Original Article

The Importance of the Time Interval Between Preoperative ^{18}F-FDG PET/CT Imaging and Neck Dissection for the Detection of Nodal Metastases in Patients with Head and Neck Squamous Cell Carcinoma

E Koroglu, S Sirin[1], S Isgoren[2]

Department of Otorhinolaryngology, Kocaeli City Hospital, Kocaeli, Departments of [1]Otorhinolaryngology and [2]Nuclear Medicine, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Abstract

Background: Detection of nodal metastasis is critical for the treatment and prognosis of head and neck cancer (HNC). Positron emission tomography/computed tomography (PET/CT) is increasingly being used to detect cervical lymph node involvement. **Aim:** The purposes of this study were to (1) investigate the diagnostic accuracy of PET/CT for the detection of neck metastasis in patients with HNC and (2) determine the effect of the time interval between surgery and PET/CT. **Methods:** Fifty patients with head and neck squamous cell carcinoma who underwent PET/CT before surgery were included in this study. Preoperative PET/CT images that determined lymph node metastasis were compared with the histopathological analysis of neck dissection samples. Neck dissections were divided into three groups according to the time interval between surgery and PET/CT (0–2 weeks, >2–4 weeks, and >4 weeks). The concordance between PET/CT and histopathology was measured using the neck sides at different time intervals. The specificity, sensitivity, accuracy, negative predictive value (NPV), and positive predictive value (PPV) of PET/CT in detecting metastatic lymph nodes in the neck were calculated. **Results:** A total of 79 neck dissections were included in the study as 29 (58%) of the patients underwent bilateral neck dissection. The overall accuracy of PET/CT in detecting nodal metastasis was highest for the 0–2 weeks interval (95.6%). During this time interval, the sensitivity, specificity, NPV, and PPV of PET/CT were 100%, 90.9%, 100%, and 92.3%, respectively. **Conclusions:** Although PET/CT is an important and reliable diagnostic method for detecting nodal metastases in patients with HNC, its reliability decreases as the time between surgeries increases. The optimal interval was 2 weeks; however, up to 4 weeks was acceptable.

Keywords: *Head and neck, nodal metastasis, positron emission tomography, squamous cell carcinoma, time interval*

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Introduction

Head and neck cancer (HNC) frequently originates in the upper aerodigestive tract. Squamous cell carcinoma (SCC) is the most common pathological subtype of HNC.[1] The most important prognostic factors are regional lymph node involvement, tumor location, and size.[2] The presence of nodal metastases not only changes the treatment plan but also reduces long-term survival.[3] Even single lymph node metastasis can reduce survival by approximately 50%.[4] In contrast, although there are no palpable lymph nodes in the neck at the time of diagnosis, patients are at risk of occult nodal metastases.[5-7] Therefore, nodal metastasis must be accurately detected before planning treatment for patients correctly, and imaging methods are needed to evaluate regional lymph node

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Address for correspondence: Dr. E Koroglu, Turgut Mahallesi Ozge Sokak No: 10 D: 2, Izmit, Kocaeli, Turkey.
E-mail: erdemkoroglu1907@gmail.com

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involvement. Ultrasonography (US), magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) can be used for regional lymph node evaluation at initial diagnosis.

Contrast-enhanced MRI and CT are routinely used to evaluate patients with HNC. They provide structural information about the size of the primary tumor, invasion, and involvement of surrounding structures but have limited ability to distinguish between non-metastatic and metastatic lymph nodes.[8,9]

PET/CT is widely used to detect nodal metastases in patients with HNC. The greatest benefit of PET/CT is the evaluation of the primary tumor, distant metastases, neck involvement, and potential synchronous secondary primers in a single modality. PET/CT detects cervical lymph node metastases more accurately than other imaging techniques.[10,11] It is reported to be a superior imaging method, especially for detecting nonpalpable lymph nodes.[10,12] Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is the most frequently used radiopharmacological agent for determining tissue metabolism by using PET/CT.[13] A standardized uptake value (SUV) indicating increased ^{18}F-FDG activity was used to differentiate between malignant and benign lesions. However, ^{18}F-FDG is not a cancer-specific agent; it shows increased uptake in many inflammatory and infectious diseases, benign salivary gland pathologies (such as Warthin's tumor), and benign bone lesions.[14,15] In addition, it should be known that false negatives may occur when the lymph node diameter is less than 10 mm and there is nodal necrosis (due to low glucose activity).[16,17]

Timely treatment following the final diagnosis is crucial. The optimal time from diagnosis to treatment initiation is less than 20 days.[18,19] Any treatment delay is also associated with an unfavorable prognosis in patients with HNC. The time interval between surgery and PET/CT might also be another reason for the false-negative results. To the best of our knowledge, the effect of the time interval between surgery and PET/CT has not yet been investigated. Therefore, this study aimed to investigate the diagnostic accuracy of PET/CT in detecting neck metastases in patients with HNC and to determine the effect of the time interval between surgery and PET/CT.

Materials and Methods

This study was designed to differentiate benign and malignant regional lymph nodes in patients with HNC using PET/CT imaging. Specifically, we determined the optimal time interval between PET/CT and surgery for detecting malignant cervical lymph nodes. We retrospectively reviewed the imaging and medical records of all patients with HNC who underwent neck dissection at Kocaeli University Hospital between November 2012 and December 2018. The results of the preoperative PET/CT examinations correlated with the histopathological results of neck dissection specimens.

Patients

The inclusion criteria of the patients in this study were as follows: a) preoperative PET/CT imaging, b) histologically proven SCC of the primary side, c) previously untreated with chemotherapy and/or radiotherapy, and d) no previous head and neck surgery.

Fifty consecutive patients were eligible for inclusion in this study. Forty-three (86%) patients were male, and seven (14%) were female. Their mean age was 59.08 years (range: 29–84 years). A total of 79 neck dissections were included in the study, and 29 patients (58%) underwent bilateral neck dissection.

PET/CT imaging

To achieve a blood glucose level of <150 mg/dL, patients were required to fast for at least 4 h before the 18F-FDG injection. After excluding patients with hyperglycemia, patients were administered ^{18}F-FDG at a dose of 7.77 MBq/kg (0.21 mCi/kg) while resting in a quiet, dark room.

Whole-body PET/CT scans were performed 1 h after ^{18}F-FDG injection. Images were acquired using a high-resolution Biograph Scanner (Siemens Medical Solutions, Knoxville, TN, USA) with a spatial resolution of 4.2 mm and 16-slice CT detectors. Image post-processing was performed using the Syngo MultiModality Workplace software (Siemens Medical Solutions). After CT imaging, PET images were obtained (5 min per bed position). Images were subjected to iterative reconstruction in the sagittal, coronal, and axial planes, and the CT data were used for attenuation correction. The maximum SUV (SUV_{max}) was calculated for each lesion.

Image interpretation and analysis

The PET/CT studies were retrospectively interpreted by two nuclear medicine physicians and a radiologist with extensive clinical experience in HNC. Discordant results were reviewed by a third, experienced nuclear medicine physician. They were blinded to histopathological results and clinical findings. All lymph nodes with increased focal FDG uptake were interpreted relative to background blood pool activity, with an asymmetric distribution considered suspicious for metastasis. The SUV-max values of the suspicious lymph nodes were automatically calculated (cutoff SUV-max > 3.0). Suspicious lymph nodes were also evaluated based on

the following criteria: extranodal extension, necrosis, and round or irregular shapes with enhancement. When the lymph nodes were positive for metastasis according to these criteria, the neck side was considered positive for statistical analysis.

Surgery and histopathology

All patients underwent neck dissection and primary tumor resection. The type (radical or selective) and side (unilateral or bilateral) of neck dissection were determined by the HNC multidisciplinary tumor board according to the primary tumor location, clinical examination, imaging data, and pathology.

The specimens were dissected, lymph nodes were identified, and each lymph node was sliced and stained with hematoxylin and eosin for histological examination. Subsequently, the number of lymph nodes, size, location, and absence or presence of metastases were recorded.

Staging

Accurate staging is the most important factor for treatment planning and prognosis of HNSCC. Preoperative imaging-based nodal staging (iN) was performed for each patient according to the American Joint Committee on Cancer (AJCC) 8th edition. The final node stage (N) was determined according to histopathological nodal findings after neck dissection. N was the gold standard for comparison of iN.

Ethical approval

This retrospective study was approved by the Kocaeli University Faculty of Medicine Ethics Committee of the Clinical Research Department (Protocol number: 2018/1315).

Statistical analysis

The ^{18}F-FDG PET/CT images were compared with the final histopathology results based on the patient and neck dissection. Regardless of the level at which the neck was dissected, only one side of the neck was used to assess the correlation between the histopathological and imaging findings. PET/CT findings were classified as true negative (absence of nodal metastasis), true positive (presence of nodal metastasis), false negative (missed diagnosis of nodal metastasis), or false positive (increased FDG uptake unrelated to nodal metastasis) according to the final pathology reports. The specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{18}F-FDG PET/CT for detecting metastatic lymph nodes were calculated according to these values. Statistical analyses were performed using SPSS Statistics version 20 (IBM Corporation, Armonk, NY, USA).

Results

Among the 50 patients, 29 (58%) underwent bilateral neck dissection; therefore, 79 patients who underwent neck dissection were included in the study. There were 43 (86%) male and seven (14%) female patients aged between 29 and 84 years (mean: 59.08 years). Patient characteristics are summarized in Table 1. The final pathology of the primary tumor was SCC in all cases. Most tumors were located in the oral cavity (n = 19, 38%), followed by the larynx (n = 16, 32%).

Table 1: Clinical characteristics of the patients

Characteristics	No. (% of data)
Patients	50 (100)
Neck Dissection	
-Bilateral	29 (58)
-Unilateral	21 (42)
Age Range:	29–84
Mean Age±SD	59.08±11.32
Sex	
-Male	43 (86)
-Female	7 (14)
Primary Site	
-Oral Cavity	19 (38)
-Larynx	16 (32)
-Oropharynx	4 (8)
-Hypopharynx	3 (6)
-Other	8 (16)
Pathological Nodal Stage	
-N0	17 (34)
-N1	3 (6)
-N2a	2 (4)
-N2b	16 (32)
-N2c	7 (14)
-N3a	-
-N3b	5 (10)

Table 2: Distribution of neck dissections according to the time interval between preoperative PET/CT

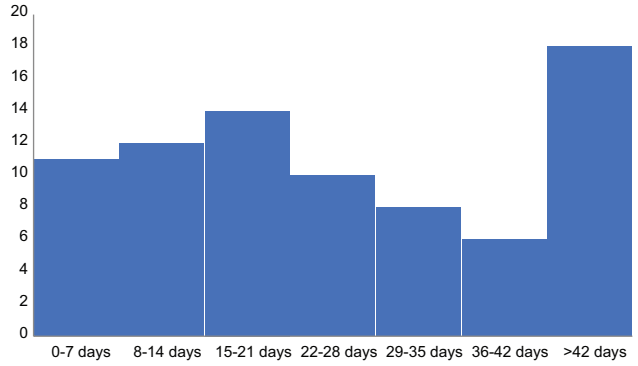

Table 3: Comparison of the histopathological results at different surgical intervals with the parameters of PET/CT in identification of metastatic lymph nodes

Time interval (number of neck dissections)	No. of neck dissections				Sensitivity	Specificity	PPV	NPV	Accuracy
	TP	FP	FN	TN					
0–2 weeks (23)	13	1	0	9	100	90	92.8	100	95.6
>2–4 weeks (24)	8	4	2	10	80	71.4	66.6	83.3	75
> 4 weeks (32)	10	6	7	9	58.8	60	62.5	56.2	59.3

TP=True Positive, FP=False Positive, FN=False Negative, TN=True Negative, PPV=Positive Predictive Value, NPV=Negative Predictive Value

Table 4: Concordance of the histopathological results at different Surgical intervals with the PET/CT results

Time interval (number of neck dissection)	Sensitivity	Specificity	PPV	NPV	Accuracy
0–2 weeks (23)	100	90	92.8	100	95.6
0–3 weeks (37)	95	82.3	86.3	93.3	89.1
0–4 weeks (47)	90.9	80	80	90.9	85.1
0–5 weeks (55)	82.1	70.3	74.1	79.1	76.3
0–6 weeks (61)	78.7	71.4	76.4	74.1	75.4
All weeks (79)	77.5	71.7	73.8	75.6	74.6

Patients underwent surgery within 2–176 days of the PET/CT study. The distribution of neck dissections performed per day is shown in Table 2. Neck dissections were divided into three groups according to the time interval between surgery and PET/CT (0–2 weeks, 2–4 weeks, and >4 weeks), and the sensitivity, specificity, PPV, and NPV of PET/CT in detecting metastatic lymph nodes in the neck were calculated by comparing the histopathological results [Table 3]. When assessing the concordance between PET/CT and pathology on the neck side, PET/CT was found to correctly identify nodal metastasis in the 0–2 weeks interval (95.6%). During this time interval, the sensitivity, specificity, PPV, and NPV of PET/CT were 100%, 90.9%, 92.3%, and 100%, respectively. For patients at the 2–4 weeks time interval, the concordance between the PET/CT and histopathology results was 75%. At this time interval, decreases in the sensitivity, specificity, PPV, and NPV of PET/CT were observed (80%, 71.4%, 66.6%, and 83.3%, respectively). However, the most significant decrease in these values was observed on PET/CT with an interval with surgery of >4 weeks (58.8%, 60%, 62.5%, and 56.2%, respectively). The overall accuracy of PET/CT during this period was 59.3%.

Neck dissections were reevaluated according to the time until surgery to determine the reliability of PET/CT in detecting nodal metastasis [Table 4]. When the time interval was extended to 4 weeks, a decrease was observed in the sensitivity, specificity, PPV, and NPV of PET/CT, but it was still reliable (90.9%, 80%, 80%, and 90.9%, respectively). Histopathological evaluation of all neck dissections (n = 79) in the study found 40 sides positive; with PET/CT, 31 of them were evaluated as positive. Of the remaining 39 neck dissections that were histopathologically negative, 28 were evaluated as negative by PET/CT.

Based on the histopathological results after neck dissection, 17 (34%) patients had stage N0, three (6%) had stage N1, two (4%) had stage N2a, 16 (32%) had stage N2b, seven (14%) had stage N2c, and five (10%) had stage N3b. PET/CT resulted in 66% accurate staging, 16% over-staging, and 18% low staging in determining the iN of patients who underwent surgery within 4 weeks after imaging.

Discussion

Regional lymph node metastasis is associated with poor prognosis in patients with HNC. Therefore, nodal involvement must be accurately identified before treatment planning. PET/CT has become an accepted and widely used imaging modality for the nodal staging of patients with HNC.[20,21] Sun *et al*.[22] conducted a meta-analysis including eight studies with per-neck-side data (734 neck sides) and 19 studies with per-neck-level data (6379 neck levels) to evaluate the accuracy of PET/CT in detecting cervical lymph node involvement in patients with HNC. In this meta-analysis, the pooled per-neck side and per-neck level sensitivities and specificities of 18FDG-PET/CT were 0.84 and 0.83, and 0.80 and 0.96, respectively.

The delay between diagnosis and definitive treatment of HNC is associated with tumor progression and upstaging.[23] This delay in treatment may be due to professional-, patient-, or facility-related factors.[24] When the findings in our study were evaluated, delays related to the patient were mostly observed in patients whose time interval between PET/CT and surgery was >4 weeks, while delays related to intensive care unit insufficiency, cancellation of multidisciplinary tumor board meetings, and anesthesia were also observed.

Although PET-CT is a frequently used method for the staging of HNC, to our knowledge, there are no studies in the literature regarding its reliability period. The findings of this study demonstrate that PET/CT imaging is most helpful for differentiating malignant lymph nodes

when the time interval between surgeries is less than 2 weeks. The sensitivity and specificity values were 1.00 and 0.90, respectively. These values were acceptable for a time interval of up to 4 weeks (0.90 and 0.80, respectively). However, the sensitivity and specificity values were not high because of false negative results when the time interval was over 4 weeks (0.59 and 0.60, respectively).

The most important finding in the current study was that PET/CT had low sensitivity and specificity for detecting nodal metastasis when the time interval between surgeries was >4 weeks. The reliability of PET/CT is controversial as false negative rates have increased significantly after this time period. These results can provide better guidance regarding decision-making for the proper management of patients with HNC. Our study contributes to the literature in terms of reliable timing of PET/CT.

Stoeckli *et al*.[25] compared PET/CT, CT, and ultrasound-guided fine-needle aspiration cytology for initial staging of the neck in HNSCC. All three examinations of 76 patients were completed within 2 weeks prior to neck dissection. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for the endpoints N0 versus N+ were 0.86, 0.77, 0.95, 0.53, and 0.85, respectively. In this study, we found that these values are superior. The small sample size (n = 23) in this group may have caused this difference.

Bae *et al*.[10] examined the clinical usefulness of PET/CT for the detection of occult neck metastasis in patients with oral cavity SCC (n = 178) in comparison with CT and MR. All 178 patients underwent PET/CT and CT/MR imaging at initial staging within 3 weeks before surgery. The sensitivity, specificity, PPV, NPV, and accuracy of neck PET/CT were 0.70, 0.79, 0.48, 0.90, and 0.77, respectively. Because patients with palpable lymph nodes in the neck were excluded from this study and only oral cavity SCC was included, the values were lower than those in our study. A recent meta-analysis showed the low sensitivity and moderate specificity of PET/CT for the detection of nodal metastases in patients with cN0 HNSCC.[14]

In a study of 73 patients, Cho *et al*.[26] demonstrated no significant difference in overall sensitivity between PET/CT and CT. However, PET/CT was found to be more sensitive than CT in excluding metastatic involvement on a given side of the neck. Imaging was performed within 6 months prior to surgery.

FDG is not a tumor-specific tracer; thus, it can accumulate in a variety of benign processes, including inflammatory, iatrogenic, and post-traumatic conditions and benign tumors.[27,28] Therefore, conditions that may cause false positives should be considered when evaluating HNC using PET/CT. Warthin's tumor causes activity in the upper neck on PET/CT; in some cases, it may be difficult to distinguish between level II lymph nodes and parotid lesions.[29] In this study, Warthin's tumor was evaluated as a metastatic lymph node, and false-positive results were obtained in a patient who underwent PET/CT examination for glottic laryngeal cancer. It is important to be aware of the possibility that Warthin's tumors may be malignant in these patients.

This study had some limitations. First, this was a retrospective study; therefore, missing data constituted a problem. In addition, a standardized intraoperative procedure cannot be implemented to label lymph nodes at the neck level. Micrometastases may have been overlooked in routine histopathological examinations; therefore, the actual sensitivity may be lower. Although all cancer types were SCC, various primary cancer sites with corresponding metastatic potentials were included in the study.

Conclusion

In conclusion, although PET/CT is an important and reliable imaging method for detecting nodal metastases in patients with HNC, its reliability decreases as the time between surgeries increases. The optimal interval was 2 weeks; however, up to 4 weeks was acceptable. However, further large-scale studies are required to confirm these findings. When deciding on neck treatment, the interval between PET/CT and surgery should also be considered.

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Conflicts of interest

There are no conflicts of interest.

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