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Correlation of Diffusion-weighted MR imaging and FDG PET/CT in the Diagnosis of Metastatic Lymph Nodes of Head and Neck Malignant Tumors

Şamil Şahin[1], Yasar Kemal Duymaz[2], Burak Erkmen[3], Burak Karabulut[4], İldem Deveci[5], Mehmet Sürmeli[5], Aslı Şahin Yılmaz[6], Aslıhan Semiz Oysu[7], Çağatay Oysu[8]

[1] Private Clinic, Istanbul, Turkey
[2] Department of Otolaryngology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey
[3] Department of Otolaryngology, University of Health Sciences, Sancaktepe Martyr Prof Dr Ilhan Varank Training and Research Hospital, İstanbul, Turkey
[4] Private Clinic, Istanbul, Turkey
[5] Private Medient Hospital, Istanbul, Turkey
[6] Department of Otolaryngology, University of Health Science, Lütfi Kırdar Training and Research Hospital, Istanbul, Turkey
[7] Department of Radiology, Marmara University, School of Medicine, Istanbul, Turkey
[8] Department of Otolaryngology, Marmara University, School of Medicine, Istanbul, Turkey

ABSTRACT

Objective: The aim of this study was to investigate the efficacy of diffusion-weighted magnetic resonance imaging (DW-MRI) as a reliable imaging modality for detecting metastatic neck lymph nodes of head and neck squamous cell carcinoma (SCC).

Methods: Thirty-two patients underwent positron emission tomography computed tomography (PET/CT) and DW-MRI were evaluated. Histopathologic analysis of lymph node metastases was used as the gold standard for assessment. We analyzed differences in sensitivity, specificity, accuracy, positive predictive value and negative predictive value among the imaging modalities using the Chi-square test. Their discriminative power evaluated using the Receiver-Operating Characteristic curve and calculation of the area under the curve. The correlation between ADCmin and SUVmax was calculated using the Spearman test. SPSS 24 was used for statistical analyses. P value of 0.05 indicates a statistically significant difference.

Results: A total of 32 patients with 50 neck dissections with head and SCC included. Sensitivity, specificity, accuracy, positive and negative predictive value of neck palpation was 72%, 60%, 70%, 62% and 80% respectively. Sensitivity, specificity, accuracy, positive and negative predictive value of DW-MRI was 87.5%, 96.2%, 92%, 95.5% and 89.3% respectively, according to ADCmin cutoff value 0.82×10-3s/mm2 . Sensitivity, specificity, accuracy, positive and negative predictive value of FDG-PET/CT was 91.7%, 100%, 96%, 100% and 92.9%, respectively, according to SUVmax cutoff value 3.4. For all neck dissections, there was a statistically significant inverse correlation between ADCmin and SUVmax (P<001).

Conclusion: DW-MRI may be as reliable as FDG-PET/CT in detecting cervical lymph node metastases. DWI and FDG PET/CT can play a complementary role in clinical evaluation. Further research is needed.

Keywords: Diffusion-weighted magnetic resonance imaging, head and neck cancer, squamous cell carcinoma, Fluoro-2-deoxy-d-glucose-Positron emission tomography

INTRODUCTION

Head and neck tumors are 5% of all malignant tumors, the sixth most common among all cancers, and the incidence is increasing in developing countries [1,2]. Squamous cell carcinoma(SCC) is the most common histopathological type and constitutes approximately 90% of all head and neck tumors [3]. The stage of the tumor is important in determining the treatment method of the patient. Lymph node involvement has an important place in the staging of the patient and significantly affects the prognosis and survival of the patient [1]. Therefore, the presence of lymph node metastases must be accurately determined.

Fluoro-2-deoxy-d-glucose-Positron emission tomography (FDG-PET) is a non-invasive imaging technique using positron

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Corresponding Author: Yaşar Kemal Duymaz **E-mail:** dryasarkemalduymaz@gmail.com

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emitting isotopes. Positron emission tomography/ Computed tomography (PET/CT) is a hybrid imaging method formed by the combination of Positron Emission Tomography and Computed Tomography devices. Because PET/CT scans the whole body, it successfully reveals the extention of the cancer [4].

Diffusion weighted imaging (DWI), one of the Magnetic Resonance Imaging (MRI) methods, is a functional method examining the random movements and microscopic diffusion of water molecules in tissues [5]. This phenomenon can be measured and can be expressed as the diffusion coefficient. Complete free diffusion of molecules is not possible in biological tissues due to constraints such as cell membranes or molecular boundaries. The measured magnitude of the conducted diffusion of molecules in the human body is known as the Apparent Diffusion Coefficient-Apparent Diffusion Coefficient (ADC). The ADC value expresses the rate of diffusional motion and is obtained by measuring and calculating the signal intensity on a series of diffusion-weighted MRI images. While malignant lesions show low ADC values, high ADC values are observed in benign lesions [6].

The aim of our study is to investigate the usability of DW-MRI, which has become widespread in recent years, as a reliable imaging method as PET/CT, which is the preferred imaging method in classical metastasis scanning, in detecting lymph node metastasis of head and neck squamous cell carcinomas.

METHODS

This study was carried out in the Ear Nose Throat Clinic and Radiology Clinic of a tertiary hospital between June 2017 and December 2017. The study was approved by the Ethics Committee on 28.02.2017 with the barcode number 4656.

121 neck dissection specimens that were applied to 91 patients who were diagnosed with head and neck SCC in our clinic between December 2014 and December 2017 and underwent neck dissection with primary tumor surgery were included in the study. Patients who did not undergo any of the PET/CT and DW-MRI methods, had an MRI performed in an external center, and whose imaging methods could not be performed in accordance with the standards due to technical deficiencies were excluded from the study. After inclusion and exclusion criteria, 50 neck dissections performed in 32 patients were included in the study (Figure 1). There was a maximum interval of 20 days between both imaging modalities.

Neck MRI examinations of 32 patients in the study series were performed on a 1.5 Tesla MR device (Siemens Avanto). T1 weighted with SE technique with 4 mm section thickness in coronal plane, T2 weighted with FAT SAT FSE technique with 4 mm section thickness in coronal plane, T1 weighted with SE technique with 6 mm section thickness in axial plane, T2 weighted with FSE technique with 6 mm section thickness in axial plane, T1-weighted sequences were added in the axial and coronal planes after intravenous contrast agent administration. Diffusion-weighted images and ADC maps were obtained for each patient by applying diffusion sensitive gradients in all three directions (x, y, z) at two different b values (0 and 1000 mm2/s). ADC maps of the lesions were automatically constructed on the main console. Then, the signal intensity of the lesion was measured by the radiologist in the radiology clinic of our hospital, and the region of interest (ROI) was defined. ROI was measured from solid areas in lymph nodes with a short axis greater than 1 cm. ADC values of the lesions were calculated from the ROI.

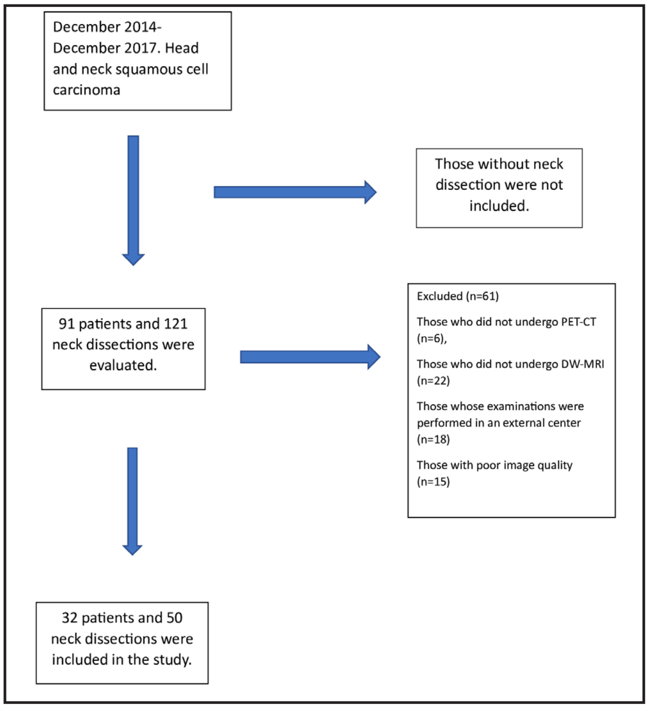


Figure 1. Inclusion criteria of patients

Before the PET/CT study, patients were fasted for an average of 10 hours. One hour before the radiopharmaceutical injection, 30 cc of oral contrast agent diluted with 1.5 liters of water was administered. Before the FDG injection, the blood glucose levels of all patients were checked. Imagimgs of patients with blood glucose levels above 200 mg/dl were not performed. 9-15 mCi (333-555 MBq) of F-18 FDG was given intravenously to the patients. The patients were rested without chewing or talking in a calm and room temperature environment until the post-injection imaging began. Whole body PET/CT imaging was performed 60-90 minutes after injection.

PET/CT imaging, with enhanced detector technology with increased sensitivity and spatial resolution, 17 cm field of view (FOV) and 5.47mm for 2D, 6mm for 3D, retractable septal allowing imaging in 2D and 3D modes, 8 Helical CT section was performed with PHILIPS Gemini TF 64 Slice PET/CT device. The patients were imaged in the supine position with their arms to the side or with the arms up. The patients were instructed to breathe normally during the acquisition. Following the CT topogram image, CT images covering the vertex-upper thigh were acquired at a tube current of 60 mA and a tube voltage of 140 kV at a rotation rate of 0.8 seconds per rotation. PET imaging started immediately after CT imaging. PET acquisition time was 2-3 minutes per bed position, according to the patient's weight and 2D/3D acquisition protocol. Scatter and attenuation corrections of PET images were performed with the CT data. Evaluation was made by obtaining MIP (maximum intensity projection) and PET, CT and PET/CT fusion images in the transaxial, coronal and sagittal planes. The suvmax values of the lymph nodes defined in the PET/CT report of the patients, which were defined as malignant lymph node in the foreground and benign lymph node in the foreground, were added together and averaged.

All neck triangles of the patients were palpated bilaterally. The size, location, stiffness of the palpable lymph nodes and their relationship with the surrounding tissues were noted. Sensitivity, specificity and accuracy in neck palpation were evaluated by comparing with histopathological results.

While evaluating the findings obtained in the study, SPSS 2.4 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating the study data. The chi-square test was used to compare qualitative data. ROC (Receiver Operating Characteristic) analysis was applied to determine the cut-off point for SUVmax and ADC. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

RESULTS

32 patients included in the study, 29 (90.6%) were male and 3 (9.6%) were female, with a mean age of 60.47 (SD: 12.72). The 50 types of neck dissections performed are shown in Table 1.

At least 1 lymph node was detected on the same side as the primary tumor in 21 (65%) patients, and at least 1 bilateral lymph node was detected in 4 (12%) patients. Lymph nodes were detected on palpation in 29 of 50 neck dissections performed in 32 patients. The calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive values of palpation were 72%, 60%, 70%, 62% and 80%, respectively (Table 2).

At least 1 lymph node was detected on the same side as the primary tumor in 14 (43%) patients, and at least 1 lymph node bilaterally in 4 (6%) patients. DW-MRI detected lymph nodes in 22 of 50 neck dissections performed in 32 patients (Figure 2). Lymph nodes below the ADC value of 0.82×10-3s/mm2 were evaluated as benign and above as malignant. Taking the ADC cut-oFF value as 0.82×10-3s/mm2, the calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive value values were 87.5%, 96.2%, 92%, 95.5% and 89.3%, respectively (Table 2). Upon the usability of the ADC value in the differential diagnosis of malignant and benign lymph nodes, the area under the curve (AUC) was 0.965 and the standard error was 2.4% in the obtained ROC curve (Figure 3).

Table 1. Data of gender, age and Primary cancer site and neck dissection

		Functional neck dissection	Radical neck dissection	Supraomohyoid neck dissection	One side Functional, other side Radical neck dissection	
Primary Tumour	Larynx	12 (66.6%)	4 (22.2%)	0	2 (11.2%)	18
	Tonsil	1 (50%)	1 (50%)	0	0	2
	Oral Cavity	6 (54.5%)	0	4 (36.3%)	1 (9.2)	11
	Parotid Gland	0	1 (100%)	0	0	1
Total		19 (59.3)	6 (18.8)	4 (12.5%)	3 (9.4%)	32
Sex		Male		Female		
		29 (90.6%)		3(9.4%)		32
Mean age(sd)		71.17(21.07)		56.33(9.56)		p=0.09

Table 2. Sensitivity, specificity, accuracy, positive predictive value and negative predictive values of neck palpation, DW-MRI and PET-CT

Method	Sensitivity	Specificity	Accuracy	PPV	NPV
Neck Palpation	72%	60%	70%	62%	80%
DW-MRI	87.5%,	96.2%	92%	95.5%	89.3%
PET-CT	91.7%	100%	96%	100%	92.9%

DW-MRI: Diffusion-weighted magnetic resonance imaging
PET-CT: positron emission tomography - computed tomography
PPV: positive predictive value
NPV: negative predictive value

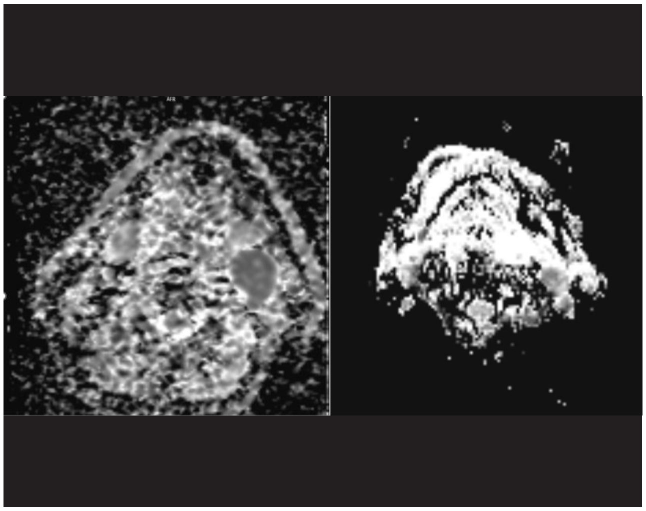
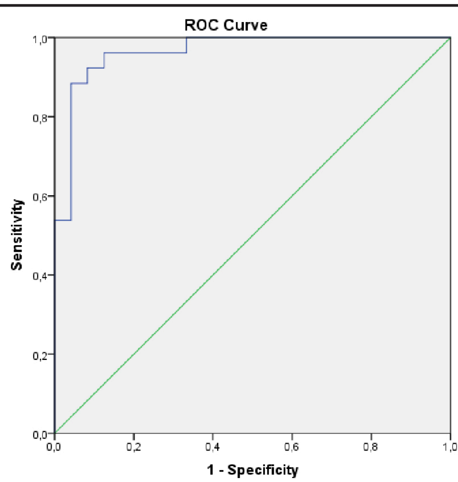


Figure 2. DW-MRI image

At least 1 lymph node was detected on the same side as the primary tumor in 14 (43%) patients, and at least 1 bilateral lymph node was detected in 4 (12%) patients. PET/CT detected lymph nodes in 22 of 50 neck dissections performed on 32 patients (Figure 4). Lymph nodes with a SUVmax level below 3.4 were considered benign and above it malignant. Taking SUVmax cut-off value of 3.4, we calculated sensitivity as 91.7%, specificity as 100%, accuracy as 96%, positive predictive value as 100%, and negative predictive value as 92.9% (Table 2). Based on the utility of SUVmax in the differential diagnosis of malignant and benign lymph nodes, the area under the curve (AUC) was 0.977 and the standard error was 2.4% in the obtained ROC curve (Figure 5).



Area Under the Curve

ADC

Area	Std. Error(a)	P	95% (Confidence Interval)	
			Upper	Lower
0,965	0,024	0,000	0,918	1,000

Figure 3. ADC- Roc Curve. (AUC:0.965 Std Error:0.024). ADC has high reliability in detecting lymph node metastases.

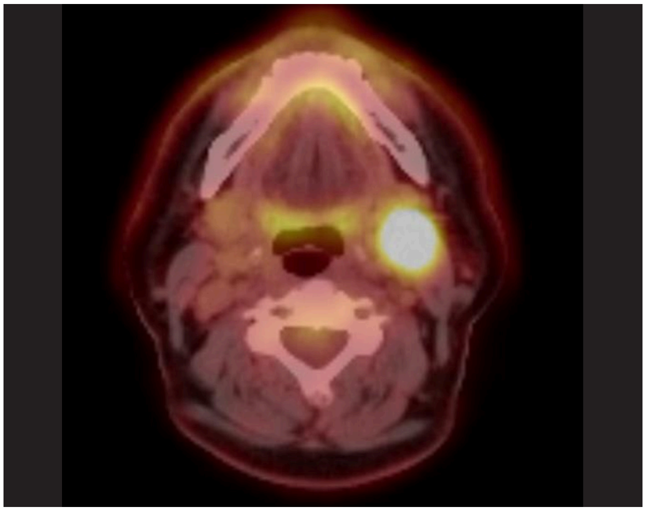
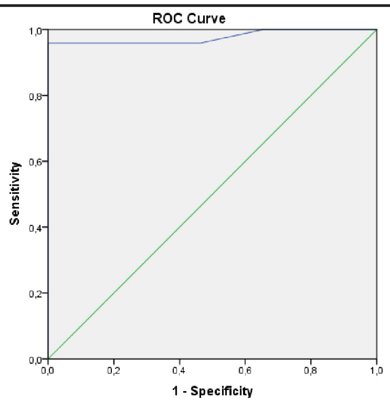


Figure 4. PET-CT image



Area Under the Curve

SUVmax

Area	Std. Error(a)	P	95% (Confidence Interval)	
			Upper	Lower
0,977	0,024	0,000	0,931	1,000

Figure 5. SUVmax- Roc Curve. (AUC:0,977 Std Error:0,024). SUVmax has high reliability in detecting lymph node metastases.

16 (50%) patients had at least 1 SCC metastasis on the same side as the primary tumor, and 3 (9%) patients had at least 1 bilateral lymph node with SCC metastasis. Lymph nodes with SCC metastases were detected in 22 of 50 neck dissections performed in 32 patients. In the pathological staging, 24 (75%) of the patients were in the advanced stage and 8 (25%) were in the early stage.

The correlation between SUVmax and ADCmin was analyzed by Spearman Correlation test. It was found that there was a statistically significant inverse correlation between both parameters. ($p<0.001$) (Figure 6).

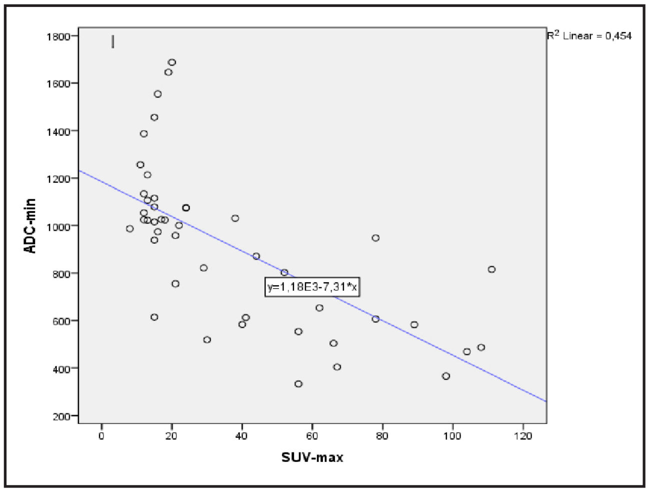


Figure 6. SUV-max and ADC correlation curve There is a statistically significant inverse correlation between SUVmax and ADC.

DISCUSSION

In our study, patients who were diagnosed with SCC in the head and neck and underwent neck dissection with primary surgical treatment were discussed. Preoperative PET/CT and DW-MR imaging and postoperative histopathological results of the patients were evaluated in terms of lymph node metastasis based on the relevant neck side. It has been found that DW-MRI is at least as successful and reliable as PET/CT in recognizing neck metastases of head and neck squamous cell carcinomas.

The most important feature of head and neck malignancies in general is that they spread to lymph nodes in the neck before spreading anywhere in the body. In other words, while distant metastases are rare in patients with head and neck malignant tumors, cervical lymph node metastasis is quite common [7]. It is accepted that lymph node metastasis is a major prognostic factor for these patients and neck relapses are the main cause of treatment failure in these patients [8,9]. For this reason, it is necessary to accurately evaluate the condition of the neck at the stage of diagnosis of the disease. The basic examination method in the evaluation of the neck is primarily palpation. However, in order for the lymph nodes to be palpable clinically, they should be 0.5 cm in diameter in the superficial regions and at least 1 cm in the deep regions. However, it has been suggested that the probability of histologically positive lymph node in a patient with negative neck palpation is between 4-60% [10]. In general, it has been reported that the correct detectability of neck metastases by palpation is between 60-65%, and false positive and negative results can be obtained [11]. Therefore, advanced radiological imaging is needed in addition to palpation in neck evaluation. These radiological methods basically enable the detection of pathological lymph nodes that cannot be detected by physical examination, the evaluation of extranodal spread in the existing lymph node, and the determination of vital organ invasions adjacent to the lymph nodes.

In our study, the rate of lymphatic metastases was 59.4%. The neck evaluation of our patients was first performed by detailed palpation method including all neck regions. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value ratio of palpation were 72%, 60%, 70%, 62% and 80%, respectively. These results were found to be similar to the results of some studies in the literature [10,11]. In accordance with the results of our study, we also think that the rate of bias and error will be high in the evaluation of pathological lymph nodes in the neck by palpation.

When the literature is examined, diffusion-weighted MR imaging has found to be useful in different parts of the head and neck. The first study in this area was on the characterization of head and neck masses by Wang et al [6]. As a result of the study, they found the mean ADC values of benign masses to be significantly higher than the average ADC values of malignant masses. Sumi et al. studied the differential diagnosis of metastatic neck lymph nodes with diffusion-weighted MRI in 2003 [12]. In a study on neck lymph nodes, it was found that the differentiation of necrotic and non-necrotic solid parts of malignant masses can be done by making ADC mapping of the mass as a new technique [13].

In the study by Sumi et al., ADC values in metastatic lymph nodes were shown to be significantly higher than in benign lymph nodes [12]. On the other hand, in the study by Abdel Razek et al., the mean ADC values measured in metastatic and lymphomatous lymph nodes were significantly lower than those measured in benign nodes [13]. Although the reason for the discrepancy between these two studies is unclear, continuing research using larger patient groups will help to clarify the uncertainty on this issue. In our study, unlike Sumi et al., metastatic mean ADC values were significantly lower than benign lymph nodes ($p<0.05$), but overlap was observed in some cases. Another factor that increases the ADC value in metastatic lymph nodes is necrosis foci, and necrosis is frequently observed in carcinoma metastases. The high ADC values of malignant lymph nodes in the study of Sumi et al. may be due to foci of necrosis.

The use of DW-MRI to differentiate malignant from benign lymph nodes has been investigated in a limited number of studies. Studies have shown that the sensitivity of DW-MRI in differentiating lymph nodes from benign and malignant ranges between 52-98% and specificity between 88-97% [6,12–14]. In the study conducted by Wang et al. in 2001, it was stated that 1.22 x 10-3mm2/s could be used as the cut-off point, with 84% sensitivity and 91% specificity, as the ADC value in the differential diagnosis of benign and malignant masses in head and neck masses. The study included a series of 97 lesions in 97 patients [6]. In the study conducted by Abdel Razek et al. in 2008 in a series of 78 pediatric head and neck masses, the cut-off value was taken as 1.25X10-3mm2/s and 1.25X10-3mm2/s can be used with a 94.4% sensitivty and specificity of 91.2% in benign and malignant head and neck masses [13]. Vandecaveye et al. evaluated the superiority of DW-MRI over other MRI techniques in the detection of head and neck squamous cell carcinoma metastases in 33 patients in 2009, taking the cut-off value of 0.94X10-3mm2/s, with a sensitivity of 84%, a specificity of 94% and an accuracy of 91% [14]. In our study, the ADC cut-off value was 0.82×10-3s/mm2 in the detection of neck lymph node metastasis in 32 patients diagnosed with head and neck squamous cell carcinoma, and the calculated sensitivity, specificity, accuracy, positive predictive value and negative predictive value values were 87.5%, 96.2%, 92%, 95.5% and 89.3% respectively. Consistent with the literature, we found that the use of DW-MRI in lymph node metastasis has a high diagnostic value.

Threshold values for diagnosing malignancy, separating lymphoma from carcinoma and separating malignant lymph nodes from benign lymph nodes have generally been studied on 1.5 T magnets to date, and these values should be defined for each MRI system separately. Because there are several variations between MRI units, pulse sequences, and functioning of the units [6]. Huisman et al. showed that ADC and fractional anisotropy values measured in brain gray and white matter were different in 1.5 and 3T devices. Therefore, it is necessary to investigate whether the ADC differences measured with 1.5T in benign and malignant neck masses are also valid at higher magnetic field strengths [15]. In the study of Srinivasan et al., a total of 33 patients with malignant and benign lesions were evaluated in a 3T MRI device, and the threshold value could be determined [16]. Magnetic resonance neck imaging of the patients in our study was studied using 1.5 Tesla magnets. Since there are limited number of studies with small patient groups in the literature on this subject, it is necessary to continue research and compare the results in different magnetic fields.

PET/CT imaging, in which both the metabolic and morphological features of the disease can be evaluated, has important advantages in staging head and neck cancers, identifying the tumor of unknown primary, monitoring the treatment, and determining the residual-recurrent tumor. Especially in oral cavity tumors, the sensitivity of PET is higher than CT and MR. The diagnostic performance of PET/CT in oral cavity tumors is 96.3%, 77.8% of CT and 85.2% of MRI [17].

PET/CT is the method of choice for staging locally advanced head and neck cancers due to its high sensitivity in distant metastasis research. In newly diagnosed oral cavity cancers, 24% additional (not detected by clinical examination, chest X-ray and thorax CT) distant metastases and a second primary tumor were detected with PET/CT. TNM staging was changed in 31% of patients with head and neck cancer staged by CT-MR. Distant metastases are unlikely in T1 disease and radiological staging is unnecessary. The necessity of radiological staging in T2 patients is controversial. PET/CT is the imaging modality of choice in locally advanced (T3-T4) patients [17].

The sensitivity of the use of FDG-PET/CT in the detection of lymph node metastases in head and neck squamous cell carcinomas was found to be 50-100% [4,18-19]. Ng et al. found that the diagnostic accuracy of FDG-PET/CT in the detection of lymph node metastasis in patients with head and neck squamous cell carcinoma was calculated according to neck levels with a sensitivity of 74.7% and a specificity of 93% [20]. Few studies have been reported evaluating SUVmax of metastatic lymph nodes in the neck. Murakami et al. calculated SUVmax cut-off 1.9 <10 mm diameter, cut-off 2.5 for 10-15 mm, and cut-off 3.0 for >15 mm, calculated according to neck levels with FDG-PET/CT sensitivity of 79% and specificity of 99% [21]. In our study, we calculated the SUVmax cut-off value as 3.4.

Sun et al. evaluated a total of 1270 patients in 24 studies in their Review study. As a result, number-based sensitivity/specificity was 91%(82-95%)/87%(80-92%), neck side-based sensitivity/specificity was 84%(75-90%)/83%(77-88%), and neck level-based sensitivity/specificity was calculated as 80% (71-87%)/96% (94-97%) [22]. In the study conducted by Kitajima et al. in 2015 on the clinical importance of SUVmax in 18F-FDG PET/CT scan for the detection of nodal metastases in patients with oral squamous cell carcinoma, the sensitivity was 67%, the specificity was %94.6 , accuracy 91.6%, positive predictive value 61.3%, negative predictive value 95.9% ; in the analysis performed according to the number of neck sides with a cut-off value of 3.5, sensitivity was 84.6%, specificity was 87%, accuracy was 86.1%, positive predictive value was 78.5% ,negative predictive value was 90.9% [23]. In our study, in the detection of neck lymph node metastasis of 32 patients diagnosed with head and neck squamous cell carcinoma, taken the SUVmax cut-off value as 3.4 in the calculation based on neck dissection, we calculated the sensitivity 91.7%, specificity 100%, accuracy 96%, positive predictive value 100%, negative predictive value as 92%. In accordance with the literature, we found that the use of PET/CT in lymph node metastasis has a high diagnostic value.

In the study conducted by Nakamatsu et al. in which 24 patients were included, lymph nodes whose pathology results were interpreted in favor of metastasis were detected in DW-MRI and PET/CT, and an inverse correlation was found between ADCmin and SUVmax values [24]. In our study, which included 32 patients based on the number of neck side and dissection, a statistically significant inverse correlation was found between ADCmin and SUVmax, similar to those of Nakamatsu et al. ($p<0.001$).

There were several limitations in our study. First, our study was retrospective. Second, relatively few patients were included in the study after the inclusion criteria. Due to the small number of patients, it was difficult to draw definitive conclusions. Further studies with prospective and larger patient series are needed.

CONCLUSION

PET/CT and DW-MRI have high reliability in detecting lymph node metastasis of head and neck squamous cell carcinomas. Combined use of both imaging modalities can be used as a guide when planning neck treatment.

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SS, BE, BK, ASY; Supervision: YKD, ID, ASY, CO; Fundings: SS, ID; Materials: MS, CO, ASO; Data Collection and Processing: SS, BK, MS, ASO; Analysis and Interpretation: YKD, MS, ASY; Literature Review: YKD, BE, BK, ID, ASO; Writing: SS; Critical Review: YKD, ASY, CO. All authors read and approved the final version.

Ethics Committee Approval: This study was carried out in the Ear Nose Throat Clinic and Radiology Clinic of a tertiary hospital between June 2017 and December 2017. The study was approved by the Ethics Committee on 28.02.2017 with the barcode number 4656.

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