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The Logarithmic Ratio of Positive Lymph Nodes Predicts Survival in Patients with Larynx Squamous Cell Carcinoma

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Abstract

BACKGROUND/AIMS: The Lymph node staging system provides significant information for laryngeal squamous cell carcinoma (LSCC) prognosis. Additional parameters are suggested in order to improve the prognostic capacity of lymph node staging. This study aimed to investigate the prognostic value of different lymph node staging methods.

MATERIALS AND METHODS: The long-term survival data and pathological features of fifty-two patients with LSCC were obtained retrospectively. The effects of metastatic lymph node count (MLNC), metastatic lymph node ratio (MLNR), and the logarithmic ratio of positive lymph nodes (LODDS) on disease-free survival (DFS), disease-specific survival, and overall survival (OS) were analyzed. Significant cut-off values for MLNR and LODDS were calculated using receiver operating characteristic analysis. In addition, Kaplan-Meier survival analysis with log-rank was used for comparisons of nodal disease-related study groups.

RESULTS: Cancer recurrence was similar between the groups by T-stage (0.963), N-stage (0.935), MLNR groups (0.297), and LODSS groups (0.244). However, the recurrence rate was significantly lower in tumors with a severe lymphoid response (0.004) and with a total dissected number of lymph nodes ≥18 (0.037). Total lymph node count (0.303), total MLNC (0.768), MNLR (0.656), and LODDS (0.356) values were similar in those patients with and those without cancer recurrence (p>0.05). No significant cut-off value was detected for either DFS or OS for MLNR or LODDS values (p=0.672, area under the curve (AUC): 0.672, 95% confidence interval (CI): 0.365-0.706; p=0.352, AUC: 0.578, 95% CI: 0.411-0.746; p=0.450, AUC: 0.615, 95% CI: 0.222-1; p=0.450, AUC: 0.615, 95% CI: 0.230-0.999, respectively).

CONCLUSION: MLNR and LODDS were significant in improving the prognostic value of TNM staging in LSSC.

Keywords: Larynx squamous cell carcinoma, metastatic lymph node ratio, the logarithmic ratio of positive lymph nodes

INTRODUCTION

Squamous cell carcinomas of the larynx (LSCC) are the most common type of head and neck carcinoma which begins from the squamous epithelium of the larynx.[1] The primary treatment is surgery, but there are treatment options which combine surgery with radiotherapy or radio-chemotherapy. The tumor, lymph node, metastasis (TNM) staging system in 8th edition of the American Joint Committee on Cancer (AJCC) defined the N-stage as the status of the lymphatic field which determines the patient's prognosis.[2] Since this cancer has an occult

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course, more than half of the patients are in advanced stages when they are diagnosed.[3] LSCC predisposes to metastasis of the neck lymph nodes, which has a significant impact on survival.[4] Thus, the status of lymph node involvement is recognized as a known prognostic factor in LSCC.[5] However, evaluating N status alone in the TNM system does not cover all dimensions in prognostic evaluation. Therefore, it is clear that stronger parameters are required over time to make the prognostic adequacy of N-status more meaningful. It has recently been reported that in those patients with lymph node-positive head and neck cancer, surgically removing fewer than 18 lymph nodes is associated with a poor prognosis.[6] In addition, an N-staging by the count of metastatic lymph nodes (MLNC) has been discussed instead of the AJCC N system.[7,8] A more recent recommendation is the metastatic lymph node ratio (MLNR), which is defined as the ratio of MLNC to total lymph node count (TLNC).[7-12] Many recent study results indicate that MLNR should be considered in determining survival. Consequently, it seems to be quite a strong new prognostic parameter. It has been shown that the log-odds value of positive lymph nodes (LODDS) can be beneficial in determining the prognosis of various solid cancers.[13,14] However, it is unclear which lymph node classification system might better predict prognosis for LSCC patients than the current AJCC system.

This study aimed to investigate the predictive effects of MLNC, MLNR and LODDS classifications on survival in LSCC patients.

MATERIALS AND METHODS

A retrospective study was designed by reviewing archive records. Patients with a definitive diagnosis of LSCC who had undergone laryngectomy at a tertiary referential hospital between April, 2008 and December, 2020 were identified. Ethics committee approval was obtained before this study was carried out from the affiliated İzmir Katip Çelebi University (approval number: 0539, date: 24.11.2022).

Eligibility criteria: Those patients who had undergone a total laryngectomy and neck dissection were included in this study. Patients with previous neck dissection or laryngeal surgery, radiation therapy, multiple primary lesions, stage 4C, residual tumor after surgery or closed surgical margin to the tumor, or those followed up for <1 year after surgery were excluded from this study. Finally, a total of 52 patients who met the eligibility criteria were included in this study. The pathological specimens of the selected patients were re-evaluated histopathologically. Patients who were lost during follow-up visits or those deceased with perioperative complications were not included in the final analysis. The socio-demographic data of the patients (e.g. age, gender, smoking habits etc.) and follow-up information (e.g. visit times, recurrence, or death) were recorded. The recurrence rate, overall survival (OS) rate, time to recurrence, and the rate of tumor-related mortality loss were also determined. Localization, T-stage, grade of the tumor, perineural and lymphovascular invasion, lymph node status, and surgical margins were examined in the pathology specimens. Inflammatory response to tumor (TILs) was scored as follows: 0=absent, 1=mild, 2=moderate, and 3=prominent and evaluated separately. Additionally, ipsilateral or contralateral nodes, TLNC, MLNC and MLNR were recorded. Four groups were identified for MLNR as follows: MLNR=0 as group 1, 0< MLNR ≤0.199 as group 2, 0.2≤ MLNR ≤0.39 as group 3, and MLNR ≥0.4 as group 4. Also, five groups were identified for LODDS; LODDS ≤-1.5 as group 1, -1.5< LODDS ≤-1.0 as group 2, -1.0< LODDS ≤-0.5 as group 3, -0.5< LODDS ≤0 as group 4, and LODDS >0 as group 5 (no patients were included in group 5 as none were seen).[15]

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 program (IBM Corp., Armonk, NY, USA). Nominal variables between groups were compared with χ^2 test. The normality distribution of scale variables was evaluated by Kolmogorov-Smirnov test and the Mann-Whitney U test was performed to compare recurrence groups (non-parametric distribution). The cut-off values for MLNR and LODDS were determined by receiver operating characteristic (ROC). Kaplan-Meier survival analysis and log-rank comparisons were performed in the nodal disease-related classification groups.

RESULTS

Within the scope of this study, 52 patients from 65 advanced LSCC patients were enrolled in the final analysis according to the eligibility criteria. The average age of the patients was 60.1±8.7 years, with 3 (5.8%) female and 49 (94.2%) male patients. During the mean follow-up period of 42.7±29.6 (minimum: 1, maximum: 84) months, 18 patients (34.6%) developed cancer recurrence, and 4 (7.7%) died. The numbers of ipsilateral, contralateral and bilateral TLNCs were 55 (median, range, 17-107), 58 (median, range, 30-87), and 52 (median, range, 36-157) respectively. The count of ipsilateral and contralateral and bilateral MLNCs were 2 (range, 0-5), 1 (range, 1-3), and 5 (range, 1-10) respectively. MLNR was 0.039±0.082 on average and the highest number of patients (n=26, 50.0%) were included in the group of MLNR group 2 (0.01-0.19). LODDS was -1.600±0.525 on average and the highest number of patients (n=33, 63.5%) were included in the group of MLNR group 1 (≤-1.5). A general summary of the findings is given in Table 1. No statistically significant group was found in terms of cancer recurrence in the T-stage (0.963), N-stage (0.935), MLNR groups (0.297), or LODSS groups (0.244). However, the recurrence rate was significantly lower

Table 1. An overall summary of findings

		Count	Column (n, %)
Gender	Male	49	94.2%
	Female	3	5.8%
Smoking status	No	3	5.8%
	Yes	49	94.2%
T-stage	T3	20	38.5%
	T4	32	61.5%
N-stage	0	24	46.2%
	1	10	19.2%
	2A	2	3.8%
	2B	8	15.4%
	2C	6	11.5%
	3	2	3.8%
Neural Invasion	None	45	86.5%
	Present	7	13.5%
Vascular Invasion	None	40	76.9%
	Present	12	23.1%
Lymphoid response	None	12	23.1%
	Mild	12	23.1%
	Moderate	15	28.8%
	Severe	13	25.0%

Table 1. Continued

		Count	Column (n, %)
Lateralization of nodal metastasis	None	24	46.2%
	Ipsilateral	20	38.5%
	Contralateral	4	7.7%
	Bilateral	4	7.7%
Lymph node metastasis	None	24	46.2%
	Present	28	53.8%
TLNC	<18	3	5.8%
	≥18	49	94.2%
Distant metastasis	None	38	73.1%
	Present	14	26.9%
Recurrence	None	34	65.4%
	Present	18	34.6%
Survival	Ex	4	7.7%
	Survive	48	92.3%
Post-op RT	None	7	13.5%
	Present	45	86.5%
Post-op CT	None	31	59.6%
	Present	21	40.4%
MLNR groups	1.00	24	46.2%
	2.00	26	50.0%
	3.00	1	1.9%
	4.00	1	1.9%
LODDS groups	1.00	33	63.5%
	2.00	12	23.1%
	3.00	5	9.6%
	4.00	2	3.8%
	Mean ± SD	**Minimum**	**Maximum**
Age	60.12±7.71	38.00	83.00
Right neck TLNC	27.33±14.46	0.00	54.00
Right neck MLNC	0.71±1.40	0.00	6.00
Left neck TLNC	32.04±20.45	0.00	127.00
Left neck MLNC	0.75±1.51	0.00	8.00
TLNC (right and left)	59.37±29.93	4.00	157.00
MLNC (right and left)	1.46±2.14	0.00	10.00
MLNR	0.04±0.08	0.00	0.50
LODDS	-1.60±0.53	-2.33	0.00

TLNC: Total lymph node count, Post-op RT: Postoperative radiotherapy, Post-op CT: Postoperative chemotherapy, MLNR: Metastatic lymph node ratio, LODDS: The log-odds value of positive lymph nodes, MLNC: Metastatic lymph node count, SD: Standard deviation.

in tumors with a severe lymphoid response and with a total dissected number of lymph nodes ≥18 (0.004 and 0.037) (Table 2). TLNC (0.303), total MLNC (0.768), MNLR (0.656), and LODDS (0.356) values were found to be similar in those patients with and those without cancer recurrence (p>0.05) (Table 3). According to ROC analysis, no significant cut-off value was obtained for either disease-free survival (DFS) or OS for MLNR or LODDS values [p=0.672, area under the curve (AUC): 0.672, 95% confidence interval (CI): 0.365-0.706; p=0.352, AUC: 0.578, 95% CI: 0.411-0.746; p=0.450, AUC: 0.615, 95% CI: 0.222-1; p=0.450, AUC: 0.615, 95% CI: 0.230-0.999, respectively, Figure 1, 2]. Also, no significant cut-off value affecting DFS or OS was found for MLNC (p=0.780 and 0.744).

N-stage and lateralization of nodal metastasis were not statistically significant for DFS function according to Kaplan-Meier survival function analysis. However, there was a significant difference between MLNR, LODDS and lymphoid response groups (log-rank: 0.955, 0.244, 0.013, 0.009, and 0.044 respectively, Figure 3-7). Again, N-stage and lymphoid response were not statistically significant for OS function according to Kaplan-Meier survival function analysis. A significant difference was found between the MLNR groups, LODDS groups and lateralization of nodal metastasis groups (log-rank= 0.627, 0.133, <0.001, <0.001, 0.009, and 0.003 respectively, Figure 8-12).

DISCUSSION

The most common head and neck cancer in the worldwide is laryngeal cancer. In recent years, LSCC has been noted for its very poor survival rates.[16] In general, a balance is attempted in the treatment in terms of the patient's quality of life, minimizing morbidity, and achieving a full cure. However, there is no single common approach to optimally manage the treatment of all patients. Therefore, the optimal approach is still controversial. Options such as a non-surgical approach (organ-sparing treatment) or a surgical approach (without organ preservation, such as primary total or partial laryngectomy) have been extensively discussed. Especially with two important studies on this subject, it has become even more controversial.[17,18] However, since most LSCC patients are diagnosed at an advanced stage, applying more radical treatment approaches becomes mandatory. Aside from the traditional AJCC staging system, some parameters such as patient age, surgical margin condition, and poor histopathological features are now routinely used for prognostic assessment and adjuvant therapy evaluation. The conventional AJCC staging system, on the other hand, loses its predictive power over time. Therefore, new parameters are required to optimize patient treatment and best manage patients, and an increasing number of markers are being defined.

In recent years, the value of the counts of dissected lymph nodes has been emphasized. However, there is debate about number of dissected lymph nodes which should be removed to be considered an adequate resection. This is because a variety of factors influence the number of lymph nodes dissected during routine surgical procedures. These are factors which are completely independent of tumor biology. In a similar fashion to the patient's anatomical structure, this may be related to the patient, as well as the surgeon's and pathologist's experience. Depending on such conditions, the patient's stage may also change. Dissection of ≥18 lymph nodes has been shown to improve OS and local control in head and neck cancers with nodal metastasis (N^+). According to one study, the total number of lymph nodes is not related to survival in patients with N-laryngeal carcinoma.[19] TLNC has been shown in studies including all head and neck cancers, including both N^- and N^+ laryngeal cancers, to be effective in OS.[20,21] Our study included both N^- and N^+ patients, and only 3 of them had a TLNC of less than 18. The fact that the recurrence rate was significantly lower in cases with a TLNC of 18 or above supports this finding.

Recent research has found that the MLNC has a better prognostic value than the commonly used AJCC N-staging system. In addition to the AJCC 8th N-stage, staging according to MLNRs grouped according to their N

Table 2. Comparison of nominal variables between recurrence groups and chi-square statistics

		Recurrence				p
		None		Present		
		Count	Row (n, %)	Count	Row (n, %)	
Gender	Male	31	63.3%	18	36.7%	0.543
	Female	3	100.0%	0	0.0%	
Smoking status	No	3	100.0%	0	0.0%	0.194
	Yes	31	63.3%	18	36.7%	
T-stage	T3	13	65.0%	7	35.0%	0.963
	T4	21	65.6%	11	34.4%	
Lateralization of nodal metastasis	None	16	47.1%	8	44.4%	0.422
	Ipsilateral	12	35.3%	8	44.4%	
	Contralateral	4	11.8%	0	0.0%	
	Bilateral	2	5.9%	2	11.1%	
Lymphoid response	None	6	17.6%	6	33.3%	0.004
	Mild	5	14.7%	7	38.9%	
	Moderate	10	29.4%	5	27.8%	
	Severe	13	38.2%	0	0.0%	
N-stage	N0	16	66.7%	8	33.3%	0.935
	N1	6	60.0%	4	40.0%	
	N2	11	68.8%	5	31.3%	
	N3	1	50.0%	1	50.0%	
Neural invasion	None	29	64.4%	16	35.6%	0.539
	Present	5	71.4%	2	28.6%	
Vascular invasion	None	26	65.0%	14	35.0%	0.915
	Present	8	66.7%	4	33.3%	
Lymph node metastasis	None	16	66.7%	8	33.3%	0.546
	Present	18	64.3%	10	35.7%	
TLNC (cut-off 18)	<18	0	0.0%	3	16.7%	0.037
	≥18	34	100.0%	15	83.3%	
Distant metastasis	None	24	63.2%	14	36.8%	0.416
	Present	10	71.4%	4	28.6%	
Survival	Ex	1	25.0%	3	75.0%	0.114
	Survive	33	68.8%	15	31.3%	
Post-op RT	None	6	85.7%	1	14.3%	0.221
	Present	28	62.2%	17	37.8%	
Post-op CT	None	23	74.2%	8	25.8%	0.093
	Present	11	52.4%	10	47.6%	
MLNR groups	MLNO=0	16	66.7%	8	33.3%	0.297
	MLNO (0.01-0.19)	18	69.2%	8	30.8%	
	MLNO (0.2-0.39)	0	0.0%	1	100.0%	
	MLNO (≥0.4)	0	0.0%	1	100.0%	
LODDS groups	LODDS (≤-1.5)	23	69.7%	10	30.3%	0.244
	-1.5< LODDS ≤-1.0	7	58.3%	5	41.7%	
	-1.0< LODDS ≤-0.5	4	80.0%	1	20.0%	
	-0.5< LODDS ≤0	0	0.0%	2	100.0%	
	LODDS >0	0	0.0%	0	0.0%	

TLNC: Total lymph node count, Post-op RT: Postoperative radiotherapy, Post-op CT: Postoperative chemotherapy, MLNR: Metastatic lymph node ratio, LODDS: The log-odds value of positive lymph nodes, Ex: Exitus.

Table 3. Comparison of scale variables between recurrence groups and Mann-Whitney U test statistics

	Recurrence				p
	None		Present		
	Mean	SD	Mean	SD	
Age	60	9	61	9	0.787
Tumor size	3.4	0.8	3.3	1.1	0.703
Right neck TLNC	28	13	25	17	0.544
Right neck MLNC	1	1	1	2	0.420
Left neck TLNC	32	14	32	29	0.346
Left neck MLNC	1	2	1	1	0.838
TLNC	60.71	23.43	56.83	40.13	0.303
MLNC	1.32	1.87	1.72	2.61	0.768
MLNR	0.03	0.04	0.06	0.13	0.656
LODDS	-1.66	0.47	-1.48	0.61	0.356

TLNC: Total lymph node count, MLNC: Metastatic lymph node count, MLNR: Metastatic lymph node ratio, LODDS: The log-odds value of positive lymph nodes, SD: Standard deviation.

stage, MLNC and MLNR were performed in a fairly large series, and MLNC and MLNR were discovered to have a much stronger prognostic value than many of the other systems used. In our study, in addition to TLNC, MLNC, MNLR, we also calculated LODDS values. Since MLNR and LODDS values did not provide a remarkable cut-off value for DFS or OS, we divided them into subgroups as the N^0 stage and the N^2 stage. For DFS and OS, we found no difference between these groups. However, for both DFS and OS, we discovered a significant difference between the MNLR and LODDS groups. Similar to our findings, a study on the LODDS value found it to be an important determinant for both DFS and OS.[22]

It has been emphasized that MLNR is also important for many tumors. The conventional AJCC staging system has been losing its power over time. More personal parameters are needed. Attempting to predict the prognosis based on the LODDS value, as well as the MLNR rate and incorporating them into patient management appears to affect both DFS and OS.

Study Limitations

We are aware that our study had significant limitations. Although we knew the smoking status, we could not evaluate alcohol status due to a lack of data. More importantly, the number of patients was limited. However, it was possible to evaluate the long-term follow-up of the patients in this group. Currently, the present study is an initial one for research into the predictive values of both MLNR and LODDS in long-term survival in our country's patient population with laryngeal squamous cell carcinoma.

CONCLUSION

As with all cancers, predictive markers are very important for appropriate treatment planning and outcome during follow-up in laryngeal carcinomas. These markers are far more important for cancers which are generally detected at a late stage, such as laryngeal carcinoma. Adding values such as MLNR and LODDS to the conventional AJCC staging system can make it more powerful.

MAIN POINTS

- The conventional AJCC staging system needs to be updated over time in order to better predict prognosis in cancer patients. More personal disease parameters are recommended to be added to the conventional staging.
- It has been emphasized that MLNR is important for many tumors.
- Attempting to predict the prognosis based on the LODDS value, as well as the MLNR rate, and incorporating them into patient management appears to affect both DFS and OS.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained before this study was carried out from the affiliated İzmir Katip Çelebi University (approval number: 0539, date: 24.11.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ö.E., A.F.B., H.S.K., Concept: N.Ö.E., A.F.B., A.İ., H.S.K., Design: N.Ö.E., A.F.B., H.S.K., Data Collection and/or Processing: N.Ö.E., A.F.B., Analysis and/or Interpretation: N.Ö.E., A.F.B., A.İ., S.A., Literature Search: N.Ö.E., A.F.B., H.S.K., S.A., Writing: N.Ö.E., A.İ.

DISCLOSURES

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Figures 1-12 link: http://glns.co/e857q