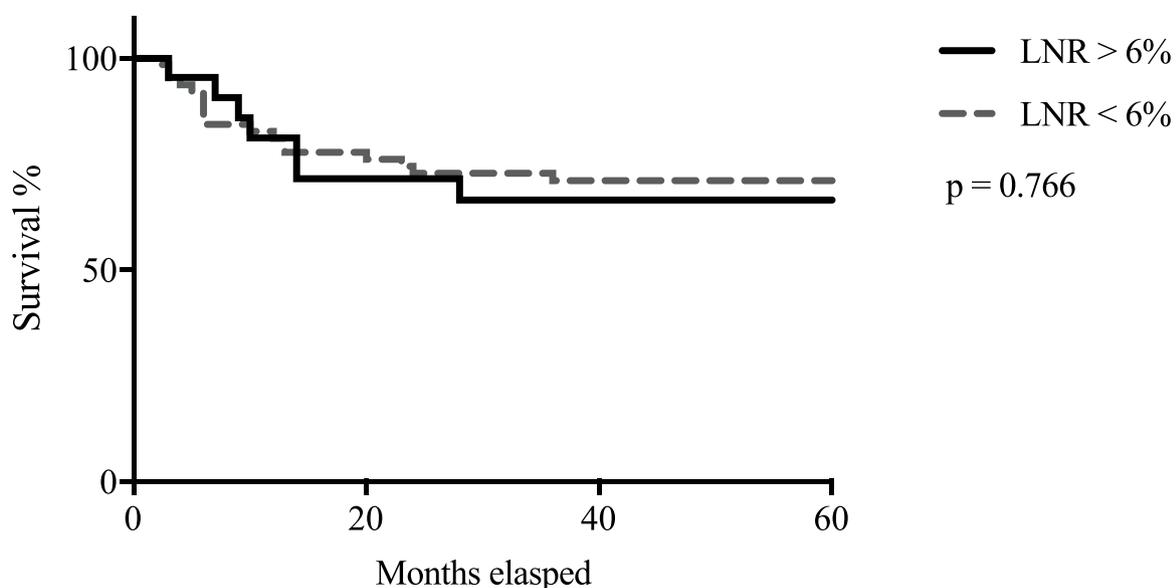


Fig. 2. Kaplan–Meier curve showing loco-regional recurrence at 5 years of follow-up. No difference was found between the two groups stratified by lymph node ratio (LNR $\geq 6\%$ and LNR $< 6\%$) ($P = 0.766$).

stage was confirmed in a cohort of 12,437 patients with head and neck squamous cell carcinoma³⁴.

Nevertheless, the determination of the LNR is potentially affected by surgical experience and technique, as well as by the processing of the pathological specimen, leading to important variability^{25,36}.

As well as investigating the potential prognostic value of LNR, this study also demonstrated the influence of perineural invasion on the prognosis of tongue cancer in the multivariate analysis. Perineural invasion, defined as a tumour involving at least 33% of the circumference of a nerve or the presence of tumour cells within the nerve sheath, was found in 14% of the study population, whereas rates of up to 52% have been reported in head and neck squamous cell carcinoma³⁷. The association between perineural invasion and cervical lymph node metastasis, high loco-regional recurrence, and poor survival rates has already been reported in previous studies^{38,39}.

Although tumour grading has already been reported as an independent prognostic factor for survival and to help in evaluating the risk of loco-regional recurrence, the present study data did not confirm these findings^{25,29}.

In this study, the LNR was found not to be a relevant prognostic factor in OSCC of the tongue. However, it is believed that the LNR could serve as a quality control for surgeons after neck dissection. Nevertheless, as this study did not indicate any prognostic value, the decision regarding adjuvant therapy should not be made solely on the basis of LNR.

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Ethical approval

Ethical approval was obtained from the local ethics committee of Zurich (KEK-ZH-Nr. 2013-0298).

Patient consent

Signed consent was obtained from all patients included in the study.

Competing interests

The authors declare that no competing interests exist.

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