Original Article
Mol Imaging Radionucl Ther 2020;29:59-64 DOI:10.4274/mirt.galenos.2019.92300

The Predictive Value of Proportional Evaluation Based on the Metabolic Activity of Cervical Lymph Nodes on PET/CT Imaging in Patients with Larynx Cancer

Larinks Kanserli Hastalarda PET/BT Görüntülemede Servikal Lenf Nodlarının Metabolik Aktivitesine Dayanan Oransal Değerlendirmenin Prediktif Değeri

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Abstract

Objectives: We aimed to evaluate the proportional values of maximum standardized uptake value (SUV_{max}) for cervical lymph nodes on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for prediction of the presence of metastasis in patients with larynx squamous cell cancer (LSCC).

Methods: This retrospective study involved 43 patients with LSCC. All patients underwent resection of the primary tumor and neck dissection within 4 weeks after undergoing ^{18}F-FDG PET/CT examinations. Receiver operating characteristic (ROC) analysis was performed to evaluate the lymph node SUV_{max}/primary tumor SUV_{max} ($SUV_{max}LN/SUV_{max}PT$), lymph node SUV_{max}/aortic SUV_{max} ($SUV_{max}LN/SUV_{max}A$), and lymph node SUV_{max}/ liver SUV_{max} ($SUV_{max}LN/ SUV_{max}L$) ratios for diagnosis of lymph node metastasis.

Results: $SUV_{max}LN/SUV_{max}A$, $SUV_{max}LN/SUV_{max}L$, and $SUV_{max}LN/SUV_{max}PT$ rates were significantly higher in metastatic lymph nodes compared to non-metastatic nodes. ROC analysis for metastasis showed that the cut-off thresholds were 3.87 for $SUV_{max}LN$; 1.78 for $SUV_{max}LN$ /$SUV_{max}A$; 1.08 for $SUV_{max}LN/SUV_{max}L$; and 0.36 for $SUV_{max}LN/SUV_{max}PT$. The diagnostic sensitivity, specificity and AUC were 83.7%, 77%, 0.856 for $SUV_{max}LN$; 79.7%, 84%, 1.78 for $SUV_{max}LN/SUV_{max}A$; 84.1%, 76%, 0.833 for $SUV_{max}LN/SUV_{max}L$; and 53.6%, 76%, 0.666 for $SUV_{max}LN/SUV_{max}PT$, respectively.

Conclusion: $SUV_{max}LN/SUV_{max}A$, $SUV_{max}LN/SUV_{max}L$, and $SUV_{max}LN/SUV_{max}PT$ ratios can be safely used for diagnosis of cervical lymph node metastasis in patients with LSCC.

Keywords: Cervical lymph node, metabolic activity, larynx cancer, positron emission tomography/computed tomography

Öz

Amaç: ^{18}F-florodeoksiglikoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) servikal lenf nodlarının maksimum standardize uptake değerine (SUV_{maks}) dayalı oransal değerlerin skuamöz hücreli larenks kanserli (LSHK) hastalarda metastaz varlığını tahmin etmedeki gücünü değerlendirmeyi amaçladık.

Yöntem: Bu retrospektif çalışmaya LSHK olan 43 hasta alındı. Tüm hastalara ^{18}F-FDG PET/BT görüntülemeden sonraki 4 hafta içinde primer tümör rezeksiyonu ve boyun diseksiyonu yapıldı. Metastatik lenf nodlarının tanısı açısından lenf nodu SUV_{maks}/primer tümör SUV_{maks} ($SUV_{maks}LN/SUV_{maks}PT$), lenf nodu SUV_{maks}/aortik SUV_{maks} ($SUV_{maks}LN/SUV_{maks}A$), lenf nodu SUV_{maks}/karaciğer SUV_{maks} ($SUV_{maks}LN/SUV_{maks}L$) oranları alıcı işletim karakteristiği (ROC) analizi yapılarak değerlendirildi.

Bulgular: $SUV_{maks}LN/SUV_{maks}A$, $SUV_{maks}LN/SUV_{maks}L$, $SUV_{maks}LN/SUV_{maks}PT$ oranları metastatik lenf nodlarında metastatik olmayanlara göre anlamlı derecede yüksek idi. ROC analizinde metastaz tespiti açısından eşik değerler, SUVmaxLN için 3,87; $SUV_{maks}LN/SUV_{maks}A$ için 1,78; $SUV_{maks}LN/SUV_{maks}L$ için 1,08; $SUV_{maks}LN/SUVmaxPT$ için 0,36 olarak bulundu. Tanısal duyarlılık, özgüllük ve AUC değerleri $SUV_{maks}LN$, $SUV_{maks}LN/SUV_{maks}A$, $SUV_{maks}LN/SUV_{maks}L$, $SUV_{maks}LN/SUV_{maks}PT$ için sırasıyla %83,7, %77, 0,856; %79,7, %84, 1,78; %84,1, %76, 0,833; %53,6, %76, 0,666 idi.

Sonuç: $SUV_{maks}LN/SUV_{maks}A$, $SUV_{maks}LN/SUV_{maks}L$, $SUV_{maks}LN/SUVmaksPT$ oranları, LSHK hastalarında metastatik servikal lenf nodlarının tanısında güvenle kullanılabilir.

Anahtar kelimeler: Servikal lenf nodu, metabolik aktivite, larenks kanseri, pozitron emisyon tomografisi/bilgisayarlı tomografi

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Received: 05.09.2019 **Accepted:** 06.09.2019

Introduction

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is being increasingly carried out to determine the stage and localization of metastatic disease in patients with larynx squamous cell cancer (LSCC). The correct diagnosis of metastatic cervical lymph nodes is important in terms of determining prognosis and providing adequate treatment. In clinical practice, CT and/or magnetic resonance imaging (MRI) are generally recommended for the assessment of tumor extension and cervical lymph node involvement (1).

Several studies in the literature reported that ^{18}F-FDG PET/CT had reliable diagnostic value for a depiction of lymph node metastasis of head and neck squamous cell (HNSCC) compared with conventional CT/MRI (2,3). Meta-analyses of ^{18}F-FDG PET/CT showed that the pooled per-patient, per-neck-side, and per-neck-level sensitivities/specificities were 0.91/0.87, 0.84/0.83, and 0.80/0.96, respectively. Across 13 studies (3460 neck levels) for which per-neck-level data were available, sensitivity and specificity were 0.84/0.96 respectively for ^{18}F-FDG PET/CT and 0.63/0.96 for conventional imaging (CT and MRI), respectively (4).

Cut-off value of 2.5 for the maximum standardized uptake value (SUV_{max}) is used commonly to differentiate between benign and malignant lesions on ^{18}F-FDG PET/CT imaging. But many biological and technical factors can affect SUV_{max} value, such as patient's weight, blood glucose level, postinjection uptake time, respiratory motion, tumor behavior, lesion size, motion artefacts, variability of the scanner, image-reconstruction parameters and contrast agent used (5,6). These factors may affect SUV values by 5% to 50% and cause false negativity or positivity (7).

In the literature, there are many studies on proportional values such as SUV_{max}LN/ SUV_{max}PT, SUV_{max}LN/SUV_{max}A, and SUV_{max}LN/SUV_{max}L for the prediction of metastatic lymph nodes in various malignancies, mainly lung cancer and breast cancer. However, the number of studies about LSCC is limited (8,9,10,11,12). In this study, we aimed to evaluate the proportional values of the SUV_{max} for cervical lymph nodes on ^{18}F-FDG PET/CT imaging for the prediction of the presence of metastasis in patients with LSCC.

Materials and Methods

This retrospective study involved 43 patients (42 men,1 woman; mean age=60.20±8.12 years, range=46-83) with LSCC.

The following criteria were defined for patient selection:

- Patients with diagnosis ofprimary LSCC made by a biopsy.

- Patients who did not undergo any treatment for LSCC before ^{18}F-FDG PET/CT imaging and had no secondary malignancy.

- Patients who did not undergo any diagnostic excisional or incisional cervical lymph node biopsy for metastasis evaluation before ^{18}F-FDG PET/CT imaging.

- Patients who underwent resection of the primary tumor and neck dissection within 4 weeks after undergoing ^{18}F-FDG PET/CT imaging.

^{18}F-FDG PET/CT imaging was performed at our institution between November 2013 and January 2018. Ethics Committee Approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with the decision number "1066" and date "12.04.2018". The written informed consent was obtained from all patients at the time of imaging.

^{18}F-FDG PET/CT studies were carried out using an integrated PET/CT scanner, which consisted of a full-ring HI-REZ LSO PET and a 6-slice CT (Siemens Biograph 6; Siemens, Chicago, USA). All patients were instructed to fast for at least 6 h before the ^{18}F-FDG injection. Blood glucose levels were measured before the study and the injection was given only when the blood glucose levels were below 11.11 mmol/L. The patients were injected with 370 to 555 MBq ^{18}F-FDG, according to body weight. After 60 minutes of waiting on a semireclined relaxed chair, the patients were imaged using an integrated PET/CT scanner. The CT portion of the study was performed without injection of intravenous contrast medium to define anatomical landmarks and attenuate correction on PET images. CT was acquired first with the following parameters: 50 mAs, 140 kV, and 5 mm section thickness. Whole-body CT was performed in a craniocaudal direction. PET images were acquired in a three-dimensional mode, from the vertex to mid-thigh, with six to eight bed positions of 3 min each, and PET data were collected in a caudocranial direction. Image reconstruction used "ordered subsets expectation maximization" algorithm of 2 iterations and 8 subsets. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany). ^{18}F-FDG PET/CT images were retrospectively interpreted by 3 experienced nuclear medicine physicians. The observers were blinded to the results of preoperative diagnostic imaging examinations such as MRI or ultrasonography and to the histopathological evidence of lymph node dissections. All cervical lymph nodes on CT which increased tracer uptake compared with background activity were accepted as metastatic. Semi-quantitative analysis of ^{18}FDG uptake was performed, through creation of a region of interest (ROI) over the primary lesion and lymph nodes. SUV_{max} was also

determined by manually placing a cylindrical ROI over the arcus aorta and right lobe of the liver. Lymph node SUV_{max} values were divided by the SUV_{max} of the primary tumour, arcus aorta (mediastinal blood pool) and liver to calculate the following:

- Lymph node SUV_{max}/primary tumour SUV_{max} ($SUV_{max}LN/SUV_{max}PT$)
- Lymph node SUV_{max}/aortic SUV_{max} ($SUV_{max}LN/SUV_{max}A$)
- Lymph node SUV_{max}/Liver SUV_{max} ($SUV_{max}LN/SUV_{max}L$)

Operations were performed in our head and neck surgical clinic based on clinical and imaging findings. Modified radical neck dissection was performed in all patients. Lymph nodes and tumors were dissected from the specimens and stained with hematoxylin and eosin for histologic analysis. Serial histologic sections were used. We compared results of preoperative examinations using ^{18}F-FDG PET/CT with those of the corresponding histopathologic examinations. If one lymph node showed increased uptake on ^{18}F-FDG PET/CT images and had some findings on CT such as ≥10 mm diameter or round shape or hypoechogenicity or irregular margin or loss of fatty hilum findings and if histopathology showed lymph node with metastasis in the same neck level, this lymph node was accepted as a true positive finding for ^{18}F-FDG PET/CT. If metastatic lymph node number on histopathology was lower than lymph node numbers that were accepted as metastatic on ^{18}F-FDG PET/CT, the lymph node showing the lowest uptake was accepted as false positive. If metastatic lymph node number on histopathology was higher than lymph node number accepted as metastatic on ^{18}F-FDG PET/CT, it was recorded as false-negative lymph node for ^{18}F-FDG PET/CT.

Statistical Analysis

While evaluating the findings of the study, IBM SPSS Statistics 22 program (IBM SPSS, Turkey) was used for statistical analysis. The normal distribution of the parameters was evaluated by the Shapiro-Wilk test and it was found that the parameters did not show normal distribution. The Mann-Whitney U test was used to compare the parameters between the two groups. Receiver operating characteristic (ROC) curve analysis was performed to identify the best cut-off value and to evaluate whether $SUV_{max}LN$ and also $SUV_{max}LN/SUV_{max}PT$, $SUV_{max}LN/SUV_{max}A$ and $SUV_{max}LN/SUV_{max}L$ ratios provided diagnosis of lymph node metastasis. For the calculation of sensitivity and specificity, the screening test was used. A p value <0.05 was accepted as statistically significant.

Results

Patients general characteristics are given in Table 1. Histopathological examination revealed 71 metastatic lymph nodes in 21 patients (mean=3.5; range=1-12). On ^{18}F-FDG PET/CT imaging, 68 lymph nodes showing

Table 1. General characteristics of patients	
Total number of patients (n)	43
Laryngectomy	
-Partial	14
-Total	29
Neck dissection	
-Bilateral	39
-Unilateral	4
Histopathologic evaluation of lymph nodes	
-Metastatic	21
-Nonmetastatic	22

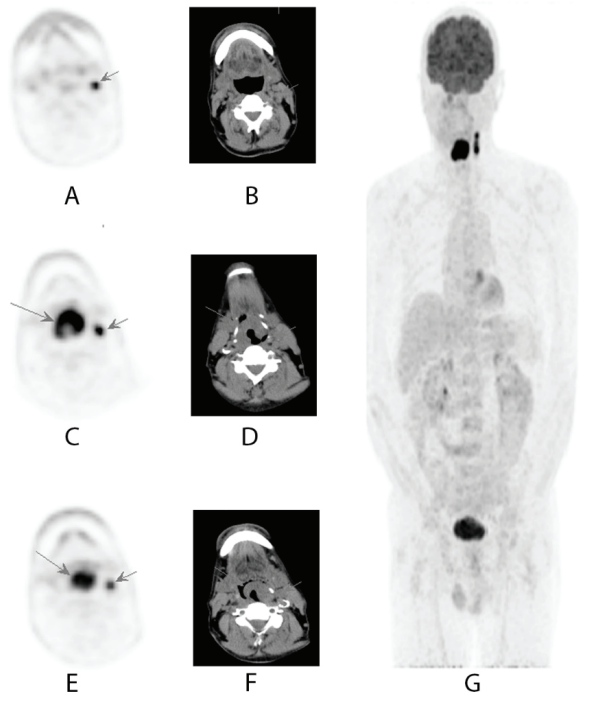

Figure 1. ^{18}F-FDG PET/CT with axial slice PET (A, C, E), axial slice CT (B, D, F) and whole-body PET (F) images of a 59-year-old patient with larynx squamous cell cancer. ^{18}F-FDG PET/CT imaging showed primary laryngeal hypermetabolic lesion and hypermetabolic lymph nodes at left upper and middle jugular region compatible with metastasis. He underwent total laryngectomy and left modified neck dissection. Histopathological examination revealed three metastatic lymph nodes

FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography

Table 2. Diagnostic performance of the quantitative metabolic parameters				
	Metastatic (n=69)	**Non-metastatic (n=25)**	**Total (n=94)**	**p**
	Avg ± SD (median)	**Avg ± SD (median)**	**Avg ± SD (median)**	
SUV_{max}LN	11.51±7.99 (10.14)	4.16±3.96 (3.25)	9.48±7.71 (5.87)	**0.000***
SUV_{max}LN/SUV_{max}L	2.77±1.73 (2.5)	1.21±1.03 (0.8)	2.35±1.72 (1.6)	**0.000***
SUV_{max}LN/SUV_{max}A	4.13±2.71 (3.5)	1.82±1.69 (1.2)	3.51±2.68 (2.3)	**0.000***
SUV_{max}LN/SUV_{max}PT	0.48±0.52 (0.4)	0.3±0.23 (0.2)	0.43±0.47 (0.3)	**0.014***
*p<0.04, Avg: Average, SD: Standard deviation, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, A: Aortic, L: Liver, PT: Primary tumor				

increased FDG uptake were evaluated by histopathological examination and metastasis was detected (Figure 1), but the histopathological examination of 26 lymph nodes showing ^{18}F-FDG involvement showed no metastasis. There was no pathological involvement on ^{18}F-FDG PET/CT in 3 lymph nodes with metastasis in 1 patient.

In patients with metastatic lymph nodes, the primary tumor SUV_{max} values were significantly higher than non-metastatic patients (26.76±10.43 vs 17.73±8.14; p=0.001). Mean SUV_{max}LN, SUV_{max}LN/SUV_{max}L ratio, SUV_{max}LN/SUV_{max}A ratio, and SUV_{max}LN/ SUV_{max}PT ratio were significantly higher in patients with metastatic lymph nodes than non-metastatic nodes (Table 2).

For diagnosis of lymph node metastasis with ROC analysis, the cut-off point for SUV_{max}LN was 3.87 (AUC 0.856, p: 0.000) with the sensitivity of 83.7%, specificity 77%, positive predictive value (PPV) 89.1% and negative predictive value (NPV) 58% (Figure 2). The cut-off point for SUV_{max}LN/SUV_{max}L was 1.08 (AUC 0.833, p=0.000), with a sensitivity of 84.1%, specificity of 76%, PPV 90.6%, and NPV 63.3% (Figure 3). The cut-off point for SUV_{max}LN/ SUV_{max}A was 1.78 (AUC 0.822, p=0.000) for the diagnosis of lymph node metastasis. The sensitivity of this value was 79.7%, specificity was 84%, PPV was 93.2%, and NPV was 60% (Figure 4). The cut-off point for SUV_{max}LN/SUV_{max}PT was 0.36 (AUC 0.666, p: 0.014) for the diagnosis of lymph node metastasis, with a sensitivity of 53.6%, specificity 76%, PPV 86.1%, and NPV 37.3% (Figure 5). When SUV_{max}LN >2.5 was taken as a criterion for the detection of metastatic lymph nodes, the sensitivity was 95.7%, the specificity was 26.9%, PPV was 78%, and NPV was 70%.

Discussion

Quantitative data obtained using ^{18}F-FDG PET/CT can be useful for lymph node assessment in addition to visual evaluation. In general practice, if a lymph node shows ^{18}F-FDG uptake and SUV_{max} value is more than 2.5, it is more

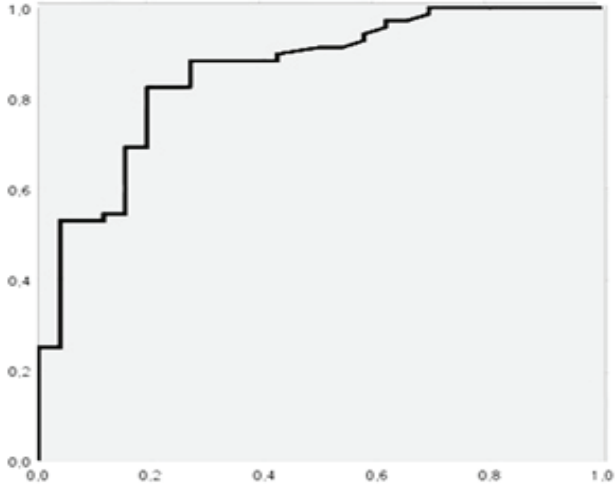

Figure 2. ROC curve for SUV_{max}LN in the diagnosis of lymph node metastasis
ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node

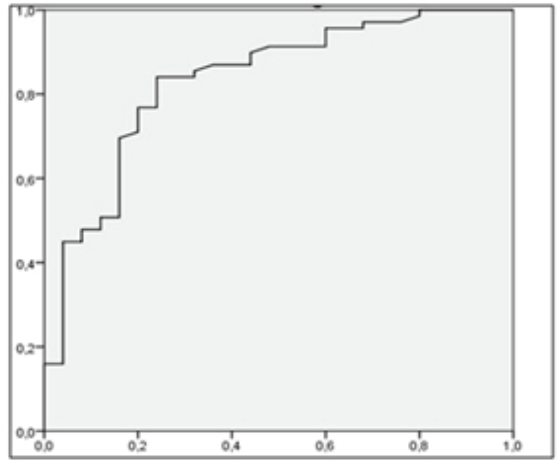

Figure 3. ROC curve for SUV_{max}LN/SUV_{max}L in the diagnosis of lymph node metastasis
ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, L: Liver

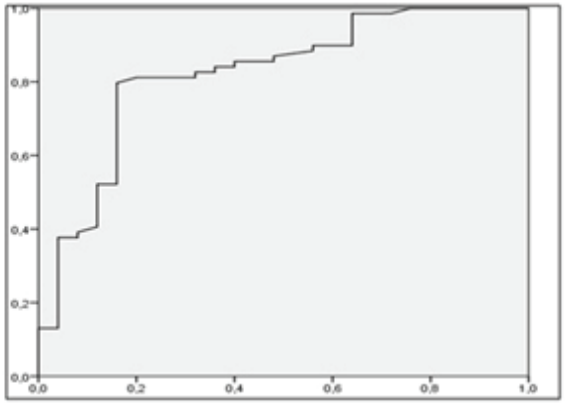

Figure 4. ROC curve for $SUV_{max}LN/SUV_{max}A$ in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value, LN: Lymph node, A: Aortic

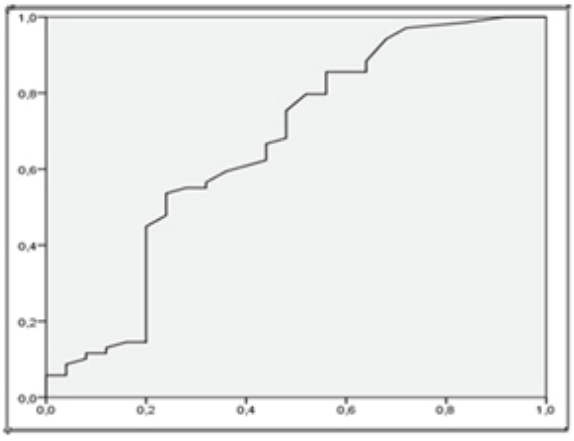

Figure 5. ROC curve for SUVmaxLN/SUVmaxPT in the diagnosis of lymph node metastasis

ROC: Receiver operating characteristic, SUVmax: Maximum standardized uptake value, LN: Lymph node, PT: Primary tumor

likely to be malignant (13). But, SUV_{max} value does not have sufficient diagnostic capability to detect metastatic lymph nodes in head and neck cancer. In our study, if SUV_{max} >2.5 was taken as the criterion for detection of metastatic lymph node, the sensitivity would be 95.7% and the specificity would be 26.9%. To increase diagnostic accuracy for detecting metastatic lymph nodes, different lymph node SUVmax cut-off value and proportional ratios reproduced from lymph node SUVmax are used (12,14,15,16,17).

In our study, the mean SUV_{max} values, $SUV_{max}LN/SUV_{max}L$ ratio, $SUV_{max}LN/ SUV_{max}A$ ratio, and $SUV_{max}LN/SUV_{max}PT$ ratio of metastatic lymph nodes were significantly higher than non-metastatic lymph nodes. In the ROC analysis, the cut-off point for $SUV_{max}LN$ was 3.87 for the diagnosis of lymph node metastasis, with a sensitivity of 83.7% and specificity of 77%. A study by Marshall et al. (16) included 114 patients with head and neck cancer and found that SUV_{max} cut-off was 3.9 and that yielded a sensitivity of 85% and specificity of 73%. Suenaga et al. (17) used a SUV_{max} cut-off value of 3.65 and found that sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT on a level by level basis were 72.9, 96.8, and 92.1%, while sensitivity, specificity, and accuracy of CT were 52.9, 98.6, and 89.6%, respectively (17).

In our study, cut-off values for $SUV_{max}LN/SUV_{max}L$ and $SUV_{max}LN/ SUV_{max}A$ were 1.08 and 1.78, respectively. The sensitivity and specificity for these cut-off values were 84.1%-76% and 79.7%-84%, respectively. These proportional values were proven to have higher AUC compared to $SUV_{max}LN/SUV_{max}PT$ ratio and have high diagnostic power for the diagnosis of metastatic lymph node. We think that this situation is due to the variance in SUV_{max} of the primary tumor due to the size or histopathological features of the tumor. The specificity of all 3 proportional values we examined in our patient group was higher when SUV_{max} >2.5 criterion was used. Lim et al. (12) studied 74 patients with HNSCC and found that nodal SUV_{max} ≥3.16 yielded a sensitivity of 74.4% and specificity of 84.9% in detecting metastatic nodes and also that nodal $SUV_{max}LN/SUV_{max}L$ ratio ≥0.90 yielded a sensitivity of 74.1% and specificity of 93.4%.

Study Limitations

There are some limitations of the present study. It was a retrospective study with a limited number of patients. As the study was retrospective, there were technical impediments to the matching of the lymph nodes detected on ^{18}F-FDG PET/CT imaging and histopathological examination. Because the precise spatial correlation between ^{18}F-FDG PET/CT and histopathology was impossible and one to one matching between them showed increased uptake on ^{18}F-FDG PET/CT and metastatic lymph nodes on histopathologic evaluation could not be attributed due to the retrospective study design; analysis of results of the study should use this model. Therefore, there is a need for prospective studies with larger samples.

Conclusion

$SUV_{max}LN/SUV_{max}A$, $SUV_{max}LN/SUV_{max}L$, and $SUV_{max}LN/ SUV_{max}PT$ ratios can be used safely for diagnostic evaluation of metastasis in cervical lymph nodes on ^{18}F-FDG PET/CT imaging in patients with LSCC.

Ethics

Ethics Committee Approval: Ethics Committee Approval was obtained from Okmeydanı Training and Research Hospital Ethics Committee with the decision number "1066" and date "12.04.2018".

Informed Consent: The written informed consent was obtained from all patients at the time of imaging.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Ü., Y.A., Y.U., Concept: S.S.K., S.K., O.G., Design: S.S.K., S.K., O.G., Data Collection or Processing: S.S.K., S.K., O.G., O.Ü., Y.A., Y.U., Analysis or Interpretation: S.S.K., S.K., O.G., Literature Search: S.S.K., S.K., O.G., Writing: S.S.K., S.K., O.G.

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