

Prognosis of neutrophil-to-lymphocyte ratio in clinical early-stage tongue (cT1/T2N0) cancer

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Background: Inflammation plays a role in the development of cancer. This study aims to analyze the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and other clinicopathological determinants in early-stage (cT1/T2N0) tongue cancer.

Materials and methods: A total of 262 patients were selected from our institute's cancer database between 2004 and 2011. Optimal cutoff value of NLR and lymph node density (LND) were determined statistically using receiver operating characteristic curve analysis for survival prediction. The 5-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) rates were estimated using the Kaplan–Meier method.

Results: The results showed that, in this cohort, the optimal cutoff value of NLR was 2.95 and for LND, it was 0.031. Patients with NLR ≥ 2.95 correlated significantly with positive N classification ($P=0.011$), T2 classification ($P=0.007$), positive perineural invasion ($P<0.001$), and a tumor thickness of >5 mm ($P=0.005$). The 5-year OS among patients with NLR <2.95 was much higher than that in patients with NLR ≥ 2.95 ($P<0.001$). Similarly, the 5-year DSS among patients with NLR <2.95 was much higher than that in patients with NLR ≥ 2.95 ($P=0.002$). The 5-year DFS among patients with NLR <2.95 was much higher than that in patients with NLR ≥ 2.95 ($P=0.004$). The 5-year OS, DSS, and DFS were significantly reduced among patients with LND >0.031 compared to those with LND <0.031 , respectively. In multivariate analysis, NLR, LND, and tumor thickness were independent prognostic factors for OS.

Conclusion: Pretreatment NLR ≥ 2.95 is significantly correlated with a larger tumor, positive neck lymph node metastasis, and positive perineural invasion. Importantly, it indicates reduced survival rate. Therefore, if the NLR ≥ 2.95 in early-stage (cT1/T2N0) tongue cancer is noted preoperatively, it reveals more invasive tumor behavior clinically. Then, aggressive treatments, including elective neck dissection, become necessary.

Keywords: neutrophil-to-lymphocyte ratio, survival, oral cancer, neck lymph node metastasis, perineural invasion

Introduction

According to data released in 2012 by the International Agency for Research on Cancer, more than 300,000 new oral cancer cases were diagnosed worldwide.³⁹ The tongue remains the most common subsite for oral cavity tumors. The American Joint Committee on Cancer (AJCC) system, including preoperative T classification and N classification, is the standard tumor-staging system and is widely used internationally. Despite increased early diagnosis, even patients with T1/T2 stage tumors would show treatment failure. Previously, many studies focused on finding the prognostic factors among patients preoperatively, such as tumor thickness, biomarkers, neck nodal status, and lymph node density (LND).^{1–4}

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Although inflammatory cells are frequently found in tumor biopsies, the relationship between cancer and the immune system has been increasingly recognized over the past 30 years.^{5,6} The neutrophil-to-lymphocyte ratio (NLR) measures the status of systemic inflammation and may be readily calculated from white blood cell counts. The NLR was reported to be an independent prognostic factor for patients with various types of cancer, and a high NLR was associated with adverse outcomes of lung, esophageal, gastric, colorectal, hepatic, and pancreatic cancers.^{7–12} Recent studies have also shown a negative prognostic value of higher NLR among patients with head and neck cancer.^{13–18} However, there are no studies on the prognostic value of NLR in early-stage (cT1/T2N0) tongue cancer. In addition, the need for elective neck dissection for clinical T1/T2N0 oral cancer was debatable in the past, despite possibly increasing survival rate.¹⁹ Clinically, it would be worthwhile to study this issue because the inflammatory status and immune response may be different between advanced-stage tumors and early-stage tumors. Exploring the relationship between potential neck lymph node metastasis and NLR is also important in clinical practice. This study aims to identify the clinical significance of NLR and other clinicopathological variables in patients with early-stage (cT1/T2N0) tongue cancer.

Materials and methods

Patients

Between January 2004 and December 2011, 262 patients with newly diagnosed cT1/T2N0 tongue squamous cell carcinoma who had undergone surgery as primary treatment at the Department of Otolaryngology, Kaohsiung Chang Gung Memorial Hospital, Taiwan, were enrolled retrospectively in this study from our cancer database. We excluded patients with chronic hepatitis or human immunodeficiency virus and those who had undergone immunotherapy and steroid or interferon treatment within 3 months before surgery. Information about preoperation hematologic parameters was collected. The NLR value was calculated by dividing the neutrophil count by the lymphocyte count. The T classification, N classification, and TNM stage were classified according to the 2010 AJCC system. The postoperative pathological data included TNM staging, tumor thickness, LND, lymphovascular invasion (LVI), perineural invasion (PNI), or extranodal extension of lymph node (ENE). The LND was calculated by dividing the number of involved lymph nodes of the disease by the total number of lymph nodes removed. The adjuvant therapy with radiation or chemoradiation of tongue cancer was based primarily on the

guidelines of the National Comprehensive Cancer Network for oral cancer. Radiation dose was at least 6,000 cGy, and the chemotherapy was cisplatin based for adjuvant therapy. The study was approved by the Medical Ethics and Human Clinical Trial Committees at Chang Gung Memorial Hospital. Patients' consent to review their medical records was not required by these committees at this hospital because the patient data remained anonymous in this study.

Statistical analyses

The optimal cutoff values of NLR and LND were determined using receiver operating characteristic curve analysis for survival prediction and then Youden's index equation for the specific value. Survival of prognostic factors was estimated using the Kaplan–Meier method, and the log-rank test determined the heterogeneity due to the specific factor. Cox proportional hazards model tested the independence of primary factors with other prognostic factors in multivariate survival modeling. All tests were two sided, and statistical significance was set at 0.05. All statistical analyses were carried out using the Statistical Package of Social Sciences software, version 20.0 (SPSS, Chicago, IL).

Results

Of the 262 patients, 87% (228) were male and 13% (34) were female; the median age of diagnosis for all was 51 years, ranging from 24 to 85 years. The mean follow-up was 67.1 months (from 2 to 137 months); 101 patients (38.5%) had a tumor thickness of <5 mm, and the remaining 161 patients (61.5%) showed a tumor thickness of \geq 5 mm. PNI was found in 48 patients (18.3%), LVI in 30 patients (11.5%), and ENE in 17 patients (6.5%). The mean NLR was 2.18 (range: 0.6–7.0), and the mean LND was 0.0197 (range: 0–0.546). At the end of the study, there were 57 (21.8%) patients who had died, and of these, 32 (12.2%) had died of tongue cancer. Local/regional failure occurred in 45 patients (17.2%). See Table 1 for the detailed baseline clinicopathological features of the 262 subjects and their survival outcomes.

The optimal cutoff value for NLR was 2.95, and that for LND was 0.031 (Figure 1). Patients with NLR \geq 2.95 correlated significantly with positive N classification ($P=0.011$), T2 classification ($P=0.007$), positive PNI ($P<0.001$), and tumor thickness of >5 mm ($P=0.005$; Table 2). The 5-year overall survival (OS) for patients with NLR <2.95 was increased significantly compared with patients with NLR \geq 2.95 (86% vs 57.6%, $P<0.001$; Figure 2A). Similarly, the 5-year DSS for patients with NLR <2.95 was increased significantly compared with patients with NLR

Table 1 Clinicopathological characteristics and outcomes of 262 patients who were diagnosed with clinical early-stage tongue cancer (cT1/T2N0)

Factor	Number (%)
Gender	
Male	228 (87.0)
Female	34 (13.0)
Drinks alcohol	
No	182 (69.5)
Yes	80 (30.5)
Betel nut chewing	
No	69 (26.3)
Yes	193 (73.7)
Smoker	
No	64 (24.4)
Yes	198 (75.6)
T classification	
T1	149 (56.9)
T2	113 (43.1)
N classification	
N0	205 (78.2)
N+	57 (21.8)
Tumor thickness	
<5 mm	101 (38.5)
≥5 mm	161 (61.5)
PNI	
No	214 (81.7)
Yes	48 (18.3)
LVI	
No	232 (88.5)
Yes	30 (11.5)
ENE	
No	245 (93.5)
Yes	17 (6.5)
LND	
<0.031	218 (83.2)
≥0.031	44 (16.8)
NLR	
<2.95	214 (81.7)
≥2.95	48 (18.3)

Abbreviations: ENE, extranodal extension; LND, lymph node density; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; PNI, perineural invasion.

≥2.95 (90.4% vs 73.3%, $P=0.002$; Figure 2B). Moreover, the 5-year DFS for patients with NLR <2.95 was increased significantly compared with patients with NLR ≥2.95 (85.3% vs 67.7%, $P=0.004$; Figure 2C).

Regarding the LND, the 5-year OS (54.2% vs 86.2%), DSS (60.7% vs 92.8%), and DFS (54.1% vs 87.8%) were also significantly reduced (all $P<0.001$, Figure 3) among patients with LND >0.031 compared with those with LND <0.031. Other pathological factors, such as T2 classification, positive N classification, tumor thickness of ≥5 mm, positive PNI, and positive ENE, were all significant predictors of poor outcome for 5-year OS, DSS, and DFS (Table 3).

Patients who were betel nut chewers showed significantly reduced 5-year OS ($P=0.003$) and DFS ($P=0.009$) compared with those without this habit. In addition, patients who were smokers showed significantly reduced 5-year OS ($P=0.016$) and DSS ($P=0.035$) compared with nonsmokers (Table 3).

In multivariate analyses, NLR ≥2.95 was associated with reduced OS in early-stage (cT1/T2N0) tongue cancer (hazard ratio [HR]: 2.29, 95% CI: 1.32–3.96) and was adjusted by other independent factors, tumor thickness, and LND (Table 4). In the model, LND – another focusing prognostic factor in this study – had an HR of 2.57 (95% CI: 1.47–4.48) in LND ≥0.031 reference to LND <0.031 for reduced OS (Table 4). Both factors, NLR ≥2.95 and LND ≥0.031, were associated with reduced DSS (HR: 2.10, 95% CI: 1.00–4.40; HR: 5.15, 95% CI: 2.55–10.42) and DFS (HR: 1.91, 95% CI: 1.02–3.59; HR: 1.98, 95% CI: 0.94–4.17) after being adjusted by other factors (Tables 5 and 6). Tumor thickness of ≥5 mm, another independent factor in this model, was also related to poor outcome in OS (HR: 3.38, 95% CI: 1.48–7.72) and DFS (HR: 6.90, 95% CI: 2.08–22.91).

Discussion

In the current study of patients with early-stage (cT1/T2N0) tongue cancer, we observed 5-year DFS, DSS, and OS rates of 82.8%, 87.8%, and 78.2%, respectively. Multivariate analysis indicated that OS was determined mainly by tumor thickness, LND, and NLR. In our study, tumor thickness with a cutoff value of 5 mm appears to be one of the significant prognostic factors related to 5-year OS and 5-year DFS. Many previous studies have shown that tumor thickness is a major predictive factor for neck lymph node metastasis and is correlated with survival or local recurrence.²⁰ The tumor thickness is also found to be an independent predictor of the 5-year DSS in tonsillar cancer.²¹ Noninvasive tools for evaluating tumor thickness by MRI²² and ultrasound²³ have proven to reliably identify patients who are likely to have a worse clinical outcome at the time of diagnosis.

Currently, the presence of neck metastasis and extranodal extension of lymph nodes remain the most significant predictors of prognosis in oral cancer.^{24,25} Recent studies have shown that traditional clinical nodal staging alone may not reliably predict prognosis or direct treatment in patients with primary squamous cell carcinoma of the tongue.²⁶ The concept of surgical staging with regard to nodal disease is a critical strategy for a range of malignancies,²⁷ taking into account both the extent of surgical clearance and the true nodal disease burden. This forms the basis of LND as an

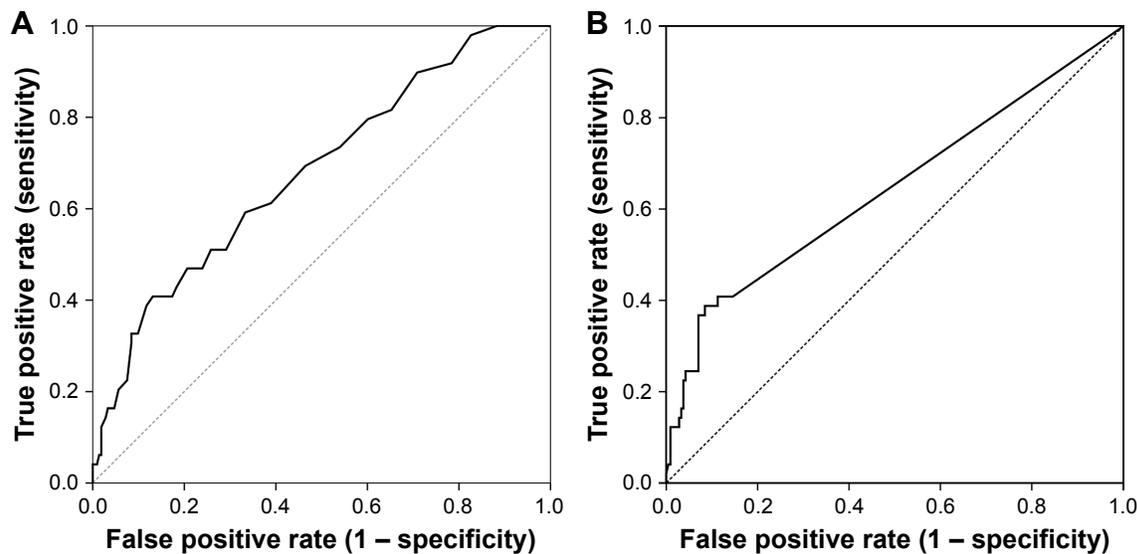


Figure 1 Receiver operating characteristic curve of (A) NLR and (B) LND for predicting the survival of early-stage tongue cancer patients with AUC equal to 68.1% and 86.9%, respectively.

Abbreviations: AUC, area under the curve; LND, lymph node density; NLR, neutrophil-to-lymphocyte ratio.

Table 2 Association analysis between NLR and other clinical/pathological factors

Factor	NLR		P-value
	<2.95	≥2.95	
Gender			0.913
Male	186	42	
Female	28	6	
Drinks alcohol			0.905
No	149	33	
Yes	65	15	
Betel nut chewing			0.041
No	62	7	
Yes	152	41	
Smoker			0.521
No	54	10	
Yes	160	38	
T classification			0.007
T1	130	19	
T2	84	29	
N classification			0.011
N0	174	31	
N+	40	17	
Tumor thickness			0.005
<5 mm	91	10	
≥5 mm	123	38	
PNI			<0.001
No	184	30	
Yes	30	18	
LVI			0.801
No	190	42	
Yes	24	6	
ENE			0.941
No	200	45	
Yes	14	3	
LND			0.092
<0.031	182	36	
≥0.031	32	12	

Abbreviations: ENE, extranodal extension; LND, lymph node density; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; PNI, perineural invasion.

important prognostic factor, as demonstrated by a number of studies in head and neck squamous cell carcinoma (HNSCC) (Table 7).^{28–35} However, no study until now has explored early-stage (cT1/T2N0) tongue cancer, which is frequently found clinically. The clinical impact of LND is different between advanced-stage and early-stage tumors. Our study confirms this data: 0.031 is much lower than those showed in Table 7.

In this study, we are the first to evaluate the value of LND in early-stage tongue cancer. Patients with LND >0.031 have significantly reduced OS, DSS, and DFS. This variable still remained significant for multivariate analysis in OS and DSS (Tables 4 and 5). In contrast, the conventional nodal staging system is inferior to LND in predicting OS, DSS, and DFS in current series noted by multivariate analysis.

In recent years, studies investigating the clinical significance of NLR in HNSCC have increased. It is believed that the white blood cell differential in HNSCC tends toward either a myeloid or a lymphoid lineage. The lymphoid preponderance was associated with better disease outcomes based on previous studies. Several studies found that higher NLR predicted reduced disease-specific survival and OS in HNSCC (Table 8).^{13–18} The prognostic value of NLR between early-stage and advanced-stage oral cancer is different. An NLR >1.9 in advanced oral cancer showed reduced DSS¹⁵ in our data, but 2.95 was much higher in the prognostic value of early-stage tongue cancer. In addition, the relationship between NLR and subsites of HNSCC was not thoroughly evaluated.

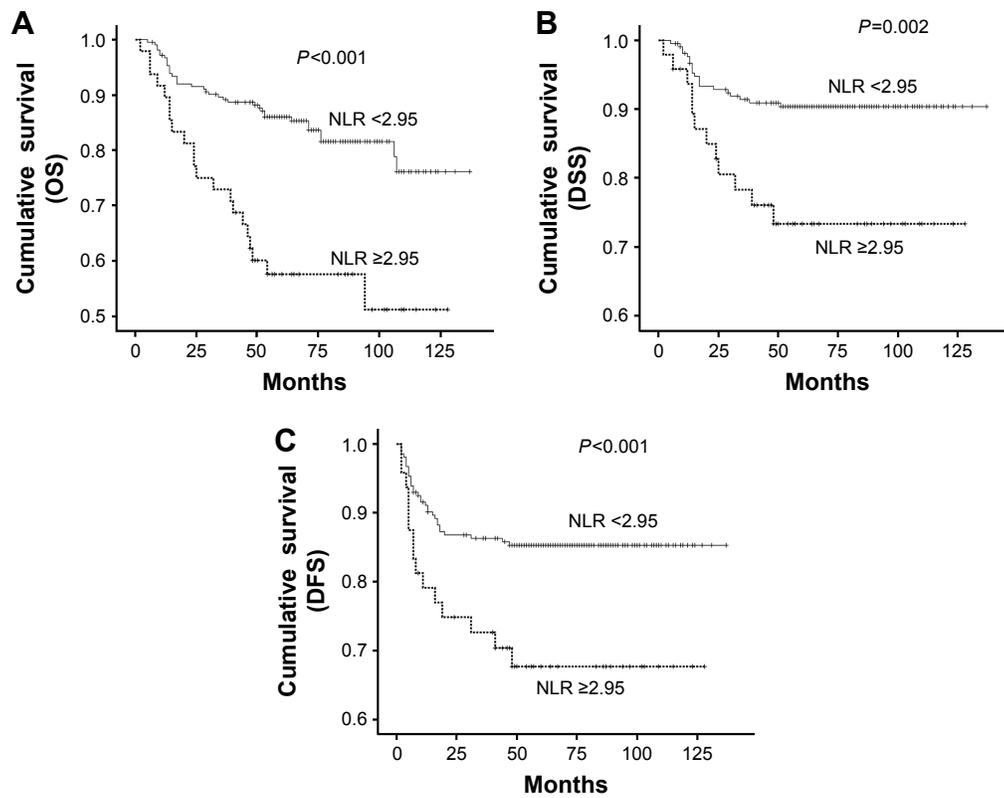


Figure 2 Kaplan–Meier analysis of patients with early-stage tongue cancer, by NLR with cutting in 2.95.

Note: (A) Overall survival, (B) disease-specific survival, and (C) disease-free survival.

Abbreviations: OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio.

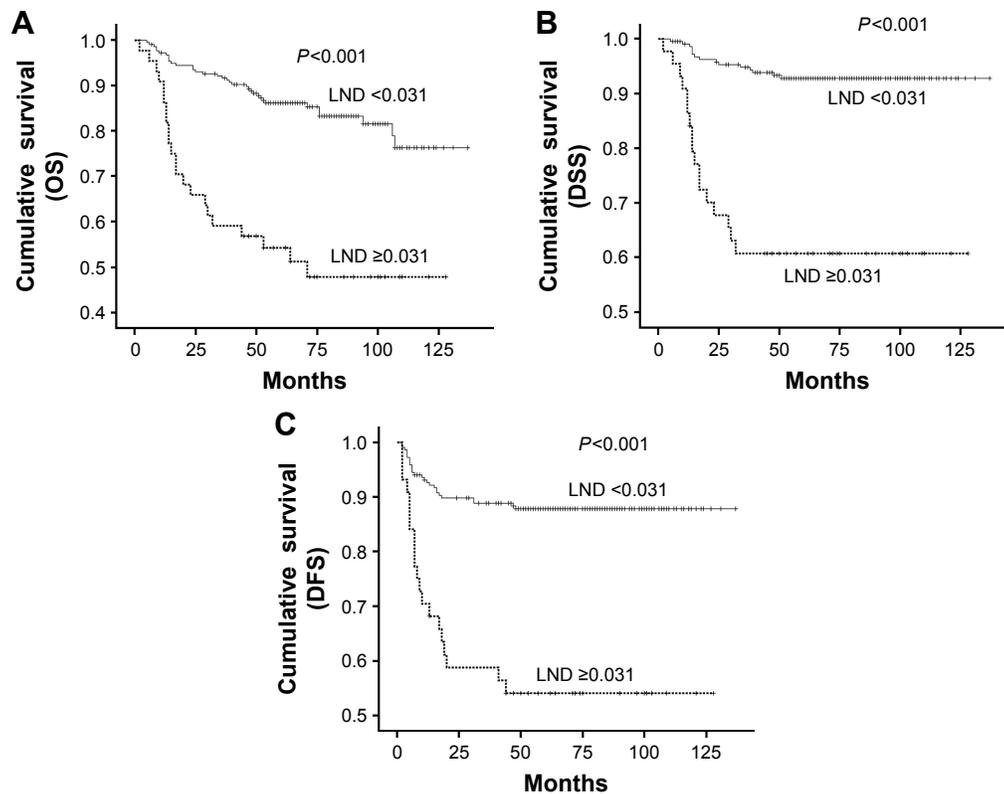


Figure 3 Kaplan–Meier analysis of patients with early-stage tongue cancer, by LND with cutting in 0.031.

Note: (A) Overall survival, (B) disease-specific survival, and (C) disease-free survival.

Abbreviations: OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival; LND, lymph node density.

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Table 3 Univariate survival analysis of prognostic factors

Factor	5-year OS	5-year DSS	5-year DFS
NLR	$P < 0.001$	$P = 0.002$	$P = 0.004$
<2.95	86.0%	90.4%	85.3%
≥ 2.95	57.6%	73.3%	67.7%
LND	$P < 0.001$	$P < 0.001$	$P < 0.001$
<0.031	86.2%	92.8%	87.8%
≥ 0.031	54.2%	60.7%	54.1%
T classification	$P < 0.001$	$P < 0.001$	$P < 0.001$
T1	88.2%	94.5%	90.5%
T2	70.9%	77.7%	71.0%
N classification	$P < 0.001$	$P < 0.001$	$P < 0.001$
N0	85.3%	92.3%	87.1%
N+	64.6%	69.8%	64.6%
Tumor thickness	$P < 0.001$	$P < 0.001$	$P < 0.001$
<5 mm	94.8%	100.0%	97.0%
≥ 5 mm	72.0%	79.3%	72.8%
PNI	$P = 0.001$	$P < 0.001$	$P < 0.001$
No	84.0%	91.8%	87.2%
Yes	65.9%	67.4%	59.5%
LVI	$P = 0.074$	$P = 0.043$	$P = 0.065$
No	88.4%	88.9%	83.8%
Yes	67.1%	74.7%	68.8%
ENE	$P < 0.001$	$P < 0.001$	$P < 0.001$
No	82.7%	89.8%	85.0%
Yes	52.9%	52.9%	41.2%
Drinks alcohol	$P = 0.078$	$P = 0.383$	$P = 0.15$
No	82.9%	88.6%	84.3%
Yes	76.0%	84.7%	77.2%
Betel nut chewing	$P = 0.003$	$P = 0.055$	$P = 0.009$
No	92.8%	94.1%	92.7%
Yes	76.5%	84.9%	78.3%
Smoker	$P = 0.016$	$P = 0.035$	$P = 0.10$
No	92.2%	95.1%	89.0%
Yes	77.1%	84.8%	79.9%

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; ENE, extranodal extension; LND, lymph node density; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PNI, perineural invasion.

Our result is comparable to these findings, showing that a high NLR is a poor prognostic factor in early-stage (cT1/T2N0) tongue cancer, although the cutoff value is different from that in previous studies. In our study, patients

Table 4 Multivariate analysis of prognostic factors for 5-year overall survival

Factor	Hazard ratio	95% CI	P-value
NLR			0.003
<2.95	1		
≥ 2.95	2.292	(1.326–3.962)	
LND			0.001
<0.031	1		
≥ 0.031	2.573	(1.476–4.487)	
Tumor thickness			0.004
<5 mm	1		
≥ 5 mm	3.383	(1.482–7.722)	

Abbreviations: LND, lymph node density; NLR, neutrophil-to-lymphocyte ratio.

Table 5 Multivariate analysis of prognostic factors for 5-year disease-specific survival

Factor	Hazard ratio	95% CI	P-value
NLR			0.048
<2.95	1		
≥ 2.95	2.106	(1.007–4.405)	
LND			<0.001
<0.031	1		
≥ 0.031	5.157	(2.551–10.427)	
T classification			0.006
T1	1		
T2	3.196	(1.39–7.352)	
LVI			0.036
No	1		
Yes	2.499	(1.06–5.892)	

Abbreviations: LND, lymph node density; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio.

with NLR > 2.95 have significantly reduced OS, DSS, and DFS that still remained significant on multivariate analysis (Tables 4–6). Interestingly, in our study, patients with NLR ≥ 2.95 correlated significantly with positive N classification, T2 classification, positive PNI, and a tumor thickness of > 5 mm. This means that patients with NLR ≥ 2.95 in early-stage (cT1/T2N0) tongue cancer show more aggressive tumor behavior, leading to dismal prognosis. This is a novel finding about the relationship between NLR and the pathological adverse features in oral cancer.

The possible mechanism of tumor aggressiveness may come from the inflammation itself, which contributes to cancer initiation and progression. The inflammatory microenvironment would induce genotoxic stress via multiple mechanisms, including reactive oxygen species and induction of activation-induced cytidine deaminase.³⁶ Inflammation's role in the development of lung cancer

Table 6 Multivariate analysis of prognostic factors for 5-year disease-free survival

Factor	Hazard ratio	95% CI	P-value
NLR			0.043
<3.0	1		
≥ 3.0	1.914	(1.02–3.595)	
LND			0.070
<0.031	1		
≥ 0.031	1.987	(0.946–4.171)	
Tumor thickness			0.002
<5 mm	1		
≥ 5 mm	6.909	(2.083–22.917)	
ENE			0.057
No	1		
Yes	2.371	(0.976–5.759)	

Abbreviations: ENE, extranodal extension; LND, lymph node density; NLR, neutrophil-to-lymphocyte ratio.

Table 7 Different studies about the lymph node density in head and neck cancer

Reference	Site	Case number	Cutoff for LND	5-year OS	5-year DSS	5-year DFS
Gil et al ²⁸	Oral cancer	386	0.06	58% vs 28%	65% vs 34%	–
Shrime et al ²⁹	Oral cancer	143	0.13	44.7% vs 16.1%	–	–
Kim et al ³⁰	Oral cancer	78	0.06	75% vs 38%	80% vs 47%	–
Amar et al ³¹	Oral cancer	182	0.06	–	–	44% vs 28%
Liao et al ³²	Oral cancer	148	0.048	66% vs 21%	78% vs 28%	75% vs 24%
Patel et al ³³	Oral cancer	4,254	0.07	49% vs 35%	60% vs 41%	–
Rudra et al ³⁴	HNSCC	38	0.2	79% vs 50%	–	89% vs 68%
Ong et al ³⁵	Tongue cancer	99	0.06	58% vs 47%	58% vs 48%	–
Our current study	Early tongue cancer	262	0.031	86% vs 54%	93% vs 61%	88% vs 54%

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; HNSCC, head and neck squamous cell carcinoma; LND, lymph node density; OS, overall survival.

Table 8 Different studies about neutrophil-to-lymphocyte ratio in head and neck cancer

Reference	Site	Case number	Cutoff for NLR	Outcome measurement
He et al ¹³	Nasopharyngeal carcinoma	1,410	1.54	OS and PFS
Fang et al ¹⁴	Oral cancer	226	2.44	OS and DFS
Perisanidis et al ¹⁵	Locally advanced oral cancer	97	1.9	DSS
Rassouli et al ¹⁷	HNSCC	273	4.27	DSS
Salim et al ¹⁸	Recurrent/metastatic HNSCC	79	2.93	DSS
Haddad et al ¹⁶	Locally advanced HNSCC	46	5	OS, MFS, LRRFS
Our current study	Early tongue cancer	262	2.95	OS, DSS, DFS

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; HNSCC, head and neck squamous cell carcinoma; LRRFS, local/regional relapse-free survival; MFS, metastatic-free survival; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression free survival.

from smoking is clear. In mice, smoking causes chronic inflammation by activating the nuclear factor-kappa B and mitogen-activated protein kinase pathways, consequently contributing to the formation of lung cancer.³⁷ Another example, circulating CD105, is recognized as a specific marker in ongoing angiogenesis related to tumor growth, and its expression was found to be elevated in inflammatory tissue. In our previous study, we proved that higher circulating CD105 promotes malignancy of cancer cells in oral cancer.³⁸ Importantly, in cancer patients, the neutrophil and/or lymphocyte counts forming NLR could be influenced by comorbid diseases, such as chronic inflammatory and autoimmune diseases, and by the intake of medications for immunodeficiency diseases, such as glucocorticosteroids and anti-inflammatory drugs. It is necessary to take notice of the above conditions before using NLR clinically.

Conclusion

Patients with early-stage (cT1/T2N0) tongue cancer and with NLR ≥ 2.95 show greater chance of aggressive clinicopathological adverse features, such as larger tumors, perineural invasion, and positive neck metastasis, leading to a reduced survival rate. If the NLR ≥ 2.95 in early-stage (cT1/T2N0) tongue cancer is noted, it should be treated as a very invasive tumor, and treatment should include elective neck dissection.

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Disclosure

The authors report no conflicts of interest in this work.

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