Diagnostic performance of FDG PET/MRI for cervical lymph node metastasis in patients with clinically N0 head and neck cancer

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Abstract. – OBJECTIVE: Treatment management in cases of head and neck squamous cell cancer (HNSCC) that are clinically negative for lymph node metastases (cN0) is still an important topic of discussion. There is increasing interest in sensitive imaging modalities that can detect the risk of occult metastases at levels below 20%. This study aimed to examine the efficacy of integrated positron emission tomography (PET)/magnetic resonance imaging (MRI) in determining neck nodal metastasis status in cN0 patients with HNSCC.

PATIENTS AND METHODS: In this retrospective study, 44 patients who underwent neck dissection with the diagnosis of HNSCC between January 2018 and August 2020 were analyzed. Clinical examinations, including ultrasonography, were performed to identify cervical metastases in HNSCC patients with preoperative cN0. A nuclear medicine specialist visually evaluated the MRI, PET, and PET/MRI results.

RESULTS: Histopathologically, 86.4% of patients were classified as N0. According to the histopathological results, MRI showed 50% sensitivity, 89.5% specificity, 91.8% negative predictive value (NPV), 42.8% positive predictive value (PPV) and 84% accuracy, while PET showed 83.3% sensitivity, 68.4% specificity, 96.2% NPV, 29.4% PPV and 70.4% accuracy. PET/MRI was more successful in distinguishing pathological N0 and N+ patients (83.3% sensitivity, 92.1% specificity, 97.2% NPV, 62.5% PPV and 90.9% accuracy).

CONCLUSIONS: PET/MRI is more sensitive and has a higher NPV compared to MRI alone, while its sensitivity was found to be comparable to that of PET. In addition, with its ability to detect pathological N0 patients, PET/MRI may significantly decrease the number of unnecessary neck dissections.

Key Words:
Cancer of head and neck, Lymph nodes, Metastases, Magnetic resonance imaging, Positron emission tomography.

Introduction

In cases of head and neck squamous cell cancer (HNSCC), the eighth most common malignancy worldwide, most patients present with clinical positivity for lymph node metastases (LNM) of the neck (cN+) at the time of diagnosis[1,2]. Nodal involvement plays a pathological role in the development of regional recurrence and distant metastasis. Therefore, it is an important prognostic factor in treatment and post-treatment surveillance[3,4].

Globally, surgery remains the first-line treatment for head and neck cancers[5]. Treatment decisions are made based on clinical examinations and imaging findings. In patients with cN+ cancers, treatment is managed with radiotherapy, neck dissection, or a combination of these approaches[6]. In patients with HNSCC clinically negative for LNM (cN0), a management strategy including a "watchful waiting policy" or elective neck dissection is applied[7]. However, watchful waiting policy may lead to nodal recurrences in the future. Elective neck therapy is indicated in the case of >20% risk of occult LNM. However, this leads to high negative predictive values (NPV)[8,9]. Therefore, accurate staging with imaging methods is of significant prognostic importance.

Modern imaging modalities such as ultrasound (US), computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) offer similar diagnostic accuracy in the assessment of cN0 neck but remain insufficient[7,9]. Fusion or new hybrid imaging modalities combining the metabolic information of PET can increase the diagnostic accuracy. PET/CT shows higher accuracy for cN+ neck with relatively lower efficacy for cN0 neck[10,11]. Preliminary findings[12] for

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PET/MRI have primarily been obtained among unselected HNSCC cohorts and deliver similar performance to PET/CT. Despite these preliminary results, PET/MRI may offer higher sensitivity and tumor conspicuity in detecting perineural spread[13,14]. The majority of current hybrid imaging studies involving cN0 patients with HNSCC have focused on PET/CT and limited findings are available for PET/MRI. Therefore, this study aimed to investigate the efficacy of PET/MRI in determining neck nodal metastasis status in cN0 patients with HNSCC.

Patients and Methods

Study population

This retrospective study was conducted between January 2018 and August 2020 in the Department of Otorhinolaryngology of the Gazi University Faculty of Medicine with the approval of the relevant Ethics Committee (Date: 21.09.2020, Decision No.: 621). Informed consent was obtained from all patients.

The radiology records of 95 patients who presented to the Department of Otorhinolaryngology with a diagnosis of head and neck cancer between January 2018 and August 2020 and who underwent neck dissection procedures were reviewed. Patients were excluded from the study if they had previously received radiotherapy or chemoradiotherapy, had undergone surgery, had not undergone PET/MRI studies, had pathologies other than squamous cell carcinoma, salivary gland, and nasopharyngeal cancers, or had relapse or cN+ cancer. Forty-four patients with cN0 diagnoses according to physical examinations and US performed in the preoperative period were included in the study.

The patients' preoperative neck PET/MRI scans were evaluated by a nuclear medicine physician with at least 5 years of experience. Postoperative pathology results were obtained from the hospital database. According to histopathological results as the gold standard, patients with LNMs in neck dissection specimens were evaluated as pN+.

Imaging Protocol

All images were obtained with an integrated 3-T PET/MRI scanner (GE SIGNA, GE Healthcare, Waukesha, WI, USA) with a time-of-flight PET detector. Patients were situated on the scanning table in the supine position and a head-neck coil was used. All patients had fasted for 6 hours before scanning and their serum glucose levels were below 200 mg/dL before the injection of 3.7 MBq/kg 18F-fluorodeoxyglucose (18F-FDG). Approximately 1 h after the injection, patients were placed on the PET/MRI scanner bed. A whole-body PET/MRI was followed for the initial localizer scan. A three-dimensional dual-echo fast spoiled gradient-echo liver-accelerated volume acquisition sequence (LAVA-FLEX) was applied for MRI-based attenuation correction (MRAC). A whole-body PET/MRI was followed by a high-resolution axial T1 weighted three-dimensional LAVA-FLEX sequence, coronal T2 weighted fast-recovery fast spin echo sequence, complete body diffusion-weighted images (DWI, b values=50, 1,000) and apparent diffusion coefficient mapping. PET emission scans were logged jointly with MRI sequences and the acquisition time per bed position was 3 min. Dedicated local head and neck dedicated MRI scans were also acquired without IV contrast injection in the same imaging session and they included axial T2-weighted water, in-phase, and out-phase images, and sagittal T2-weighted propeller images. For attenuation correction, an atlas-based attenuation correction map was used for the head and a vendor-based algorithm using MRI-based attenuation correction data was applied for the remaining body parts.

Image Interpretation

All images were visually assessed retrospectively by a nuclear medicine specialist at a vendor-based workstation (AW Volume Share 5, GE Healtcare, Waukesha, WI, USA). One month after the preoperative MRI and PET assessments, combined PET/MRI images were assessed by the same nuclear medicine specialist, who was blinded to the histopathological results. In MRI, a minimum axis diameter of >10 mm, a round or spherical shape, and a necrotic or indistinct spiculated node were considered radiological criteria for malignant nodes. In visual PET evaluations, the presence, number, and localizations of 18F-FDG positive neck lymph nodes, which had tracer uptake above the background, were recorded for each patient. This was evaluated regardless of lymph node size. Integration images from regional PET and MRI images were combined for LNM detection. LNM positivity by combined PET/MRI was defined as the presence of i) MRI positive but PET negative, ii) PET positive but MRI negative, or iii) both PET and MRI positive neck lymph nodes. If both MRI and PET images gave negative results, the case was considered negative for the presence of LNM by combined PET/MRI. The PET/MRI images of four different patients are shown in Figure 1.

Statistical Analysis

The normal distribution of numerical variables was assessed by Kolmogorov-Smirnov test. Test results found to be non-parametric, and data were shown as median (min-max). Categorical variables were indicated as numbers and percentages. Diagnostic performance analysis was conducted with receiver operating characteristic (ROC) curve analysis. The diagnostic accuracies of the MRI, PET, and PET/MRI scans were assessed based on histopathological results as the gold standard for the assessment of LNM. Diagnostic performance was demonstrated by specificity, sensitivity, NPV and positive predictive value (PPV), and accuracy. *p*-value <0.05 was taken as statistical significance. MedCalc Software (version 11.4.2, MedCalc Software, Ostend, Belgium) was used in determining diagnostic accuracy.

Results

The median age of the cN0 patients with HNSCC was 66 years and 84.1% were male. A human papillomavirus test of all patients was negative before neck dissection. The primary site was the larynx/hypopharynx in most cases (43.2%), followed by the oral cavity (29.5%). T stage of the primary lesion, 19 cases were T4, 7 cases were T3, 8 cases were T2, 9 cases were T1, and 1 case was Tx. Bilateral dissection was performed for 23 patients and ipsilateral dissection was performed for 21 patients. 38 cases were histopathologically classified as pathologically negative cervical lymphadenopathy

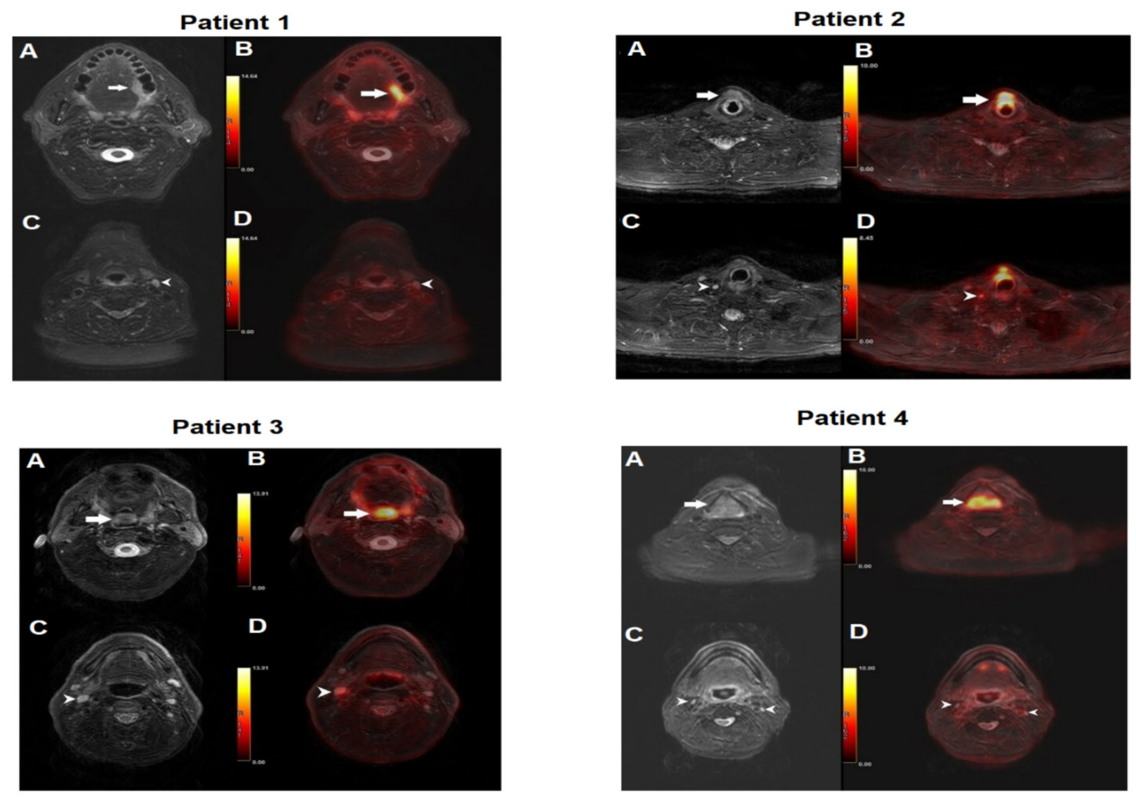

Figure 1. PET/MRI images of patients. **A-C**, Axial T2-w water images. **B-D**, PET/MR fusion images. White arrows indicate the primary lesion. Patient 1: A 65-year-old female patient followed-up with the diagnosis of tongue SCC. The lymph node size was 8x6 mm. Histopathology is N+, during PET negative, MRI negative, and PET/MRI negative. Patient 2: A 71-year-old male patient followed-up with the diagnosis of laryngeal SCC. The lymph node size was 6x4 mm. Histopathology was N0, while PET positive, MRI negative, and PET/MRI positive. Patient 3: A 57-year-old male patient followed-up with the diagnosis of uvula SCC. The lymph node size was 13x10 mm. Histopathology was N0, while PET positive, MRI positive, and PET/MRI positive. Patient 4: A 63-year-old male patient followed-up with the diagnosis of laryngeal SCC. The lymph node size was 7x4 mm. Histopathology is N0 and confirmed by imaging methods.

(pN0). The demographic and pathological results of the patients are shown in Table I.

The median time from PET/MRI examinations to operation was 7 days. According to MRI results, 34 cases were pN0, consistent with the histopathological results, while 4 cases were classified as false positives. Among the 38 cases with pN0, 26 cases were confirmed by PET results, while 12 cases were classified as false positives. PET/MRI results confirmed the pN0 diagnosis for 35 cases, while it classified 3 cases as false positives and correctly classified 2 of 4 patients with pN1 (Table II).

The diagnostic performances of the imaging results in predicting histopathological results are shown in Table III. According to the histopathological results, MRI had 50% sensitivity, 89.5% specificity, and 84% accuracy, while PET had 83.3% sensitivity, 68.4% specificity, and 70.4% accuracy. PET/MRI was more successful in distinguishing pN0 and pN+ cases (83.3% sensitivity, 92.1% specificity, and 90.9% accuracy). In addition, PET/MRI had a higher the area under the curve value and superior diagnostic performance.

Discussion

In patients with cN0 HNSCC, the decision to operate depends on the probability of occult neck

Table I. Demographic and pathological results of the patients.

Variables	*Study population n=44*	
Sex, n %		
Male	37	84.1
Female	7	15.9
Age, years	66	19-85
HPV, n %	0	0
Primary area, n %		
Larynx/hypopharynx	19	43.2
Oral cavity	13	29.5
Skin	8	18.2
Sinonasal	2	4.5
Parotid	2	4.5
Primary tumor site, n %		
Right	16	36.4
Left	22	50.0
Midline	6	13.6
Dissection site, n %		
Right	10	22.7
Left	11	25.0
Bilateral	23	52.3
cT Stage, n %		
T1	9	20.5
T2	8	18.2
T3	7	15.9
T4	19	43.2
TX	1	2.3
pT Stage, n %		
T1	6	13.6
T2	11	25.0
T3	13	29.5
T4	12	27.3
TX	2	4.5
pN Stage, n %		
N0	38	86.4
N1	4	9.1
N2A	0	0
N2B	1	2.3
N2C	0	0
N3	1	2.3
Median time from PET/MRI to surgery, day	7	1-10

Data are shown as median and min-max or number and percentage (%). cT, clinical T stage; HPV, human papillomavirus; pT, pathological T stage; pN, pathological N stage.

Table II. Staging agreement between pathological and imaging methods.

Imaging	Pathological N0 n = 38		N1 n = 4		N2B n = 1		N3 n = 1	
MRI, n %								
N0	34	89.5	3	75.0	0	0	0	0
N1	3	7.9	0	0	1	100.0	0	0
N2A	0	0	0	0	0	0	0	0
N2B	1	2.6	1	25.0	0	0	1	100.0
N2C	0	0	0	0	0	0	0	0
N3	0	0	0	0	0	0	0	0
PET, n %								
N0	26	68.4	1	25.0	0	0	0	0
N1	9	23.7	2	50.0	1	100.0	0	0
N2A	0	0	0	0	0	0	0	0
N2B	1	2.6	1	25.0	0	0	1	100.0
N2C	2	5.3	0	0	0	0	0	0
N3	0	0	0	0	0	0	0	0
PET/MRI, n %								
N0	35	92.1	1	25.0	0	0	0	0
N1	2	5.3	2	50.0	1	100.0	0	0
N2A	0	0	0	0	0	0	0	0
N2B	1	2.6	1	25.0	0	0	1	100.0
N2C	0	0	0	0	0	0	0	0
N3	0	0	0	0	0	0	0	0

Data are shown as number and percentage (%). MRI, magnetic resonance imaging; PET, positron emission tomography.

Table III. Diagnostic performance of imaging results.

Imaging	pN0 n=38	pN+ n=6	PPV (%) 95% CI	NPV (%) 95% CI	Accuracy (%) 95% CI	AUC 95% CI
MRI						
N0	34 89.5†	3 50.0	42.8	91.8	84.0	0.708
N+	4 10.5	3 50.0‡	18.1-71.8	83.5-96.2	69.9-93.4	0.552-0.835
PET						
N0	26 68.4†	1 16.7	29.4	96.2	70.4	0.770
N+	12 31.6	5 83.3‡	18.8-42.9	83.1-93.9	54.8-83.2	0.618-0.883
PET / MRI						
N0	35 92.1†	1 16.7	62.5	97.2	90.9	0.879
N+	3 7.9	5 83.3‡	34.7-83.9	85.4-99.5	78.3-97.5	0.746-0.958

Data are shown as number and percentage (%). †, indicates specificity. ‡, indicates sensitivity. AUC, area under the curve; CI, confidence interval; MRI, magnetic resonance imaging, NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

metastases, and the incidence is approximately 15%[15]. Since most of these patients do not have cervical lymph node involvement, overtreatment of the neck should be avoided[16]. Imaging methods may significantly contribute to the assessment of cervical lymph node status in the preoperative period to detect patients who will benefit from elective neck dissection. The findings of this study reveal that the PET/MRI results in cN0 patients show high agreement with pathological results and PET/MRI can be considered an essential guide in choosing between a "watchful waiting policy" or elective neck dissection.

It is challenging to diagnosis HNSCC, a subtype of head and neck cancer, with imaging techniques. However, the use of imaging tools such as MRI and PET/CT has resulted in significant advances in diagnosing primary and recurrent tumor tissues. MRI has become a favored imaging method for the local staging of head and neck cancers as confirmed by the European Society of Medical Oncology[17]. However, different imaging modalities applied for cN0 patients exhibit similar diagnostic performances with high specificity and insufficient sensitivity[7,9]. This may result in inadequate treatment and worsen the patient's prognosis. In the present study, MRI demonstrated high rate of true negatives in distinguishing patients with pN0. However, it showed false negatives for half of the pN+ patients. Thus, the overtreatment of 4 false-positive patients could have caused morbidity and complications and in the 3 false-negative patients, inadequate treatment could have resulted in recurrence. It was verified that PET/MRI may be able to prevent such negative consequences with high diagnostic performance by yielding fewer false positive and false negative results.

In malignant cells, the ability to produce energy decreases with rapid glycolysis and aerobic pathways[18]. Thus, FDG uptake increases due to the increased expression of glucose transporter 1 (GLUT)-1 and GLUT-3 molecules on cell surfaces[19]. This vital mechanism distinguishes PET from other imaging methods and may provide significant benefits in detecting pN+ for cN0 patients. However, the difficulty of anatomical correlation may limit the superiority of PET in assessing loco-regional lesions and differences between physiological and malignant metabolisms[20]. On the other hand, identifying small lymph nodes with micrometastases remains challenging with all diagnostic methods, including PET/MRI[21]. The fact that lymph nodes are normal in size does not mean they are not metastatic. Furthermore, the idea that all enlarged lymph nodes will be metastatic is incorrect[22]. These difficulties can be overcome with the ability of PET/MRI to measure both soft tissue contrasts and metabolic activities[23]. In addition, PET/MRI is less affected by implanted surgical materials[24].

The first data on PET/MRI confirmed that it can be used to diagnose HNSCC. However, it did not appear to offer significant advantages over PET/CT and MRI alone in assessing local tumors and recurrence[25]. More recently, some studies[20,26] are reporting the opposite. It has been shown[20,26] that PET/MRI detects primary tumors with higher sensitivity and more primary tumor lesions than MRI and PET alone. The current findings show that PET/MRI had higher specificity and NPV values than MRI and PET alone in detecting pN0 patients. However, the sensitivity of PET/MRI was similar to that of PET alone, while it was higher than MRI alone. The high sensitivity of PET in lymph node staging is regarded as its most significant advantage in comparison to morphological evaluations[27]. Hybrid imaging has proven to be more sensitive in lymph node staging than MRI alone. However, PET is not regarded as an imaging method capable of altering surgical management due to the possibility of miss micrometastases[28,29].

There have been few studies[25,30] on the use of PET/MRI to assess LNM in patients with HNSCC. In a study conducted by Platzek et al[30] with 38 HNSCC patients, according to the histopathological results, metastatic disease was detected in 16 patients or 21 of 67 dissected neck sides. The specificity and sensitivity for neck-side involvement in patients with LNM were 85% and 91% for PET/MRI, 85% and 86% for PET, and 87% and 67% for MRI. Platzek et al[30] also evaluated level-based lymph node analysis and determined specificity and sensitivity of 97% and 66% for MRI, 97% and 87% for PET, and 95% and 89% for PET/MRI. In another study conducted by Schaarschmidt et al[25] with 12 HNSCC patients, the efficacy of PET/MRI was evaluated according to histopathological lymph node levels after neck dissection. Accordingly, 2 patients with pN0, 3 patients with pN1, 5 patients with pN2b, and 2 patients with pN2c were detected. PET/MRI and MRI alone confirmed the N stage at respective rates of 71% and 75%. Schaarschmidt et al[25] also performed level-based lymph node analysis and determined specificity, sensitivity, NPV, and PPV of 99%, 78%, 98%, and 84% for MRI and 99%, 81%, 98%, and 89% for PET/MRI. We obtained similar values of sensitivity, specificity, and NPV in the present study. On the other hand, we found different PPV. This may be due to the inclusion of only N0 patients in our study. Thus, the prevalence of pN+ patients may have differed. NPV, PPV, and accuracy values are affected by prevalence. We detected pN+ in 13.6% of cN0 patients with HNSCC, which was close to the values reported in previously cited works[25,30]. The present study demonstrated the efficacy of PET/MRI with a larger sample of 44 patients.

Limitations

Although this study contains the largest sample among research to date evaluating the efficacy of PET/MRI in cN0 patients with HNSCC, it has some limitations. Firstly, the study design was retrospective. Secondly, the number of patients is still relatively small. Thirdly, as PET/MRI is still a new and relatively expensive method, it remains rather challenging to use. Finally, we included only N0 patients. Prospective studies with a larger patient population, including cN+ patients, would provide more information regarding the use of PET/MRI.

Conclusions

PET/MRI is more sensitive and has a higher NPV compared to MRI examinations alone, while its sensitivity was found to be comparable to that of PET alone. In addition, with its ability to detect N0 patients, PET/MRI may significantly decrease the number of unnecessary neck dissections.

Funding

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Ethics Approval

The study was performed in accordance with the Declaration of Helsinki and approved by the Faculty of Medicine Clinical Research Ethics Committee of the Gazi University (Date: 21.09.2020, Decision No.: 621).

Informed Consent

Written informed consent was obtained from all patients.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author (S. Cebeci).

Conflicts of Interest

The authors declare they have no conflicts of interest.

Authors' Contributions

Conceptualization: S. Cebeci. Data curation: S. Cebeci, U. Aydos, A.Yeniceri, D. Pula, M. Duzlu, L.O. Atay, M. Yilmaz. Formal analysis: S. Cebeci, U. Aydos, A.Yeniceri, D. Pula, M. Duzlu, L.O. Atay, M. Yilmaz. Methodology: S. Cebeci, U. Aydos, A.Yeniceri, D. Pula, M. Duzlu, L.O. Atay, M. Yilmaz. Project administration: S. Cebeci. Visualization: S. Cebeci, U. Aydos, and M. Yilmaz. Writing – review and editing: S. Cebeci, U. Aydos, and M. Yilmaz. All authors read and approved the final manuscript.

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References

1) Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71: 7-33.
2) Iovanescu G, Birsasteanu F, Boruga VM, Apostol A, Stefanescu EH, Budu VA, Baderca F, Trifu SC, Mogoanta CA, Bonte DC, Ivan MV. Clinical, ultrasound and histopathological correlation of clinically N0 neck nodes in patients with cancers of the pharynx and larynx. Rom J Morphol Embryol 2020; 61: 433-439.
3) Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers 2020; 6: 92.
4) Jankovic I, Kovacevic P, Jankovic D, Stevanovic G, Momcilovic S. Lymphatic drainage map of the head and neck skin squamous cell carcinoma detected by sentinel lymph node biopsy. Eur Rev Med Pharmacol Sci 2021; 25: 5228-5234.
5) Joo YH, Cho JK, Koo BS, Kwon M, Kwon SK, Kwon SY, Kim MS, Kim JK, Kim H, Nam I, Roh JL, Park YM, Park IS, Park JJ, Shin SC, Ahn SH, Won S, Ryu CH, Yoon TM, Lee G, Lee DY, Lee MC, Lee JK, Lee JC, Lim JY, Chang JW, Jang JY, Chung MK, Jung YS, Cho JG, Choi YS, Choi JS, Lee GH, Chung PS. Guidelines for the Surgical Management of Oral Cancer: Korean Society of Thyroid-Head and Neck Surgery. Clin Exp Otorhinolaryngol 2019; 12: 107-144.
6) Klausner G, Troussier I, Blais E, Carsuzaa F, Zilli T, Miralbell R, Caparrotti F, Thariat J. Neck management in head and neck squamous cell carcinomas: where do we stand? Med Oncol 2019; 36: 40.
7) Liao LJ, Lo WC, Hsu WL, Wang CT, Lai MS. Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck-a meta-analysis comparing different imaging modalities. BMC Cancer 2012; 12: 236.
8) Leusink FK, van Es RJ, de Bree R, Baatenburg de Jong RJ, van Hooff SR, Holstege FC, Slootweg PJ, Brakenhoff RH, Takes RP. Novel diagnostic modalities for assessment of the clinically node-negative neck in oral squamous-cell carcinoma. Lancet Oncol 2012; 13: e554-e561.
9) Liao LJ, Hsu WL, Wang CT, Lo WC, Lai MS. Analysis of sentinel node biopsy combined with other diagnostic tools in staging cN0 head and neck cancer: A diagnostic meta-analysis. Head Neck 2016; 38: 628-634.
10) Ozer E, Naiboğlu B, Meacham R, Ryoo C, Agrawal A, Schuller DE. The value of PET/CT to assess clinically negative necks. Eur Arch Otorhinolaryngol 2012; 269: 2411-2414.
11) Driessen D, Dijkema T, Weijs WLJ, Takes RP, Pegge SAH, Zamecnik P, van Engen-van Grunsven ACH, Scheenen TWJ, Kaanders J. Novel Diagnostic Approaches for Assessment of the Clinically Negative Neck in Head and Neck Cancer Patients. Front Oncol 2020; 10: 637513.
12) Huellner MW. PET/MR in Head and Neck Cancer - An Update. Semin Nucl Med 2021; 51: 26-38.
13) Samolyk-Kogaczewska N, Sierko E, Dziemianczyk-Pakiela D, Nowaszewska KB, Lukasik M,

Reszec J. Usefulness of Hybrid PET/MRI in Clinical Evaluation of Head and Neck Cancer Patients. Cancers (Basel) 2020; 12: 511.

14) Szyszko TA, Cook GJR. PET/CT and PET/MRI in head and neck malignancy. Clin Radiol 2018; 73: 60-69.

15) Finegersh A, Moss WJ, Saddawi-Konefka R, Faraji F, Coffey CS, Califano JA, Brumund KT, Orosco RK. Meta-analysis of risk of occult lymph node metastasis in the irradiated, clinically N0 neck. Head Neck 2020; 42: 2355-2363.

16) Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst 2008; 100: 712-720.

17) Gregoire V, Lefebvre JL, Licitra L, Felip E, Group E-E-EGW. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5: v184-v186.

18) Kim BS, Kang J, Jun S, Kim H, Pak K, Kim GH, Heo HJ, Kim YH. Association between immunotherapy biomarkers and glucose metabolism from F-18 FDG PET. Eur Rev Med Pharmacol Sci 2020; 24: 8288-8295.

19) Yang H, Zhong JT, Zhou SH, Han HM. Roles of GLUT-1 and HK-II expression in the biological behavior of head and neck cancer. Oncotarget 2019; 10: 3066-3083.

20) Lee SJ, Seo HJ, Cheon GJ, Kim JH, Kim EE, Kang KW, Paeng JC, Chung JK, Lee DS. Usefulness of Integrated PET/MRI in Head and Neck Cancer: A Preliminary Study. Nucl Med Mol Imaging 2014; 48: 98-105.

21) Kim SG, Friedman K, Patel S, Hagiwara M. Potential Role of PET/MRI for Imaging Metastatic Lymph Nodes in Head and Neck Cancer. AJR Am J Roentgenol 2016; 207: 248-256.

22) Torabi M, Aquino SL, Harisinghani MG. Current concepts in lymph node imaging. J Nucl Med 2004; 45: 1509-1518.

23) Platzek I. (18)F-Fluorodeoxyglucose PET/MR Imaging in Head and Neck Cancer. PET Clin 2016; 11: 375-386.

24) Klinke T, Daboul A, Maron J, Gredes T, Puls R, Jaghsi A, Biffar R. Artifacts in magnetic resonance imaging and computed tomography caused by dental materials. PLoS One 2012; 7: e31766.

25) Schaarschmidt BM, Heusch P, Buchbender C, Ruhlmann M, Bergmann C, Ruhlmann V, Schlamann M, Antoch G, Forsting M, Wetter A. Locoregional tumour evaluation of squamous cell carcinoma in the head and neck area: a comparison between MRI, PET/CT and integrated PET/MRI. Eur J Nucl Med Mol Imaging 2016; 43: 92-102.

26) Platzek I, Beuthien-Baumann B, Schneider M, Gudziol V, Langner J, Schramm G, Laniado M, Kotzerke J, van den Hoff J. PET/MRI in head and neck cancer: initial experience. Eur J Nucl Med Mol Imaging 2013; 40: 6-11.

27) Wax MK, Myers LL, Gona JM, Husain SS, Nabi HA. The role of positron emission tomography in the evaluation of the N-positive neck. Otolaryngol Head Neck Surg 2003; 129: 163-167.

28) Heusch P, Sproll C, Buchbender C, Rieser E, Terjung J, Antke C, Boeck I, Macht S, Scherer A, Antoch G, Heusner TA, Handschel J. Diagnostic accuracy of ultrasound, (1)(8)F-FDG-PET/CT, and fused (1)(8)F-FDG-PET-MR images with DWI for the detection of cervical lymph node metastases of HNSCC. Clin Oral Investig 2014; 18: 969-978.

29) Nahmias C, Carlson ER, Duncan LD, Blodgett TM, Kennedy J, Long MJ, Carr C, Hubner KF, Townsend DW. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. J Oral Maxillofac Surg 2007; 65: 2524-2535.

30) Platzek I, Beuthien-Baumann B, Schneider M, Gudziol V, Kitzler HH, Maus J, Schramm G, Popp M, Laniado M, Kotzerke J, van den Hoff J. FDG PET/MR for lymph node staging in head and neck cancer. Eur J Radiol 2014; 83: 1163-1168.