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Lymph Node Ratio Predictive of Survival in Node-Positive Head and Neck Cancer

Lenf Nodu Pozitif Baş-Boyun Kanserli Hastalarda Sağ Kalımı Öngören Lenf Nodu Oranı

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ÖZ

Amaç: Lenf nodu oranı (LNR), pozitif lenf nodlarının toplam eksize edilmiş lenf nodlarına oranını temsil eder. Baş ve boyun SCC'si nedeniyle cerrahi yapılmış hastalarda LNR ile sağkalım arasındaki ilişki değerlendirildi.

Araçlar ve Yöntem: Çalışmaya cerrahi rezeksiyon ve boyun diseksiyonu yapılan baş ve boyun skuamöz hücreli karsinomlu 33 hasta dahil edildi. Kaplan-Meier analizi ve log-rank testi, hastalıksız sağkalım (DFS) ve genel sağ kalımdaki (OS) farklılıkları karşılaştırmak için kullanıldı.

Bulgular: Ortalama LNR değeri 0.1, ortalama yaş 57, 28 erkek ve 5 kadın hasta dahil edildi. Medyan DFS 10.4 aydı ve medyan OS 32.5 aydı. Kaplan-Meier sağkalım analizi ile DFS ve OS karşılaştırıldığında, medyan LNR≥0.1 olan hastaların, oranları bu eşik değerlerin altında olan hastalara göre anlamlı derecede daha kötü DFS (p:0.029) ve OS (p:0.036) olduğunu bulduk. Diğer bilinen rekürrens ve sağkalım prediktörleri göz önüne alındığında, LNR'nin DFS (p=0.036, HR 0.38, % 95 CI 0.15-0.93) ve OS (p=0.042, HR 0.40% 95 CI 0.17-0.96) ile anlamlı şekilde ilişkili olduğu bulundu.

Sonuç: Çalışmamız, yüksek LNR'nin baş-boyun kanserli hastalarda sağkalım için bağımsız bir prediktörü olduğunu gösterdi. Baş-boyun kanserli hastalarda LNR, rekürrens ve sağkalımı tahmin etmek için ek bir parametre olarak kullanılabilir.

Anahtar Kelimeler: baş-boyun kanseri; lenf nodu oranı; lenf nodu pozitif; rekürrens; sağ kalım

ABSTRACT

Purpose: Lymph node ratio (LNR) represents the ratio of positive lymph nodes to total excised lymph nodes. We analyzed the correlation between LNR and outcomes in patients who have undergone surgery for SCC of the head and neck.

Materials and Methods: Thirty-three patients with head and neck squamous cell carcinoma (HNSCC) who underwent surgical resection and neck dissection were included. Kaplan-Meier analysis and log-rank test were used to compare differences in disease-free survival (DFS) and overall survival (OS).

Results: In total, 28 males and 5 females with a median of age 57 years were identified, with a median recorded LNR of 0.1. The median DFS was 10.4 months, and the median OS was 32.5 months. When DFS and OS were compared by Kaplan-Meier survival analysis, we found that patients with the median LNR≥0.1 had significantly worse DFS (p:0.029) and OS (p:0.036) than patients with ratios below these threshold values. Considering other known predictors of recurrence and survival, we found that LNR was significantly associated with DFS (p=0.036, HR 0.38, 95% CI 0.15-0.93) and OS (p=0.042, HR 0.40, 95% CI 0.17-0.96).

Conclusion: Our study showed that high LNR was an independent predictor of outcome in patients with HNSCC. In HNSCC, LNR can be used as an additional parameter to predict recurrence and survival.

Keywords: head and neck cancer; lymph node ratio; recurrence; survival

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INTRODUCTION

Cervical lymph node involvement is an important prognostic factor for head and neck squamous cell carcinoma (HNSCC), and even the presence of a positive lymph node is associated with a decrease in overall survival (OS) of up to 50%.[1] For nodal (N) staging, the 8th edition of the American Joint Cancer Committee (AJCC) uses for metastatic lymph node number, contralateral lymph node status, metastatic lymph node size, and extracapsular extension (ECE).[2] Pathological factors currently used in the risk stratification of patients and to guide treatment include advanced tumor (T) classification, advanced N classification, perineural invasion (PNI), lymphovascular space invasion (LVSI), vascular tumor embolism, close/involved margins, and ECE.[3]

Lymph nodes ratio (LNR), defined as the ratio of the number of positive lymph nodes to the total number of lymph nodes removed, is used as a prognostic factor in patients with multiple cancers, such as oral SCC, bladder cancer, esophageal cancer, colorectal adenocarcinoma, papillary thyroid carcinoma, and cervical cancer.[4-5]

In our study, we aimed to show whether LNR is a prognostic factor that can guide the treatment decision and predict survival.

MATERIALS and METHODS

Patients

We collected all HNSCC patients who underwent treatment with surgical resection and neck dissection at the Department of Medical Oncology, Necmettin Erbakan University, from October 2009 to January 2020. Clinicopathological data were obtained retrospectively from the patients' records of our hospital. Exclusion criteria included patients without lymph node metastasis in lymph node dissection were excluded from the study. In addition, patients with metastasis at the time of diagnosis and missing data were excluded from the study. Data of a total of 33 patients who met the inclusion criteria were analyzed.

Necmettin Erbakan University clinical research ethics committee approval was obtained (Decision number: 2020/2750 Date: 17.7.2020).

Lymph Node Ratio

The LNR was calculated using the ratio of the number of positive lymph nodes reported to the total number of lymph nodes excised.

Statistical Analysis

All statistical analyses were performed using the SPSS statistical software package (version 22.0). Survival analysis was performed by Kaplan–Meier curves with log-rank tests for significance. Univariate Cox regression analysis was performed to identify predictors of disease-free survival (DFS) and overall survival (OS). Two-sided p values of <0.05 were considered statistically significant.

RESULTS

Clinicopathological Characteristics of Patients

Among the 33 patients, 84.8% were male and 15.2% were female. The median age of this cohort was 57 years. Most of the primary tumor sites were larynx (54.6%) and tongue (24.2%). The median number of lymph nodes excised was 27 (range 7–50), and the median number of metastatic lymph nodes was 3 (range 1-34). The median LNR was 0.1. Patients with an LNR higher than 0.1 accounted for 51.5% of the whole cohort. As adjuvant therapy, 5 patients received radiotherapy, and 23 patients received platinum-based concurrent chemoradiotherapy. Five patients did not receive adjuvant therapy. Table 1 shows the clinicopathological parameters of the patients.

Prognostic Impact of LNR

The median DFS and OS of this cohort were 10.4 months and 32.5 months, respectively (Figure 1 and Figure 2). Kaplan–Meier survival analysis revealed a correlation between LNR and overall and disease-free survival times. Patients with LNR higher than 0.1 had significantly poorer DFS (9 months vs. 16.9 months, p:0.029) and OS (22.6 months vs. 38.6 months, p: 0.036) than those with LNR less than 0.1. The Kaplan–Meier curves of DFS and OS based on LNR are shown in Figures 3 and 4.

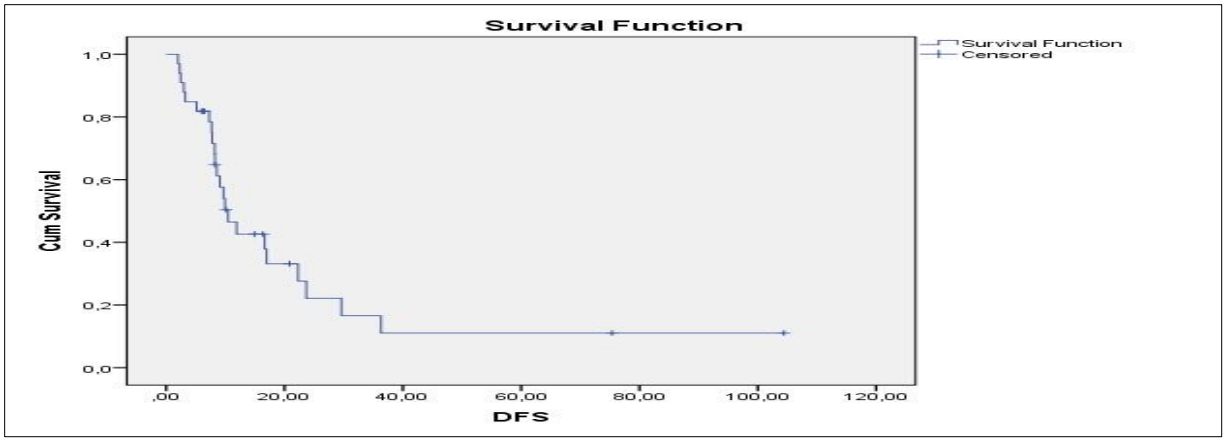

Figure 1. Kaplan–Meier curve of DFS for all patients

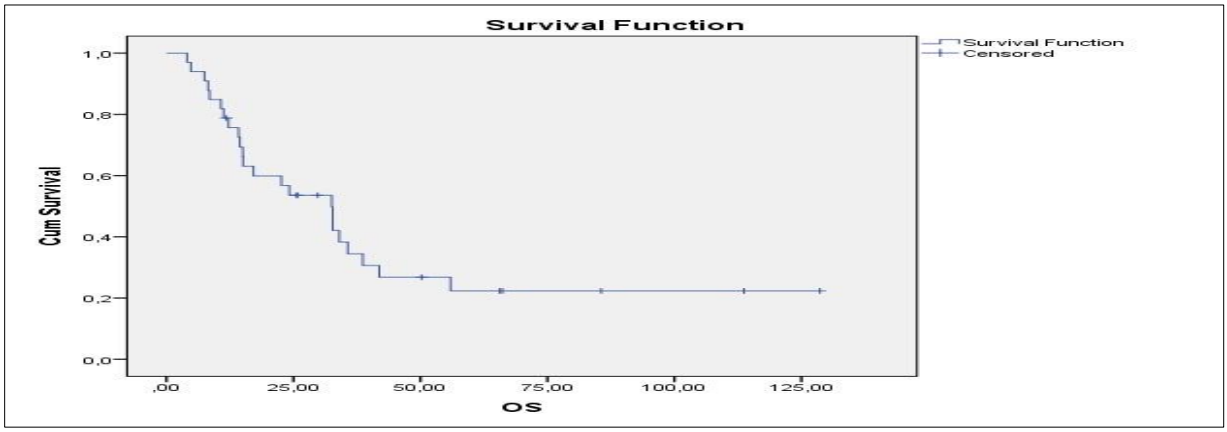

Figure 2. Kaplan–Meier curve of OS for all patients

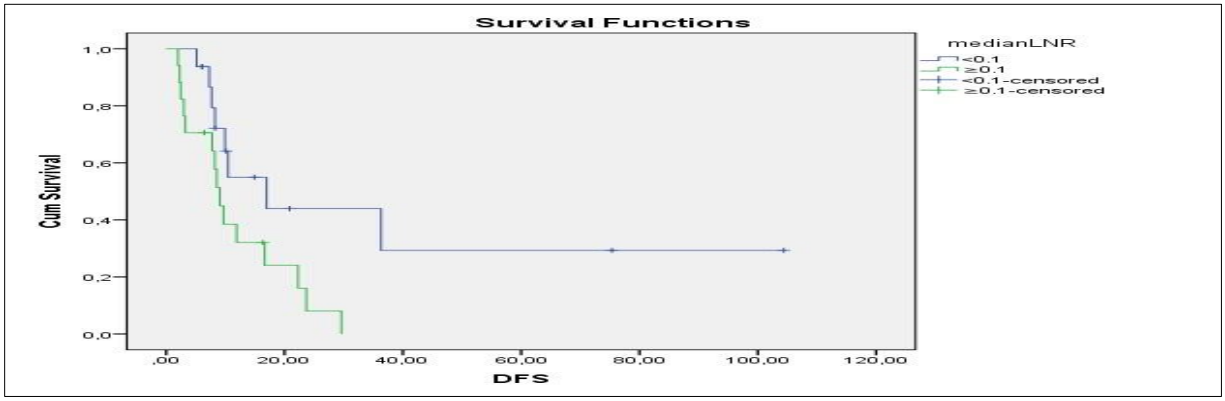

Figure 3. Kaplan–Meier curve of DFS based on LNR

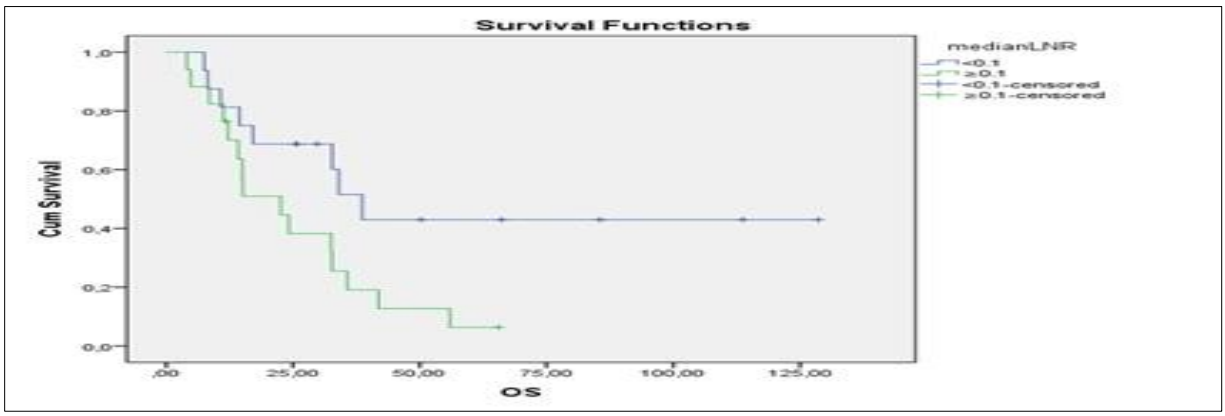

Figure 4. Kaplan–Meier curve of OS based on LNR

In univariate analysis, the LNR was the only statistically significant predictors of a shorter DFS (hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.15-0.93; p = 0.036) and OS (HR 0.40, 95% CI 0.17-0.96; p:0.042). In multivariate analysis, the LNR was the only statistically significant predictors of a shorter DFS (HR 0.40, 95% CI 0.15-1.05; p = 0.043) and OS (HR 0.36, 95% CI 0.14-0.36; p:0.037). The results of univariate and multivariate analyses are shown in Tables 2 and 3.

Table 1. Patient characteristics

Characteristics	Mean
Age (median, min.-max.)	57 (36-80)
Gender (n,%)	
Male	28 (84.8)
Female	5 (15.2)
TNM stage (n,%)	
III	4 (12.1)
IVa	9 (27.3)
IVb	19 (57.6)
IVc	1 (3)
LVI (n,%)	
Yes	14 (42.4)
No	19 (57.6)
Histological grade (n,%)	
Well	15 (45.5)
Moderately	8 (24.2)
Poorly	10 (30.3)
ECE (n,%)	
Yes	20 (60.6)
No	13 (39.4)
Number of lymph nodes excised (median, range)	27 (7-50)
Number of metastatic lymph nodes (median, range)	3 (1-34)
LNR (n,%)	
<0.1	16 (48.5)
≥0.1	17 (51.5)

Abbreviations: LVI: Lymphovascular invasion; ECE: Extracapsular extension; LNR: Lymph node ratio

Table 2. Univariate analysis of factors associated with DFS and OS

Variables	DFS		OS	
	p	HR (%95 CI)	p	HR (%95 CI)
Age	0.91	0.99 (0.95-1.03)	0.91	0.99 (0.95-1.04)
Gender (Male vs. Female)	0.64	0.73 (0.21-2.58)	0.15	0.40 (0.12-1.28)
T stage (T1-2 vs. T3-4)	0.90	0.95 (0.41-2.20)	0.58	0.78 (0.33-1.86)
Number of metastatic lymph nodes	0.24	1.02 (0.98-1.07)	0.38	1.02 (0.97-1.07)
LVI (Yes vs. No)	0.26	0.59 (0.24-1.44)	0.26	0.61 (0.26-1.43)
ECE (Yes vs. No)	0.49	0.74 (0.31-1.77)	0.65	1.21 (0.51-2.85)
LNR (<0.1 vs. ≥0.1)	0.036	0.38 (0.15-0.93)	0.042	0.40 (0.17-0.96)

Abbreviations: LVI: Lymphovascular invasion; ECE: Extracapsular extension; LNR: Lymph node ratio; DFS: Disease-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval

Table 3. Multivariate analysis of factors associated with DFS and OS

Variables	DFS		OS	
	p	HR (%95 CI)	p	HR (%95 CI)
LVI (Yes vs. No)	0.48	0.72 (0.29-1.78)	0.48	0.72 (0.28-1.79)
ECE (Yes vs. No)	0.99	1.00 (0.40-2.51)	0.17	1.94 (0.73-5.12)
LNR (<0.1 vs. ≥0.1)	0.043	0.40 (0.15-1.05)	0.037	0.36 (0.14-0.93)

Abbreviations: LVI: Lymphovascular invasion; ECE: Extracapsular extension; LNR: Lymph node ratio; DFS: Disease-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval

DISCUSSION

We evaluated the association of LNR with DFS and OS in a small cohort of patients with HNSCC who underwent surgical resection and neck dissection. We found that LNR≥0.1 was independently associated with worse DFS and OS in the overall study population.

Locoregional disease carries a high risk for local recurrence (15 to 40%) and distant metastasis in head and neck cancers and is associated with a poor prognosis (5-year overall survival, <50%).[6] In addition, high-risk factors for recurrence and metastasis include adverse pathological factors such as ECE, positive resection margins, PNI or vascular tumor embolism, and oral cavity or oropharyngeal tumors with IV or V level lymph nodes.[7] In the literature, the location and number of positive nodes in head and neck cancers with lymph node metastasis are shown as the most important prognostic factors.[8] Combined therapies (surgery, radiotherapy, and chemotherapy) are used to minimize this risk.[9] Factors such as the number of metastatic lymph nodes, ECE, and LVI, which were shown to be prognostic factors in many previous studies, were not found to be significant in our study. We think that this is due to the small number of patients in our study.

Lymph node ratio, the ratio of positive lymph nodes to total excised lymph nodes have been proposed to overcome a limited neck dissection and the resulting under-staging effect.[10] In some studies, LNR has been shown to predict clinical outcomes in head and neck cancer patients. Moreover, recent studies have shown that LNR is an independent and perhaps better prognostic factor for OS than pathological N staging.[11] Chen et al. Classified patients as LNR

<0.1 and LNR>0.1 in all patient groups (with or without lymph node metastasis), and they found that 3-year OS, local failure-free survival (LFFS), and distant metastasis-free survival (DMFS) were better in the group with LNR<0.1 than in the group with LNR>0.1. Only lymph node-positive patients were divided into 3 groups as LNR <0.06, 0.06-0.17, and> 0.17. In the group with LNR>0.17, 3-year OS and LFFS were statistically significantly worse, DMFS was also worse, but not statistically significant.[5] Abdeyrim et al. in the meta-analysis of 13 studies involving hypopharyngeal and laryngeal cancers, showed that higher LNR was significantly associated with shorter OS, disease-specific survival (DSS), and DFS. The cut-off of eligible studies ranged from 0.03 to 0.14, with the least significant LNR being 0.044.[12] Wang YL et al. classified larynx cancer patients with lymph node metastasis into three risk groups LNR cutoff points (LNR≤0.09, 0.09–0.2, >0.2). They found that 5-year cause-specific survival and OS for LNR≤0.09, 0.09–0.2, >0.2 were 55.1%, 40.2%, 28.8% and 43.1%, 31.5%, 21.8%, respectively. Mizachi A. et al. found that 5-year OS and DSS in patients with LNR>0.1 in cutaneous squamous cell carcinoma of the head and neck were 43.1% and 67.8% (LNR<0,1: 5-year OS and DSS; 66.3% vs. 91.3%, respectively). Similarly, in cutaneous squamous cell carcinoma of the head and neck, Tseros et al. found that the mean times to disease progression (TTDP) and OS in patients with LNR>0,21 were 31.8 months and 36 months (LNR<0,21: TTDP and OS; 38.6 months vs. 42 months, respectively), these values were statistically significant.[13-15]

A common cut-off value for LNR has not been established. The statistically significant LNR cut-off values for local recurrence, OS, and DFS in the literature are > 6% for cutaneous HNSCC, > 20% for oral cavity and laryngeal cancer, > 0.2 for laryngeal cancer, > 0.1 for hypopharyngeal cancer, >0.1 for cutaneous HNSCC, >0,21 for cutaneous HNSCC, >13 % for oral cavity cancer.[13-19] Prabhu et al. showed that the patients with LNR> 20% were at high risk of locoregional recurrence and death and suggested that these patients should be evaluated for adjuvant chemoradiation.[17]

Our study has some limitations. First, it was a retrospective analysis of a relatively small cohort. Second, all patients underwent surgical resection and neck dissection and had lymph node metastasis, whereas adjuvant therapy and primary tumor locations were heterogeneous.

As a result, we found that LNR was a prognostic factor for recurrence and survival, in accordance with the literature data. We believe that the cut-off value and the definition of LNR will be determined by more comprehensive studies in the future; it will be included in the staging system and will directly affect the treatment decision.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Authors' Contributions

Concept/Design: MK, MKE. Data Collection and/or Processing: MKE, MK, MK. Data analysis and interpretation: MK, MA. Literature Search: MK. Drafting manuscript: MK.

REFERENCES

1. Cerezo L, Millan I, Torre A, et al. Prognostic factors for survival and tumor control in cervical lymph node metastases from head and neck cancer. A multivariate study of 492 cases. Cancer. 1992;69(5):1224-1234.
2. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99.
3. Chow LQM. Head and Neck Cancer. N Engl J Med. 2020;382(1):60-72.
4. Vasan K, Low TH, Gupta R, et al. Lymph node ratio as a prognostic factor in metastatic cutaneous head and neck squamous cell carcinoma. Head Neck. 2018;40(5):993-999.
5. Chen CC, Lin JC, Chen KW. Lymph node ratio as a prognostic factor in head and neck cancer patients. Radiat Oncol. 2015;10(1):1-6.
6. Braakhuis BJ, Brakenhoff RH, Leemans CR. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: biological risk factors. Ann Oncol. 2012;23(10):x173-x177.
7. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-1952.
8. Mamelle G, Pampurik J, Luboinski B, Lancar R, Lusinchi A, Bosq J. Lymph node prognostic factors in head and neck squamous cell carcinomas. Am J Surg. 1994;168(5):494-498.
9. Pignon JP, le Maître A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92(1):94.

10. Ampil FL, Caldito G, Ghali GE. Can the lymph node ratio predict outcome in head and neck cancer with single metastasis positive-node? Oral Oncol. 2014;50(4):e18-20.
11. Yildiz MM, Petersen I, Eigendorff E et al. Which is the most suitable lymph node predictor for overall survival after primary surgery of head and neck cancer: pN, the number or the ratio of positive lymph nodes, or log odds? J Cancer Res Clin Oncol. 2016;142(4):885-893.
12. Abdeyrim, A., He, S., Zhang, Y. et al. Prognostic value of lymph node ratio in laryngeal and hypopharyngeal squamous cell carcinoma: a systematic review and meta-analysis. J of Otolaryngol - Head & Neck Surg. 2020;49(1):31.
13. Wang YL, Li DS, Wang Y, Wang ZY, Ji QH. Lymph node ratio for postoperative staging of laryngeal squamous cell carcinoma with lymph node metastasis. PLoS One. 2014;9(1):e87037.
14. Mizrachi A, Hadar T, Rabinovics N, et al. Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck. Eur Arch Otorhinolaryngol. 2013;270(2):647-653.
15. Tseros EA, Gebski V, Morgan GJ, Veness MJ. Prognostic Significance of Lymph Node Ratio in Metastatic Cutaneous Squamous Cell Carcinoma of the Head and Neck. Ann Surg Oncol. 2016;23(5):1693-1698.
16. Vasan K, Low TH, Gupta R. et al. Lymph node ratio as a prognostic factor in metastatic cutaneous head and neck squamous cell carcinoma. Head Neck. 2018;40(5):993-999.
17. Prabhu RS, Hanasoge S, Magliocca KR et al. Lymph node ratio influence on risk of head and neck cancer locoregional recurrence after initial surgical resection: implications for adjuvant therapy. Head Neck. 2015;37(6):777-782.
18. Hua YH, Hu QY, Piao YF, Tand Q, Fu ZF. Effect of number and ratio of positive lymph nodes in hypopharyngeal cancer. Head Neck. 2015;37(1):111-116.
19. Shrime MG, Bachar G, Lea J, et al. Nodal ratio as an independent predictor of survival in squamous cell carcinoma of the oral cavity. Head Neck. 2009;31(11):1482-1488.