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Evaluation of lymph node ratio and lymph node yield as prognosticators of locoregional recurrence in p16-associated oropharyngeal squamous cell carcinoma

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Abstract

Background: The prognostic value of lymph node yield (LNY) and lymph node ratio (LNR), or the ratio of number of metastatic LNs to total number dissected, has not been well established in p16-associated oropharyngeal squamous cell carcinoma (OPSCC).

Methods: This retrospective cohort study evaluated locoregional disease-free survival (LRDFS) in 82 patients with p16+ OPSCC who underwent neck dissection at a single institution from 2009 to 2017. LNR and LNY cutoffs were estimated using time-dependent receiver operator characteristic (ROC) curves. Prognostic significance of these cutoffs was compared with Eighth Edition AJCC Nodal Staging.

Results: An increased LNR 0.129 was associated with worse 2-year LRDFS (66.9% vs 96.8%, $P = .005$). LNY was not significantly associated with LRDFS ($P = .304$). An LNR-based risk model was a better prognosticator than Eighth Edition AJCC Nodal Staging (Harrell's C , 0.9065 vs 0.7668).

Conclusions: LNR has good prognostic utility in predicting LRDFS in p16+ OPSCC, but further evaluation of this measure is warranted.

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AUTHOR CONTRIBUTIONS

Swanson and Margaret Nurimba had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design were contributed by Nurimba and Swanson. Acquisition, analysis, and interpretation of data and drafting of the manuscript were contributed by Nurimba, Hines, Kokot, Swanson, and Sinha. Administrative, technical, or material support was contributed by Nurimba, Kokot, Swanson, and Sinha. Study supervision was done by Swanson.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords

HPV; lymph node ratio; lymph node yield; neck dissection; neck metastasis; oropharynx; p16

1 | INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC), especially when associated with high-risk human papillomavirus (HPV), is rapidly increasing in incidence globally.^{1,2} Locoregional spread of OPSCC is significantly associated with worse overall survival and increased recurrence. Observations that HPV-associated (HPV+) OPSCC have different survival outcomes than HPV-negative (HPV-) OPSCC led to the 2017 revision of the American Joint Committee on Cancer (AJCC) tumor, lymph node, metastasis (TNM) staging guidelines.^{3,4} Although this revision continued to account for adverse pathologic features such as extracapsular extension in HPV-OPSCC, classification of HPV+ OPSCC nodal stage in surgically managed patients is stratified by a number of pathologically positive lymph nodes, which does not account for the extent or quality of a surgical resection. Two proposed metrics to account for this are lymph node ratio (LNR) and lymph node yield (LNY).

LNY refers to the total number of dissected nodes in a surgical resection and has been studied as a quality metric for neck dissections.⁵ Several studies suggest that inadequate neck dissections are associated with increased recurrence risk and worse survival outcomes in oral cavity cancers^{6,7} and other head and neck cancers.^{8,9} These studies suggest that in patients treated with primary surgical resection, a minimal LNY of 15 to 18 nodes is associated with significantly improved survival outcomes,^{8,9} even in the setting of a pathologically node-negative neck.¹⁰ These findings may be attributed to an increased likelihood of detecting and removing cervical metastases with increased nodal yield.¹¹ However, studies on LNY in HPV-associated OPSCC are rare and may be less accurate as a majority of patients have historically been treated with primary radiotherapy,¹² which has been shown to decrease nodal yield compared to those patients who undergo surgery alone or adjuvant radiotherapy after surgery.¹³ In more recent years, the recognition of long-term adverse outcomes secondary to primary radiotherapy has led further exploration into the role of upfront surgery in OPSCC.^{14,15} As such, further work is needed to establish the role of LNY on survival and recurrence in patients with HPV-associated OPSCC in patients treated with primary surgical resection with adjuvant therapy.

Conversely, LNR, also known as lymph node density (LND), is the ratio of affected lymph nodes to total nodal yield (LNY) in a surgical resection. LNR incorporates both LNY and traditional lymph node staging and serves as a means to account for both number of pathologic lymph nodes and the quality of the extent of neck dissection with LNY. LNR has been shown to be useful prognostic indicators of survival outcomes for bladder,¹⁶ pancreatic,¹⁷ and stomach^{18,19} cancers. It has also been shown to serve as a prognostic factor for patients with thyroid and oral cavity head and neck cancers.^{20–24} Overall, these studies show that increased LNR significantly worsens overall survival and locoregional disease-free survival (LRDFS) in head and neck cancers. However, data regarding LNR in

the setting of OPSCC and HPV are limited and controversial. Some studies suggest that LNR is a robust prognosticator for both HPV+ and HPV–OPSCC^{25,26} while another suggest that LNR is only useful in HPV-negative OPSCC.²⁷ Additionally, a well-defined cutoff for LNR has yet to be well established in the setting of OPSCC when stratified for HPV status. Many studies evaluating LNR use cutoffs ranging from 0.06 to 0.10 as these cutoff values have previously been established in other head and neck cancers.^{24,28}

The primary aims of this study are to evaluate the impact of LNR and LNY on recurrence risk, establish cutoffs for LNY and LNR, and assess their capabilities as a prognosticator of recurrence compared with AJCC Eighth Edition Nodal Stage in the context of HPV+ OPSCC.

2 | METHODS

2.1 | Study design and patient selection

A retrospective chart review was performed to identify all patients with OPSCC at a single academic tertiary care center between January 1, 2009, and December 31, 2017 (n = 103). Patients who underwent primary surgical resection with concomitant unilateral or bilateral modified radical neck dissection with a minimum of 12 months of follow-up time were included in the study. Exclusion criteria were defined as prior radiotherapy for head or neck squamous cell carcinoma (HNSCC) (n = 8), unknown (n = 2), or negative p16 status (n = 11). Patients who underwent primary chemoradiation followed by surgical resection and neck dissection were excluded from the study. The University of Southern California Health Sciences Institutional Review Board approved this study (IRB HS-18-00768), with waiver of informed consent. All data were deidentified.

2.2 | Data collection

Demographic information including sex, age at the time of surgery, race, smoking history, alcohol use history, insurance type, and primary language were recorded. Records of past medical history included history of diabetes, cardiovascular disease, presence of pre-operative symptoms, and overall severity of comorbidities for each patient, which were scored using the Charlson Comorbidity Index (CCI). Patients were divided into three groups: mild, with CCI scores of 1–2; moderate, with scores of 3–4; and severe, with scores 5. Pathologic data were abstracted from medical records. HPV positivity was determined using p16 immunohistochemistry. Primary site tumor pathology included p16 status, tumor site, tumor grade, surgical margins, lymphovascular invasion (LVI), and perineural invasion (PNI). Of patients with pathologic neck metastasis (pN+), the number of positive nodes, the number of total nodes dissected, and extracapsular extension (ECE) were recorded. The LNR for each patient, defined as the number of positive lymph nodes divided by the total number of lymph nodes excised in each neck dissection, was retrospectively calculated using pathological data. During the study period of 2009 to 2017, postoperative pathological staging was performed according to the Seventh Edition of the AJCC TNM Classification System. As such, revised Eighth Edition AJCC TNM Classification was retrospectively applied for this analysis using pathology records. Follow-up data including the need for adjuvant chemotherapy and/or adjuvant radiation therapy, time to biopsy-proven

recurrence, location of recurrence, or death were collected. At our institution, decisions for adjuvant chemotherapy and/or radiation therapy were made in conjunction with the radiation oncologist, medical oncologist, pathologist, and radiologist. Indications for adjuvant therapy included any of the following: advanced tumor stage (T3 or T4), greater than one positive lymph node on neck dissection, or presence of at least one high-risk pathological feature including perineural invasion, lymphovascular invasion, or extracapsular extension.

2.2.1 | Validation of pathological data—Standardized operating procedures for collection of pathological data prior to this study were defined as follows. Lymph nodes were grossly identified in neck dissection samples and removed for individual microscopic analysis, with inclusion of adipose tissue made on a case-by-case basis. Lymph nodes with capsules were included in the count for LNY. Matted lymph nodes were estimated for total number of lymph nodes by the pathologist. As pathological data were generated by variable surgeons, pathology dissectors, and pathologists, a blinded pathology review of 25% of cases was performed (AJM) to ensure the data quality of LNR and LNY. Data from the blinded pathology review were compared with pathology reports to evaluate inter-reader consistency as a measure of data quality control. Blinded LNY and LNR were defined as concordant, or within the margin of error, if the absolute difference ($|$) between the values for the blinded and pathology review was less than the standard errors ($SE = SD/\sqrt{n}$) calculated for LNY (± 2 lymph nodes) and LNR (± 0.016) on the original pathology reviews.

2.3 | Study outcome measures

The primary outcome measures in this study were the association between LNR and LRDFS. LRDFS was defined as the number of months from the date of diagnosis to locoregional recurrence, defined as local recurrence or regional lymph node metastasis to the neck without evidence of distance metastasis. Patients who died or were lost to follow-up without recurrence were censored.

2.4 | Statistical analysis

Time-dependent receiver operator characteristic (ROC) curves and 95% confidence intervals were estimated using the inverse probability of censoring weighting method (IPCW)²⁹ and plotted to generate the integrated area under the curve (IAUC) over time. Univariate time-specific ROCs were generated based on the timepoint with the greatest AUC on the IAUC and subsequently analyzed to calculate cutoffs, sensitivities, specificities, and Youden indices³⁰ (J) and Euclidian distance (D). We assessed potential cutoffs using two different ROC-based models: (a) the Euclidian optimization model, which minimizes the Euclidian distance D from the curve to the upper left edge of the ROC diagram and (b) the Youden index model, which maximizes the distance from the curve to the chance line. Cutoffs identified by the Euclidian and Youden optimization models were compared with cutoffs previously established in the literature.

Stepwise Cox proportional hazards regression analysis was performed to identify significant covariates for each outcome of interest and subsequently controlled for on multivariate analysis. Only variables with less than 10% missing covariates were considered for the model. Variables were entered in the model if significant at an alpha of 0.25 and remained

in the model if significant at an alpha of 0.10. Survival curves were adjusted for significant covariates identified on multivariate analysis and plotted. The prognosticator ability of each risk model was assessed using Harrell's concordance statistics. Correlation analysis between LNR and histopathologic factors including Eighth Edition AJCC overall stage, nodal stage, tumor grade, extracapsular extension, perineural invasion, lymphovascular involvement, and margin positivity was performed using a bootstrapped model for Cramer V ordinal analysis.

Statistical analysis was performed using the IBM SPSS 24.3 software (SPSS Inc., Chicago, Illinois) and SAS University Edition 2.7 9.4 M5 (SAS Institute Inc., Cary, North Colorado).

3 | RESULTS

3.1 | Patient characteristics

Table 1 highlights baseline patient characteristics. A total of 82 patients with p16+ OPSCC were included in the study. The study cohort was 86.6% male with a median age of 58 years. Most patients were never smokers (56.1%) and had moderate (CCI 3–4, 57.3%) to severe (CCI 5, 31.7%) comorbid disease. On pathology review, most patients were staged T1 (34.1%) or T2 (59.8%) and N1 (54.9%) or N2 (28.0%) per Eighth Edition AJCC guidelines. The median number of positive lymph nodes was 2 (range 0–20), median LNY was 43 nodes (range 6–109), and median LNR was 0.044 (range 0–1). Most patients had stage I (61%) or stage II (34.1%) OPSCC. The median follow-up time after surgery was 29.4 months).

3.2 | Assessment of data quality

On blinded pathology review (Table S1), LNR fell within the margin of error in 85.7% ($n = 18$ of 21) of specimens, with those specimens out of the margin of error noted to have large lymph nodes with extracapsular extension or matted nodes within a nodal level. LNY fell within the margin of error in just over half of specimens (52.3%, $n = 11$ of 21).

3.3 | Estimation of LNR and LNY cutoffs

Univariate time-dependent IAUCs were constructed to assess the ability of LNR and LNY to predict locoregional recurrence (Figure 1A,C). Although LNR was a stronger predictor of locoregional recurrence (Harrell's $C = 0.7494$, $IAUC = 0.7564$) compared with LNY (Harrell's $C = 0.6172$, $IAUC = 0.6225$), there was significant overlap in confidence intervals between curves.

To determine optimal LNR cutoffs, we analyzed time-specific ROCs (Figure 1B,D) for LNR and LNY at the timepoint with the greatest AUC (14 months and 10 months, respectively) on the univariate time-dependent IAUCs. Evaluation of time-specific ROCs using the Euclidian and Youden optimization models (Table S2) resulted in a proposed LNR cutoff of 0.129 ($J = 0.782$, $D = 0.218$) and proposed LNY cutoff of 31 lymph nodes ($J = 0.750$, $D = 0.250$). Compared with the historical LNR cutoff of 0.10, our proposed LNR cutoff of 0.129 had similar sensitivity (100%) and better specificity (78.2% vs 71.8%). Our LNY cutoff of 31 nodes had better sensitivity (100% vs 0%) but worse specificity (75% vs 93.8%) compared with the historical cutoff of 18 nodes. However, as Euclidian and Youden

optimization models were concordant for both LNR and LNY, the proposed cutoffs of 0.129 for LNR and 31 nodes for LNY were utilized for risk stratification in this study.

3.4 | Impact of LNR and LNY on locoregional recurrence risk

A stepwise Cox proportional hazard regression analysis was performed to evaluate the impact of LNR and LNY on locoregional recurrence risk in the context of other relevant covariates. On univariate Cox proportional hazard regression analysis (Table S3), increased LNR ≥ 0.129 was found to be a significant covariate impacting recurrence risk ($P = .0092$) while decreased LNY < 31 nodes did not significantly impact recurrence risk ($P = .727$). Additionally, our univariate analysis found that each 0.05 increase in LNR was associated with a 10% increased risk locoregional recurrence (HR 1.106, 95% CI 0.974–1.257). Because of this, multivariate models were only constructed to evaluate overall LNR and an LNR cutoff of 0.129 compared to Eighth Edition AJCC pN-Classification (Table 2). In the LNR cutoff multivariate regression model, adjuvant therapy ($P = .066$) and LNR ($P = .005$) were identified to have the strongest impact on risk of locoregional recurrence. Similarly, in the Eighth Edition AJCC pN-Classification Model, nodal classification ($P = .032$) and lack of adjuvant therapy ($P = .094$) were risk factors for locoregional recurrence. An additional model was constructed to examine LNR as a continuous variable and found that after controlling for significant covariates, extracapsular extension ($P = .042$) and adjuvant therapy ($P = .048$) were significant risk factors for locoregional recurrence. In this model, each 0.05 increase in LNR was associated with a 16% increased risk of locoregional recurrence (HR 1.164, 95% CI 0.988–1.372).

3.5 | Relationship between LNR and LRDFS

Based on these Cox proportional hazard multivariate regression models, covariate-adjusted survival curves for N-stage and LNR cutoffs are plotted in (Figure 2). Locoregional recurrence hazard rates were significantly different based on Eighth Edition AJCC N-Classification ($P = .0301$) or LNR cutoff of 0.129 ($P = .005$). Two-year LRDFS (Table 3) was significantly worse in patients with LNR ≥ 0.129 compared with < 0.129 (66.9% vs 96.8%, $P = .0004$).

3.6 | Evaluation of an LNR cutoff risk model compared with N-classification risk model

Multivariate time-dependent IAUCs were developed to assess whether an LNR cutoff risk model could better predict locoregional recurrence compared with the Eighth Edition N-Classification Risk Model (Figure S1). Concordance statistics revealed that LNR (Harrell's C, 0.9065) was a better prognosticator of locoregional recurrence risk than Eighth Edition AJCC N-Classification (Harrell's C, 0.7668) when adjusting for all significant covariates. However, plotting of time-dependent IAUCS demonstrated that both models have wide overlapping confidence intervals.

3.7 | Correlation of LNR with histopathologic factors

Cramer V nominal correlation analysis between LNR and other histopathologic factors revealed that there was a significant correlation between LNR and ECE (Cramer V, 0.294; 95% CI, 0.114–0.456) and moderate correlations between LNR and other pathologic

features such as tumor grade and positive margins (Table S4). There was no association between LNR and LVI or PNI. LNR was strongly correlated with nodal stage (Cramer V, 0.816; 95% CI, 0.666-.951) and Eighth Edition AJCC Nodal Staging (Cramer V, 0.662, 95% 0.538–0.818).

4 | DISCUSSION

OPSCC represents a heterogeneous group of head and neck cancers with survival outcomes that have recently been further stratified by its association with HPV. Our data identified various risk factors and disease characteristics that are associated with LRDFS, particularly extent of nodal disease and adjuvant therapy. A major finding of our analyses is the significant association between LNR and LRDFS. Of all variables included in our analysis, increased LNR was the greatest risk factor for LRDFS, even compared with histopathologic high-risk features such as PNI, LVI, ECE, and positive margins. LNR < 0.129 was associated with significantly diminished risk for locoregional recurrence in p16+ OPSCC.

Many studies show that differences in survival outcomes can be attributed to demographic differences such as race/ethnicity, age, and gender^{31–33} or risk factors such as increased comorbid disease^{34,35} and smoking.^{36,37} Our study, however, was unable to detect significant differences in LRDFS outcomes based on race/ethnicity, age, gender, smoking, or comorbid disease. These differences could be because of our small sample size or selection bias as a tertiary academic center. Similarly, no significant differences were seen due to extent of comorbidities, which may be due to grouping of comorbidity scores and reporting bias that is inherent to a retrospective chart review of medical records documented by different care providers.

Consistent with other studies,^{3,4,38} our results showed that extensive nodal metastatic disease significantly impacts locoregional recurrence risk. Our analyses also found correlations between LNR and adverse pathologic features such as advanced N-stage, ECE, PNI, LVI, and positive margins, similar to a previous study of 809 patients with OPSCC.²⁴ Although pathologic features such as ECE, PNI, and LVI were associated with increased hazard ratios for DFS and LRDFS on our univariate Cox regression models, wide confidence intervals limit the generalizability of these conclusions. This may be due to small sample size and inclusion of heterogeneous adjuvant therapy regimens.

Our study found that each increase in nodal yield by one lymph node was associated with a 2.3% diminished risk of locoregional recurrence, similar to a study of LNY in oral cavity carcinoma.³⁹ However, no association was found between a LNY cutoff of 31 nodes and LRDFS, contrary to other studies in the literature that found that diminished nodal yield significantly impacts survival outcomes and locoregional recurrence risk.^{6–9} Like other high-volume academic centers,⁶ our median LNY in this study was 43 nodes. Given that this is substantially higher than other proposed LNY cutoffs of 15 to 18 nodes,^{6–9} we did not expect to find a significant effect of LNY on LRDFS outcomes. Additionally, we were unable to tease out any further associations between LNY and LRDFS in N0 patients due to small sample size but believe that this remains a topic that is poorly addressed in OPSCC literature. Finally, similar to a study of LNR and LNY

that demonstrated significantly different LNYs with introduction of a pathologist technician to aid in macroscopic identification of lymph nodes prior to microscopic examination by pathologists,⁹ the poor concordance between our blinded review and pathology reports highlights that significant inter-reader variation in pathological analyses of neck dissection specimens poses a barrier to utilizing LNY as a prognostic factor.

A count of positive lymph nodes is currently utilized in the Eighth Edition AJCC Nodal Classification guidelines for HPV+ OPSCC³ due to its ability to better reflect survival, others argue that LNR more adequately measures prognosis as it accounts for the number of positive lymph nodes as well the extent and quality of a surgical neck dissection. Our study adds to the growing body of literature that suggests that LNR is a robust prognosticator for locoregional recurrence in OPSCC. Although an LNR cutoff of 0.129 was greater than other cutoff previously established in other studies for OPSCC stratified by HPV status,^{21,26} this cutoff was similar to a study of oral cavity carcinomas that determined that a cutoff of 0.13 was useful in stratifying patients as high-risk for decreased survival.⁴⁰ Our study is the first to utilize time-dependent ROC analysis to generate a LNR cutoff, as suggested by Iocca et al,⁴¹ and suggests that this LNR cutoff may be a better prognosticator for locoregional recurrence compared with Eighth Edition Nodal Classification. However, as this cutoff was determined using the LRDFS data available at our institution, this cutoff is not generalizable to overall survival and disease-free survival.

Given that many OPSCC patients undergo primary chemoradiation, the prognostic value of LNR established in this study is relevant only for the subset of patients that are treated with upfront surgery. As we did find that adjuvant therapy significantly decreased the risk of locoregional recurrence, it remains to be determined whether LNR may be able to guide adjuvant therapy and cancer surveillance decisions with larger scale studies. Finally, as highlighted by discordant results in 14.3% of specimens within our blinded pathology review, we acknowledge that this metric may not be particularly useful in patients with matted bulky lymphadenopathy that replaces most of a nodal station or spans multiple nodal stations, for whom discrete numbers of positive nodes to total nodal yield is difficult to establish. In these cases, we argue that clinicians should factor metrics such as gross ECE into their clinical decision making for adjuvant therapy. As such, further population-based studies evaluating the impact of LNR on recurrence and survival outcomes in the context of OPSCC and HPV status are warranted. It is important to note that variations in technique and quality, both from surgical and pathological analysis standpoints, can pose barriers to larger, multicenter studies on LNR. Nevertheless, efforts to design controlled, prospective studies should be intensified.

Limitations of this study include those inherent to a retrospective cohort study, including small sample size and selection bias. Other limitations include incomplete follow-up data and inclusion of heterogeneous tumor subsites and stages as well as diversified adjuvant radiotherapy and chemotherapy regimens. Because our institution is a tertiary academic center, surgical consultations do not necessarily follow up in-network, impacting our sample size and available follow-up length. Similarly, as most recurrences occur within a year of diagnosis, more complete follow-up data are needed to better understand the impact of LNR on delayed recurrence rates and overall survival.

5 | CONCLUSIONS

At our institution, increased LNR 0.129 was associated with significantly worse LRDFS and served as a robust predictor of locoregional recurrence. Furthermore, largescale studies of LNR and LNY in the context of HPV-associated OPSCC are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

A, Time-dependent area under the curve, and B, time-specific receiver operator curve at 14 months depicting the ability of lymph node ratio to predict locoregional recurrence. C, Time-dependent area under the curve, and D, time-specific receiver operator curve at 10 months depicting the ability of lymph node yield to predict locoregional recurrence

FIGURE 2.

Risk-adjusted survival curves depicting locoregional disease-free survival as stratified by A, Eighth Edition AJCC Nodal Classification and B, LNR cutoff of 0.129

TABLE 1

Patient baseline characteristics

Age, years	Tumor location, no. (%) of patients	
Mean $\pm$ SD	60.1 $\pm$ 10.9	Tonsil 37 (45.1)
Median (range)	58 (37–89)	BOT 29 (35.4)
Sex, no. (%) of patients		Overlapping sites 16 (19.5)
Male	71 (86)	Tumor size (cm)
Female	11 (13)	Mean $\pm$ SD 2.66 $\pm$ 1.22
Race, no. (%) of patients		Median (range) 2.7 (0–5.9)
White	59 (72)	Tumor grade, no. (%) of patients
Hispanic/Latino	7 (9)	G1/GX 6 (7.3)
Black	8 (10)	G2 44 (53.7)
Asian/Other	8 (10)	G3 32 (39.0)
Smoking status, no. (%) of patients		Margins, no. (%) of patients
Current	5 (6)	Yes/inconclusive 18 (22.0)
Former	27 (33)	No 64 (78.0)
Never	46 (56.1)	PNI, no. (%) of patients
Unknown	4 (4.9)	Yes 37 (45.1)
Alcohol use, no. (%) of patients		No/unknown 45 (54.9)
Never	31 (37.8)	LVI, no. (%) of patients
Current	42 (51.2)	Yes 32 (39.0)
Former	3 (3.7)	No/unknown 50 (61.0)
Unknown	6 (7.3)	Positive nodes, no. (%) of patients
CCI, no. (%) of patients		Mean $\pm$ SD 3.6 $\pm$ 4.2
Mild (1, 2)	9 (11)	Median (range) 2.0 (0–20)
Moderate (3, 4)	47 (57.3)	LNY
Severe (5)	26 (31.7)	Mean $\pm$ SD 45 $\pm$ 19
Adjuvant therapy, no. (%) of patients		Median (range) 43 (6–109)
Radiotherapy	30 (36.6)	LNR
Chemoradiotherapy	27 (32.9)	Mean $\pm$ SD 0.103 $\pm$ 0.149
None	25 (30.4)	Median (range) 0.044 (0–1)
Follow-up time, months		ECE, no. (%) of patients

Mean ± SD	29.4 ± 22.3	Yes	33 (40.2)
Median (range)	24.2 (12.4–90.2)	No/unknown	49 (59.8)
Eighth Edition AJCC Classification/Staging			
pT-Class		pN-Class	
T1/TX	28 (34.1)	N0	14 (17.1)
T2	43 (52.4)	N1	45 (54.9)
T3	9 (11.0)	N2	23 (28.0)
T4	2 (2.4)		
pM-Class		TNM Staging	
MX/M0	81 (98.8)	I	50 (61.0)
M1	1 (1.2)	II	28 (34.1)
		III	3(3.7)
		IV	1 (1.2)

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; ECE, extracapsular extension; LNR, lymph node ratio; LNY, lymph node yield; LVI, lymphovascular invasion; PNI, perineural invasion; pM-Class, Pathologic Metastasis Classification; pN-Class, Pathologic Nodal Classification; pT-Class, Pathologic Tumor Classification; TNM, Tumor/Nodal/Metastasis Staging.

TABLE 2

Stepwise multivariate Cox proportional hazards regression analysis for risk factors of locoregional recurrence in p16-associated OPSCC

LNR					
<i>Variable</i>	n = 82				
LNR					
Each 0.05 increase	1.164	0.988	1.372		0.069
ECE					
ECE vs none	6.164	1.068	35.714		0.042*
Adjuvant therapy					0.048*
Radiation vs none	0.254	0.041	1.575		0.254
Chemoradiation vs none	0.076	0.008	0.703		0.076
LNR cutoff model					
<i>Variable</i>	[HR]	95% CI			n = 82 <i>P</i> -value
LNR					
<0.129 vs 0.129	0.047	0.006	0.391		0.005*
Adjuvant therapy					0.066
Radiation vs none	0.265	0.048	1.469		0.127
Chemoradiation vs none	0.094	0.010	0.853		0.036*
AJCC pN-Class model					
<i>Variable</i>	[HR]	95% CI			n = 82 <i>P</i> -value
pN-Class					0.032*
N1 vs N0	0.457	0.028	7.576		0.584
N2 vs N0	6.024	0.026	62.632		0.108
N2 vs N1	13.158	1.498	111.111		
Adjuvant therapy					0.094
Radiation vs none	0.331	0.059	1.855		0.209
Chemoradiation vs none	0.098	0.011	0.913		0.041*

Abbreviations: AJCC, American Joint Committee on Cancer; ECE, extracapsular extension, LNR, lymph node ratio, pN-Class, Pathologic Nodal Classification.

TABLE 3

Lifetables depicting impact of increased LNR on LRDFS

Month	LNR < 0.129				LNR 0.129			
	Locoregional recurrence (n)	Number at risk (n)	LRDFS		Locoregional recurrence (n)	Number at risk (n)	LRDFS	
0	0	61	1.000		0	21	1.000	
4	0	57	1.000		0	21	1.000	
8	0	51	1.000		2	19	0.905	
12	0	45	1.000		2	17	0.905	
16	0	35	1.000		4	12	0.795	
20	1	30	0.968		5	11	0.736	
24	1	28	0.968		6	10	0.669	

Abbreviations: LNR, lymph node ratio; LRDFS, locoregional disease-free survival.