# Comparison of three lymph node staging methods for predicting outcome in patients with stage III-IV hypopharyngeal squamous cell carcinoma

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**Abstract**

Background: Lymph node ratio (LNR), log odds of positive lymph nodes (LODDS), and the number of postoperative lymph node staging (pN) are prognostic indicators of various cancers. However, comparison of the prognostic values of these indicators remains unclear in hypopharyngeal squamous cell carcinoma (HPSCC). This study aims to compare the prognostic values of LNR, LODDS and pN in stage III-IV HPSCC. Methods: We conducted a retrospective study on 166 patients with stage III-IV HPSCC. LNR and LODDS were divided into two groups using X-tile version 3.6.1. Univariate and multivariate analyses of the risk of overall survival (OS) and disease-free survival (DFS) were performed using the log-rank (Mantel-Cox) test and the Cox proportional hazards model, respectively. We compared the prognostic value of LNR with that of LODDS and pN using receiver operating characteristic (ROC) curves. Results: According to the X-tile, the cut-off values are 0.11 for LNR and -0.91 for LODDS. LNR, LODDS, and pN were significantly correlated with DFS by univariate analysis ($P < 0.05$). Multivariate analysis demonstrated that LNR was an independent prognostic factor for DFS ($P < 0.01$). Multivariate analysis also revealed that postoperative tumour staging (pT) classification, LNR, and surgical margins were independent prognostic factors for OS. Compared with pN and LODDS, LNR showed a stronger predictive power for DFS. Conclusion: LNR may be a better predictor for DFS than pN and LODDS in stage III-IV HPSCC patients. LNR in the highest tertile ([?] 0.11) may cause poor OS and DFS. LODDS in the highest tertile ([?]-0.91) may cause poor DFS.

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demonstrated that LNR was an independent prognostic factor for DFS ($P < 0.01$). Multivariate analysis also revealed that postoperative tumour staging (pT) classification, LNR, and surgical margins were independent prognostic factors for OS. Compared with pN and LODDS, LNR showed a stronger predictive power for DFS.

**Conclusion:** LNR may be a better predictor for DFS than pN and LODDS in stage III-IV HPSCC patients. LNR in the highest tertile ([?] 0.11) may cause poor OS and DFS. LODDS in the highest tertile ([?]-0.91) may cause poor DFS.

**Keywords:** hypopharyngeal squamous cell carcinoma, lymph node ratio, log odds of positive lymph nodes, prognosis.

key points:

1. We conducted a retrospective study on 166 patients with stage III-IV HPSCC.
2. aims to compare the prognostic values of LNR, LODDS and pN in stage III-IV HPSCC.
3. LNR in the highest tertile ([?] 0.11) may cause poor OS and DFS.
4. LODDS in the highest tertile ([?]-0.91) may cause poor DFS.
5. Compared with pN and LODDS, LNR showed a stronger predictive power for DFS.

## Introduction

HPSCC is one of the foremost head and neck cancers. The overall 5-year survival rate remains approximately 40%, with the occurrence of local and distant recurrences after treatment in a few cases(1). Although the tumor-node-metastasis (TNM) classification is a widely used prognostic factor for many solid tumors, the staging system has been reported to be associated with poor prognosis of patients with HPSCC(2). Furthermore, N status in the TNM system provides only limited prognostic information. In order to clarify which patients are more suitable for aggressive treatment to reduce mortality and recurrence rates. Improvements in the staging system and patient risk stratification, particularly for post-operative patients, are required..

Lymph node metastasis is a well-known prognostic factor for HPSCC. Most recent studies on the parameters include the total number of harvested lymph nodes (HLNs) and the number of positive lymph nodes (PLNs)(3, 4). Low values of the parameters, which are affected by the cervical lymphatic dissection technique, may result in misdiagnosis and eventually lead to an inaccurate treatment. The LNR, defined as PLNs /HLNs, is a better prognostic indicator. It also shows a better predictive potential because it combines the information on regional metastatic disease burden and type of cervical lymphatic dissection; thus, it accommodates the advantages of both parameters while bypassing their disadvantages (5, 6). Another index, the LODDS, defined as log (PLNs +0.5)/((HLNs- PLNs ) +0.5), is correlated with the prognosis of head and neck tumors as well (7). SIRI has been proved to have independent prognostic value in head and neck tumors(8). Our previous study also found that SIRI had a better predictive value than neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) in HPSCC patients.

Past research has found that LNR and LODDS staging may be superior to PLNs staging in patients with incomplete lymph node clearance because they are not significantly affected by the total number of LNs examined(9-14). LODDS has been used to predict the prognosis of several tumors, but there is little clinical evidence for the role of LODDS in HPSCC. For the first time, this study compared the predictive values of LNR, LODDS and PLNs for OS and DFS in stage III-IV HPSCC patients and revealed new parameters to improve the predictive power.

## Materials and methods

### Study design and patient selection

A total of 304 patients with complete medical records and pathologically confirmed primary HPSCC without secondary primary and distant metastatic lesions were recruited. All these patients were diagnosed and treated at the Eye, Ear, Nose and Throat Hospital of Fudan University, China, between January 1,

2003, and December 31, 2014.They were classified according to the American Joint Committee on Cancer (AJCC)/TNM-Union for International Cancer Control (UICC) Staging Classification, 7th edition. Of these 304 patients, 176 patients with pathological stages III-IV were selected. The exclusion criteria included : (1)patients who had undergone cervical lymphatic dissection, chemotherapy, or radiation therapy before surgical treatment; (2)ECOG score >1 ;(3) a chronic inflammatory condition, such as hepatitis B virus and hepatitis C virus, gastritis or nephritis;(4) aggressive inflammatory disease or co-infection; (5) an autoimmune disease or treatment with steroids; (6) hematological disease. Ultimately, 166 patients were included in the study analysis.

Follow-up and clinical endpoints

A follow-up of disease progression and time to death was performed on all patients by telephone and outpatient records every three months for the first two years and every six months until the end. The last follow-up visit was performed on January 10, 2018, and OS was recorded from the date of surgery until death. DFS was defined as the time between the start of therapy and tumor relapse (locoregional recurrence and/or distant metastases) or non-cancer causes of death.

Statistical Analysis

The optimal cut-off points of LNR and LODDS were determined using X-tile version 3.6.1 (Yale University), according to the highest Chi-squared value and lowest P-value in DFS. LNR and LODDS were categorized into two groups based on the results attained from X-tile. The SIRI was defined as (N*M)/L, where N, M, and L were the absolute count of neutrophils, monocytes, and lymphocytes obtained from the pretreatment blood test. The median determined the cut-off value for the SIRI, MLN, and HLN. OS and DFS curves were plotted according to the Kaplan–Meier method using SPSS (version 25.0) and were built with Graphpad Prism (version 8.0). Univariate and multivariate analyses for the risk of OS and DFS were performed using the log-rank (Mantel-Cox) test and the Cox proportional hazard models, respectively. A P-value of 0.05 (two-tailed) was considered statistically significant.

## Results

Patient Characteristics

The baseline patient clinical characteristics are described in**Table 1** . The median age of the patient population was 58 years (ranging from 38 to 81 years). Most of the patients were male (162, 97.6%). Of these 166 patients, 66.9% had a history of smoking, and 57.2% had a history of drinking. There were 7 patients (4.2%) in pT1 stage, 14 patients (8.4%) in pT2 stage, 91 patients (54.8%) in pT3 stage, and 54 patients (37.9%) in pT4. Furthermore, 7.2% of patients did not have pathological nodal involvement, while others had (46 for pN1, 88 for pN2, and 20 for pN3). More than half of the patients (123 patients, 74.1%) were diagnosed as stage IV at pathological diagnosis. The study included 135 (81.3%) patients with pyriform sinus carcinoma, 6 (3.6%) with postcricoid region carcinoma, and 25 (15.1%) with posterior pharyngeal carcinoma.

Patients had a median number of 15 (range from 1 to 71) resected lymph nodes, a median PLN number of 2 (range from 0 to 14), a median LODDS of -0.845 (range from -1.92 to 0.73) and the median LNR of 0.1 (range from 0 to 1). SIRI median value was 1.46 (range from 0 to 11.2). Moreover, 9.6% of patients (n=16) had pathology suggestive of the involvement of the thyroid gland. Most patients (n=118, 71.1%) received adjuvant therapy postoperatively.

Nodal status and cutoff value

We used X-tile to define the optimal cut-off points for LNR and LODDS. We extracted the points with the highest Chi-squared value and the lowest P-value. Taking DFS as the dependent variable, two categories were obtained for the LODDS values: patients with LODDS values lesser than -0.91 (n = 69, 41.5%), and patients with LODDS values exceeding -0.91 (n = 97, 58.5%). Patients with LODDS [?] -0.91 faced a 7.22 times higher risk of recurrence compared with those with LODDS <-0.91 ($P < 0.001$). The LNR values were divided into two categories using DFS as the dependent variable: patients with LNR values less than 0.11

(n = 91, 54.8%) and patients with LNR values more than 0.11 (n = 75, 45.2%). Considering the patients with LNR < 0.11 as the reference, patients with LNR [?]0.11 had a 6.63 times higher risk of recurrence (P <0.001).

Survival analysis

Using ROC curves, we compared the prognostic value of LODDS with that of LNR and pN. As shown in **Fig. 1** and **Table 2** the ROC curves corresponding to each parameter analyzed, taking OS as the dependent variable, pN displayed the highest area under the curve (AUC) (0.72, 95% CI: 0.64-0.8). While using DFS as the dependent variable, LNR demonstrated the highest AUC (0.712, 95% CI: 0.63-0.8). The results of the ROC analysis comparing the sensitivity and specificity of predicting survival indicated that LNR was the best predictor of DFS, outperforming pN and LODDS.

Using the Kaplan–Meier methodology, the estimated probability of DFS was found to be 78.7% at one year, 67.7% at three years, and 47.3% at five years. On the other hand, the estimated probability of OS was 80.7% at one year, 49.9% at three years, and 40.8% at five years. Regarding the treatment failure pattern, the rate of local failure was 8.4% (14/166), regional failure was 19.9% (33/166), combined local and regional failure was 7.8% (13/166), and distant failure was 20.5% (34/166) (**Fig. 2, 3)** .

In univariate analysis, the significant risk factors for OS were high pT classification (p=0.002), high LNR (p=0.031), margin (p<0.001), staging (p=0.047) and large tumor size (p=0.003) (Table 2). The significant risk factors for DFS were high SIRI value (p=0.019), high LNR (p<0.001), high LODDS (p<0.001), high pN classification (p=0.002), and staging (p=0.002) (**Table 3** ). In multivariate analysis, we found that LNR, pT classification, and surgical margins were significantly correlated with OS (P < 0.05). As shown in **Table 4** , LNR was significantly correlated with patient DFS (P = 0.001).

**Discussion**

HPSCC is one of the most common head and neck malignant tumours. Advanced HPSCC often results in death with local recurrence and distant metastasis within five years after treatment. Despite medical advances, the 5-year survival rate remains at approximately 40%(1). Some studies suggested that 80% of patients with HPSCC who underwent surgery at the initial diagnosis had pathology suggestive of neck metastases upon examination(15, 16). The local lymph node metastasis can increase the recurrence and mortality of HNSCC. Hence, the metastatic load of lymph nodes is one of the most important prognostic indicators of HNSCC(17-19).

The AJCC/ UICC tumor, node, metastasis (TNM) staging system is widely used for HPSCC, in which pN is described for the size, location, laterality, number, and extra-envelope invasion (ENE) of positive lymph nodes. However, it is vulnerable to the total number of surgically removed lymph nodes, for which we need improvement on the predictive risk stratification model(20). LNR, the ratio of MLN to HLN, is a surrogate mathematical marker affected by several factors, including the extent of cervical lymphatic dissection, the surgeon's cervical dissection technique, and the quality of pathologic evaluation(21). Multiple studies have validated the value of LNR in various tumors, including HPSCC, for predicting prognosis. However, a major limitation of LNR is that there is no corresponding discriminatory power for the ratio of 0 and 1. The predictive value of LODDS has been validated in various tumors (10, 11, 13, 14). LODDS distinguishes patients without positive lymph nodes by adding 0.5 to both positive and negative lymph nodes. Its predictive value in stage III and IV HPSCC has not been tested yet.

Several clinical studies have verified the predictive value of LNR in HPSCC. Yu and colleagues conducted a study involving 279 patients with HPSCC, where the subjects received pretreatment (radiotherapy/chemotherapy) before neck dissection. The multifactorial analysis showed that LNR was an independent predictor of prognosis(22). Another study of 81 patients with HPSCC suggested a better prognosis for pN1 with LNR < 0.1 and pN2 patients(23). A meta-analysis of stage III and IV LSCC and HPSCC suggested that LNR was a better prognostic indicator than pN(6). Our study has selected 166 patients with HPSCC who underwent primary lesion resection with cervical lymph node dissection at initial diagnosis, with or

without adjuvant therapy (radiotherapy/chemotherapy) after surgery. We set a cut-off value of 0.11 for LNR based on the patient's DFS. Patients with LNR [?]0.11 had significantly poorer OS and DFS values (P<0.05).

Patients with LNR values of 0 and 1 can be further risk stratified by LODDS, which has been shown to have a better predictive value for tumor prognosis than pN and LNR in oral squamous cell carcinoma(13), esophageal cancer(11), breast cancer(14), gastric cancer(12), bladder cancer(10), and colorectal cancer(9). However, studies in LSCC(24) and cervical squamous carcinoma (25) suggested LODDS was predictive of progression but did not provide any improved predictive performance over LNR, which is coherent with our findings. In our study, LODDS was associated with both OS and DFS, and a LODD [?]0.91 was associated with poorer DFS (P<0.001) but not with OS. We believe this is caused by the dataset only having 5 patients with an LNR value of 1 and 12 patients having an LNR value of 0, which does not allow display the true advantage of LODDS over LNR.

In our study, for the first time, we selected patients with stage III-IV HPSCC and verified the predictive value of LODDS. We also evaluated the predictive value of pN, LNR, and LODDS for advanced HPSCC and found that pN was a stronger predictor than LNR and LODDS for OS, and LNR was stronger than pN and LODDS for DFS. In the multivariate analysis, LNR showed a greater predictive value for DFS than pT, pStage, surgical margins, SIRI, and LODDS. Meanwhile, LNR, pT, and surgical margins all had independent predictive values for OS. In contrast to other studies, our study suggested that HLN [?]15 did not improve DFS. These contradictive findings may be related to the fact that our research came from a single center and was retrospective. Our study is also limited by a small clinical sample size with potential selection and recall bias. We expect multi-center, prospective studies to be available in the future.

## Conclusion

We evaluated the predictive value of LODDS in patients with advanced HPSCC, and LODDS [?] -0.91 was correlated with poorer DFS (p<0.001). We compared the predictive value of both ratios (LNR and LODDS) and pN for OS and DFS and did not find a greater predictive effect of LODDS over LNR and pN. Meanwhile, LNR provided a greater predictive value than pN and LODDS in predicting DFS.

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