ANTICANCER RESEARCH *42*: 287-292 (2022)
doi:10.21873/anticanres.15484

Predictive Factors of Late Cervical Lymph Node Metastasis Using Intraoral Sonography in Patients With Tongue Cancer

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Abstract. *Aim: The objective of this study was to investigate the predictive factors of late cervical lymph node metastasis in patients with tongue cancer, based on the intraoral ultrasonographic (IUS) findings of the primary tongue lesion. Patients and Methods: Patients with T1/2N0M0 primary tongue cancer (n=106) were examined using IUS between September 2014 and September 2020. The relationships between the incidence of late cervical lymph node metastasis with the longest diameter, thickness, margin type, internal echo intensity, and internal or peripheral vascularity of the tongue lesion on Doppler IUS were assessed. Results: Multivariate analysis indicated that irregular margins of the lesion and the presence of internal echo intensity were significantly related to the incidence of late cervical lymph node metastasis. Conclusion: Irregular margins and internal echo intensity of the tongue cancer lesion assessed using IUS may predict the occurrence of late cervical lymph node metastasis in T1/2N0M0 cases.*

Cancers of the oral cavity cancer are common in some regions (1, 2), and the number of cases is increasing (3-6). Among cancers of the oral cavity, tongue cancer is the most common, with a reported incidence of 40%-50% (1) or 55.5% (6). Most patients with Stage I and II tongue cancer are not treated through prophylactic neck dissection, but through the management of the primary tumor alone, often only with surgery or brachytherapy. However, the incidence of late cervical lymph node metastasis in Stage I and II tongue cancer is reported as 8.2%-48.2% (7, 8). Lymph node metastasis is one of the factors affecting the prognosis of patients with tongue cancer (9), and the suitability of prophylactic neck dissection and routine follow-up has been discussed for the treatment of Stage I and II tongue cancer. The disease-specific survival rate (7, 10, 11) and 5-year survival rate (12) are better with prophylactic neck dissection than with close follow-up. However, follow-up is recommended because the results of randomized prospective trials have shown no differences in 5-year disease-specific survival (13-16). To date, no clear protocol has been established. Therefore, if patients at high risk for late cervical lymph node metastasis can be recognized by pre-treatment examination, prophylactic neck dissection in high-risk patients with Stage I and II tongue cancer can improve prognosis.

Therefore, diagnostic procedures that can predict the incidence of late cervical lymph node metastasis before radical treatment of the primary tongue cancer should be developed. Intraoral ultrasonographic examination (IUS) for the diagnosis of tongue cancer has been considered suitable for this purpose. The potentiality of IUS for the treatment of tongue cancer has been previously reported (17-20). The relationship between IUS and histopathological features has also been demonstrated (21, 22). In addition, there have been reports of the relationship between IUS features in tongue cancer and the incidence of cervical lymph node metastasis (18, 23-28). Features of cancer, such as the longest diameter (18), thickness (18, 23-25), margin shape (18, 26), and tumor vascularity, determined using color Doppler IUS (27, 28) have been shown to predict the occurrence of cervical lymph node metastasis in patients with tongue cancer. Therefore, the aim of this study was to investigate whether these features could serve as predictors of late cervical lymph node metastasis in patients with early-stage tongue cancer.

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Key Words: Tongue cancer, squamous cell carcinoma, ultrasonography, Doppler, cervical lymph node metastasis.

Patients and Methods

Patients. One hundred and twenty-four patients who had primary tongue cancer were studied by IUS at Hiroshima University Hospital between September 2014 and September 2020. Of these, 106 patients were histopathologically diagnosed with squamous cell carcinoma, T1N0M0 or T2N0M0, according to the 8th edition version of the Union for International Cancer Control's TNM classification of malignant tumors (29) and had received definitive treatment in our hospital. These patients were included in the present study. The duration of follow-up for late cervical lymph node metastasis was a minimum of one year following the initial treatment of primary tumor. The incidence of late cervical lymph node metastasis was diagnosed by histopathology after the neck dissection.

The study was approved by the ethics committee of Hiroshima University and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained in the form of opt-out in according to the local institutional ethics committee guidelines.

Ultrasonography. The ProSound alpha 7 system (Hitachi-Aloka Medical, Japan) using a 7.5 MHz/38 or 50 mm linear probe was used for ultrasonography. The acoustic coupling material of 10mm thickness was put on the probe surface, and it was wrapped with a water-filled rubber probe cover. Using B-mode and color Doppler IUS, the following were examined: the longest diameter, maximum thickness, margin type, presence of internal echo intensity, and internal and peripheral vascularity of the tumor. These methods were based on our previous reports (18, 19). Depending on the patterns, the margins of the lesions were classified into two types: smooth and irregular. Representative images of the measurement of the longest diameter, thickness, margin type, internal echo intensity, and internal and peripheral vascularity are shown in Figure 1. The lesion was defined as a hypoechoic area extending deep from the mucosal surface. The region with low-echo images was defined as internal area of the lesion. Presence of many hyperechoic regions in the lesion was defined as the presence of internal echo intensity. High internal vascularity was documented when abundant blood flow was evident in the lesion, and peripheral high vascularity when abundant blood flow was evident within the range of approximately 10 mm from the borders of the lesion. The IUS was carried out by two dentists (MF and MK). The longest diameter and lesion thickness were examined, and the margin types, presence of internal echo intensity, and internal and peripheral vascularity were evaluated by MK.

Statistical analysis. The association of age, sex, T-factors, longest diameter, thickness, margin type, presence of internal echo intensity, and internal and peripheral vascularity with the incidence of late cervical lymph node metastasis was investigated. The longest diameter and lesion thickness were assessed by the receiver operating characteristic (ROC) analysis, and the area under the curve (AUC) (0.9-1.0, 0.9-0.7, 0.7-0.5; high, moderate, low accuracy) cutoff values were calculated. The cutoff values were determined (sensitivity + specificity − 1) by the Youden's index. The Wilcoxon rank-sum test was used to compare the relationships of age, longest diameter, and thickness with the incidence of late cervical lymph node metastasis, and the chi-square test and Fisher's exact test were used to analyze the relationships of sex and IUS findings such as longest diameter, thickness, margin type, presence of internal echo intensity, and internal and peripheral vascularity with the occurrence of late cervical lymph node metastasis. Univariate and multivariate analyses was carried out to compare the variables between the cervical lymph node metastatic and non-metastatic groups. The JMP Pro version 15.0 (SAS Institute, Cary, NC, USA) was applied for every statistical analysis. The statistically significant level was set at $p<0.05$.

Table I. *Patient characteristics*.

Number of patients (n)	n=106
Gender	Male: 60, Female: 46
Age, years, mean±standard deviation (median)	62.2±16.8 (66)
Distribution of clinical T-factors	T1: 41, T2: 65
Treatment of the primary lesion	Surgery: 77, Radiotherapy (Brachytherapy): 29
Number of late lymph node metastasis	30

Results

Patient characteristics are summarized in Table I. A total of 106 patients were 60 males and 46 females with a mean age of 62.2 years. The T-factors were categorized into T1 (n=41) and T2 (n=65). The patients were treated with surgery alone (n=77) or radiation therapy alone (n=29). Thirty patients (28.3%) had cervical lymph node metastasis. The median duration of follow-up was 35 months (range=12-128 months). Univariate and multivariate analyses that compared the variables between the non-metastatic and the metastatic groups are summarized in Table II. The mean longest diameter or thickness in the non-metastatic and metastatic groups were 19.1 mm and 24.6 mm or 4.0 mm and 6.3 mm, respectively, which were significantly different in the univariate analysis ($p=0.0123$ and 0.0007, respectively). The ROC analysis for the longest diameter revealed the AUC value as 0.68 and the cutoff value as 25.6 mm and that for thickness showed the AUC value as 0.73 and the cutoff value as 3.3 mm (Figure 2). Sixty-one and 15 patients in the non-metastatic group and 7 and 23 patients in the metastatic group exhibited lesions with smooth and irregular margins, respectively. Univariate analysis indicated statistically.

Significant differences between the two groups ($p<0.0001$). Nine and 67 patients in the non-metastatic group and 14 and 16 patients in the metastatic group exhibited lesions with and without internal echo intensity. Univariate analysis indicated statistically significant differences between the two groups ($p=0.0004$). Forty-nine and 27 patients in the non-metastatic group and 27 and 3 patients in the metastatic group exhibited lesions with high and low peripheral vascularity. Univariate analysis indicated statistically significant differences between the two groups ($p=0.0086$). Age, sex, T-factors, and internal vascularity were not significantly different between the non-metastatic and metastatic groups. In multivariate analysis, the margin type

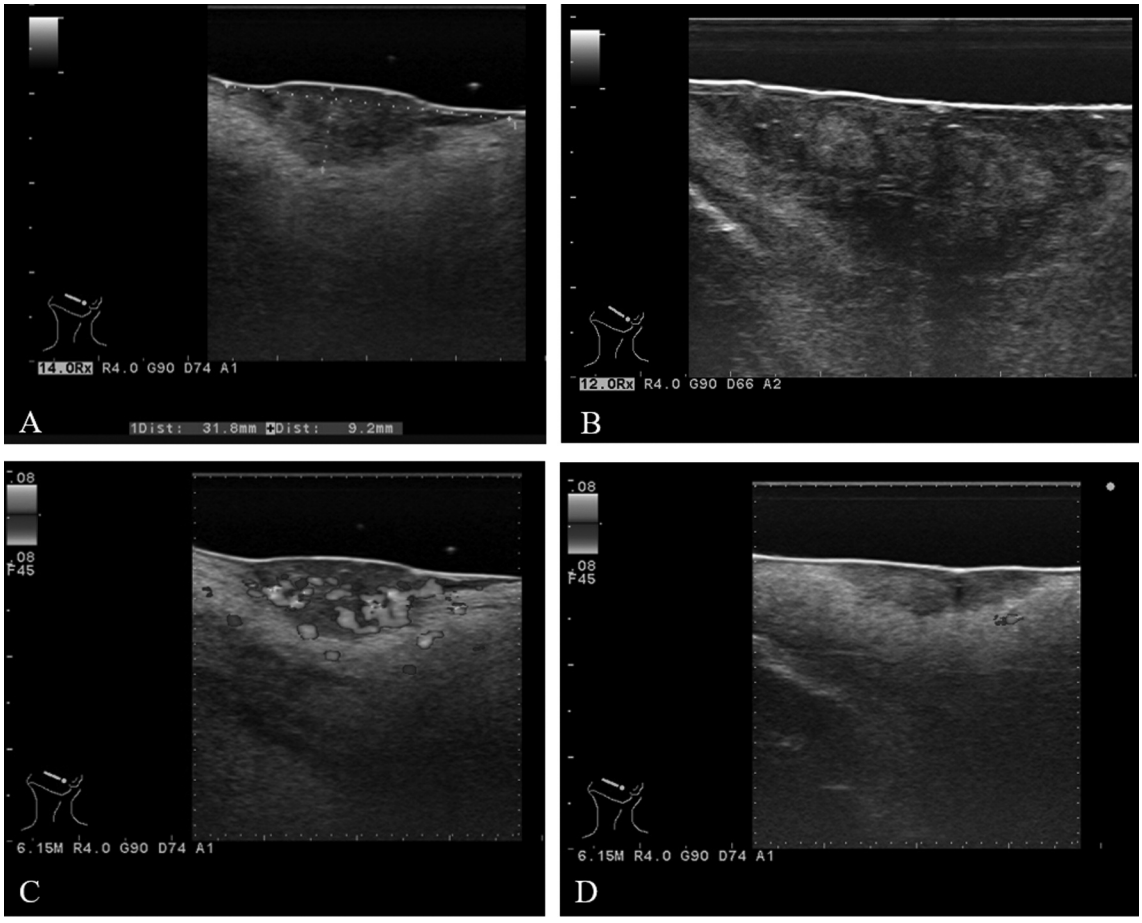

Figure 1. *Measurement method and assessment criteria for intraoral ultrasonography (IUS). Methods for measuring the longest diameter and thickness (A); a representative case showing internal echo intensity (B), high internal and peripheral vascularity (C), and low internal and peripheral vascularity (D). Internal echo intensity is the hyperechoic area in the lesion (B). Abundant signs of high internal and peripheral vascularity on Doppler ultrasound image (C).*

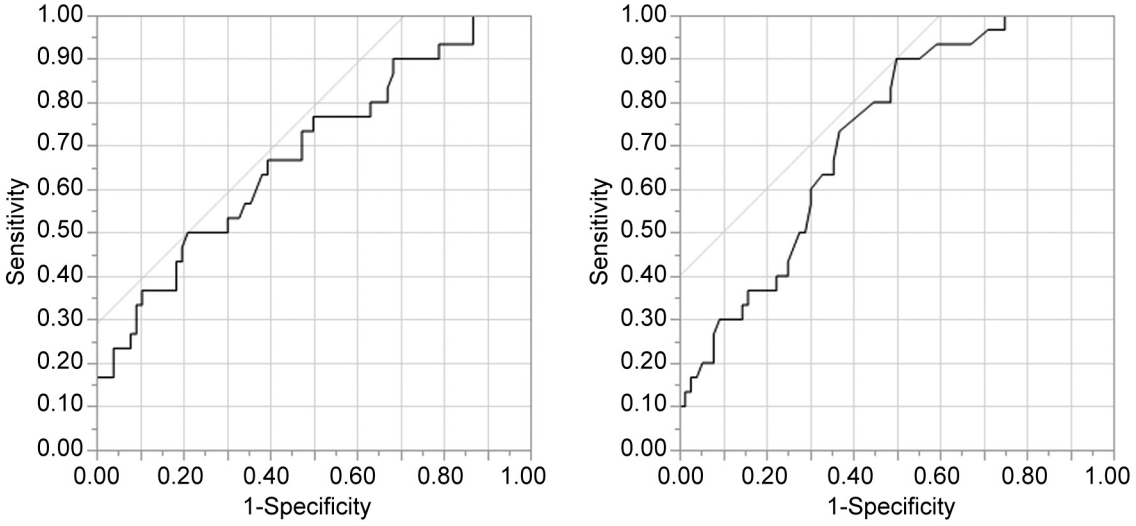

Figure 2. *Analysis of receiver operating characteristic (ROC). Analysis of ROC for the longest diameter (left) and thickness (right) in the non-metastatic and metastatic groups. The area under curve (AUC) value in ROC analysis of the longest diameter by the Youden's index is 0.68, and the cut-off value is 25.6 mm. In ROC analysis of the thickness by the Youden's index, the AUC value is 0.73, and the cut-off value is 3.3 mm.*

Table II. *Univariate and multivariate analysis for comparing variables between the non-metastatic and metastatic groups.*

	Non-metastasis (n=76)	Metastasis (n=30)	Univariate *p*-Value	Multivariate *p*-Value
Age, years, mean±SD (median)	63.0±17.7 (67.0)	60.3±15.0 (62.5)	0.2513	–
Gender, Male/Female	40/36	20/10	0.2016	–
T-factor, T1/T2	32/44	9/21	0.2766	–
Longest diameter, mm, mean±SD (median)	19.1±7.2 (18)	24.6±8.7 (24.2)	0.0042*	–
Longest diameter (mm)				
≥25.6 mm	16	15	0.0046*	0.12513
<25.6 mm	60	15		
Thickness, mm, mean±SD (median)	4.0±2.6 (3.25)	6.3±3.3 (4.95)	0.0003*	–
Thickness (mm)				
≥3.3 mm	38	27	0.0001*	0.60476
<3.3 mm	38	3		
Margin				
Smooth	61	7	<0.0001*	0.00040*
Irregular	15	23		
Internal echo intensity				
Present	9	14	0.0004*	0.01595*
Absent	67	16		
Internal vascularity				
High	26	10	1.0000	–
Low	50	20		
Peripheral vascularity				
High	49	27	0.0086*	0.90431
Low	27	3		

*Statistically significant difference. SD, Standard deviation.

and presence of internal echo intensity were significantly related to the incidence of late cervical lymph node metastasis (p=0.00040 and 0.01595, respectively).

Discussion

Carcinomas of the tongue occasionally metastasize to the regional cervical lymph nodes, which significantly affects survival. The present study investigated the relationship between the incidence of late cervical lymph node metastasis in patients with early-stage tongue cancer and IUS findings of the primary tongue lesions.

The present findings indicated that irregular margins of the tongue lesions were associated with late lymph node metastasis. Our previous study had also showed the association between irregular margins and the incidence of late cervical lymph node metastasis (18). Late cervical lymph node metastasis can be predicted from the margin type determined using IUS. Presence of internal echo intensity is suggestive of an infiltrative tumor with a moth-eaten appearance, probably corresponding to the irregular margin type.

The implications of Doppler IUS for tongue cancer have been reported in several studies. Ariji *et al*. analyzed tongue cancer sites using Doppler IUS (27). More abundant vascularity was observed in the tumor area in the lymph node metastasis group than that in the non-lymph node metastasis group, and a significant occurrence of lymph node metastasis was reported when the ratio of vascular images was ≥10%. In their study, the Doppler signals were assessed within the tumor and 5 mm outside the borders, which appeared hypoechoic on IUS. The univariate analysis in our study showed no significant difference between the groups with and without cervical lymph node metastasis in terms of the presence of high internal vascularity. However, it showed significantly greater peripheral vascularity in the metastatic group, but the multivariate analysis showed no significant difference. The internal and peripheral vascularity were evaluated separately, which may be one of the reasons for the different results. Yamamoto *et al*. reported that the percentage of the areas with blood flow signals in the tumor showed no statistical difference between patients with and without cervical lymph node metastasis (28). However, they reported that the number and width of blood flow signals at the tumor borders were significantly higher in the group with lymph node metastases than in the group without lymph node metastases. Our results also showed no significant increase in the vascularity of the tumor in the group with lymph node metastasis, but a significant increase in the vascularity of the peripheral area of the tumor in the group with lymph node metastasis, though only by univariate analysis. The cancerous mucosal epithelium proliferates and extends deep to the area close to the mucosal surface filled with epithelial cell

components. The mucosal epithelium is composed only of cellular components and is not vascularized (30). As the thickness of the cancerous mucosal epithelium increases with the expansion of the lesion, the blood flow becomes poor because the epithelial cell component is contained within the mucosal surface (23). Blood flow is considered to increase by angiogenesis and inflammatory reaction in the interstitial components of the deep and peripheral areas of the lesion. Therefore, the number of cases with hypoechoic areas within the vascular areas was considered small at 36/100. Future studies should compare the vascularity around the tumor border and IUS findings, which can be a factor that affects the occurrence of metastasis, with histopathological findings.

This study has several limitations. First, the images used in this study were still images, captured and stored during examination. Therefore, vascularity in motion may not have been accurately depicted. Therefore, in the future, the IUS images should be saved as a video for the accurate determination of vascularity. Next, IUS images in this study were obtained by 38 mm or 50 mm linear probes. As the difference in image quality between the probes has not been examined, it will be necessary to examine the difference in image quality between the probes and use a probe that can obtain the optimum image. Finally, in this study, data were collected by analysis of images with the human vision. However, some variation in the diagnosis is inevitable while some information cannot be extracted from images with the human vision. Therefore, we plan to extract objective data using image analysis software employing artificial intelligence-supported diagnosis and investigate factors related to late cervical lymph node metastasis.

Conclusion

The analysis of IUS findings showed that the irregular margin and the presence of internal echo intensity of the lesion was associated with the incidence of late cervical lymph node metastasis. The incidence of late cervical lymph node metastasis was related to longest diameter and thickness with cut-off values of 25.6 mm and 3.3 mm, respectively. Irregular margin or presence of internal echo intensity on IUS was an effective predictor for late cervical lymph node metastasis in patients with N0 tumors. Thus, in patients with N0 stage tumors, prophylactic neck dissection in addition to treatment of the primary tumor or close follow-up of the cervical lymph nodes after treatment of the primary tumor may reduce the risk of metastasis or improve prognosis if the late cervical node metastasis can be predicted before initial treatment by using IUS.

Conflicts of Interest

None declared.

Authors' Contributions

Masaru Konishi contributed to the conceptualisation, methodology, software, the data curation, writing – original draft preparation and reviewing and editing; Minoru Fujita, to the data curation and the writing – reviewing and editing; Kiichi Shimabukuro, Pongsapak Wongratwanich and Naoya Kakimoto, to the writing – reviewing and editing.

Acknowledgements

The Authors would like to express their gratitude to all the staff members in the department of Oral and Maxillofacial Radiology, Hiroshima University Hospital.

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Received October 7, 2021
Revised November 21, 2021
Accepted November 22, 2021