
Effect of Time-of-Flight Technique on the Diagnostic Performance of ^{18}F -FDG PET/CT for Assessment of Lymph Node Metastases in Head and Neck Squamous Cell Carcinoma

Chun-Yan Li*^{1,2}, Sarah Klohr*¹, Haneen Sadick³, Christel Weiss⁴, Karl Hoermann³, Stefan O. Schoenberg¹, and Maliha Sadick¹

¹Institute of Clinical Radiology and Nuclear Medicine, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Heidelberg, Germany; ²Department of Nuclear Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; ³Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Heidelberg, Germany; and ⁴Department of Biostatistics, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Heidelberg, Germany

Precise assessment of lymph node metastases is critical to the treatment outcome and overall survival of patients with head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to investigate the effect of time-of-flight (TOF) technique on the diagnostic performance of ^{18}F -FDG PET/CT for assessment of lymph node metastases in HNSCC patients.

Methods: In 39 patients with an initial diagnosis of HNSCC, preoperative staging ^{18}F -FDG PET/CT was performed to assess lymph node metastases before surgery and histologic verification. Potential lymph node metastases were evaluated and documented separately for the right and left neck in accordance with the head and neck lymph node level classification. Two experienced readers measured lesion volume and uptake for every PET-positive lymph node. Sensitivity, specificity, image quality, and the PET characterization of the lesion (benign or malignant) were compared between different reconstruction methods (TOF PET and standard high-definition PET) and matrices for both readers. **Results:** TOF PET significantly increased the maximal standardized uptake value (SUV_{max}) but had no significant effect on lesion volume. However, a higher SUV_{max} did not result in a significant increase in small-lesion detection. Sensitivity and image quality were slightly improved with TOF PET but not significantly so. Matrix, on the other hand, had a significant effect on detected lesion numbers, sensitivity, and image quality. **Conclusion:** For preoperative assessment of lymph node metastases in HNSCC, ^{18}F -FDG PET/CT using TOF technique increases SUV_{max} in lesions and improves image quality but has no significant impact on small-lesion detectability.

Key Words: head and neck squamous cell carcinoma; lymph node metastases; time-of-flight; ^{18}F -FDG PET/CT

J Nucl Med Technol 2014; 42:181–187

DOI: 10.2967/jnmt.114.141192

Received Apr. 4, 2014; revision accepted May 30, 2014.

For correspondence or reprints contact: Chunyan Li, Institute of Clinical Radiology and Nuclear Medicine, University Hospital Mannheim, Medical Faculty Mannheim of the University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.

E-mail: julie850310@gmail.com

*Contributed equally to this work.

Published online Jun. 26, 2014.

COPYRIGHT © 2014 by the Society of Nuclear Medicine and Molecular Imaging, Inc.

Head and neck squamous cell carcinoma (HNSCC) is still a common cause of death. It is the fifth most common malignancy in the world, with approximately 650,000 new cases reported annually (1). The presence and extent of lymph node metastases is critical for prognosis evaluation and treatment planning. The number, distribution, and size of lymph nodes are equally important for nodal staging of head and neck cancer (2). Ultrasound and conventional cross-sectional imaging, which depend mainly on size criteria, have difficulty in differentiating between reactive lymph nodes and tumor-infiltrated nodes. Diffusion-weighted MR imaging of the head and neck region has been shown to improve the outcome of lymph node staging (3). A new dedicated software application, syngo ZOOMit (Siemens Healthcare), has substantially improved image quality and reduced susceptibility artifacts in pancreatic diffusion-weighted MR imaging (4) and has also shown practical potential in the head and neck region because it reduces distortion and better delineates cervical lymph nodes. Although head and neck CT scanning and MR imaging are still considered the standard imaging tests for HNSCC, there has been more evidence suggesting that PET should routinely be added to improve staging of nodal or distant disease, detection of unknown primary lesions, and surveillance for recurrence (5). ^{18}F -FDG PET alone was reported to achieve a sensitivity of 87%–90% and a specificity of 80%–93% in nodal staging (6). The sensitivity, specificity, and accuracy of dual-modality PET/CT were reported to be 81.1%, 98.2%, and 95.0%, respectively (7). Dedicated head and neck contrast-enhanced CT achieves even higher diagnostic accuracy (96%) than standard contrast-enhanced CT (81%) or whole-body PET/CT (89%) for detection of lymph node metastases (8).

On the other hand, some studies have not demonstrated a significant improvement in diagnostic performance for PET/contrast-enhanced CT compared with anatomic cross-sectional imaging, such as MR imaging (7,9). It remains

challenging for PET/CT to detect early-stage cancer, head and neck cancer in patients with a clinically negative neck, and occult metastases. False-negative findings may result from the limited spatial resolution of PET or the presence of necrotic lymph nodes, whereas inflammatory lesions can lead to false-positive results. In addition, the head and neck region remains an anatomic challenge because of its many small, complex structures, which create higher requirements for spatial resolution and better image quality.

Meanwhile, technologic advances in both hardware and software allow continuous improvement of the physical and clinical performance of PET/CT. The most recent innovation is represented by time-of-flight (TOF) technique, which localizes the annihilation event with much higher precision by calculating the time difference between the arrival of 2 coincident photons (10). TOF technique was originally proposed in the 1980s but was then abandoned because TOF gain could not compensate for its poor stopping power and low light output (11,12). With the availability of new fast scintillator detectors such as lutetium oxyorthosilicate and lutetium yttrium oxyorthosilicate, TOF PET again became of interest for the clinical setting (13). Intensified research focusing on its new applications has shown advantages such as better definition of small lesions, improved uniformity, and reduced noise (10,14,15). In contrast to the gained experience with TOF PET in phantom imaging studies, its performance in dedicated clinical indications has not been thoroughly investigated. There have been only a few clinical studies, especially in the field of head and neck imaging focusing on HNSCC.

In a prospective setting, we assessed the optimization of PET/CT imaging protocols for diagnostic evaluation of the head and neck region in patients with HNSCC. Initially, the effect of high-definition PET/CT reconstruction parameters on accuracy in the detection of HNSCC lymph node metastases was analyzed (16). The purpose of the current clinical study was to investigate the effect of TOF PET on ¹⁸F-FDG PET/CT in the preoperative detection of HNSCC lymph node metastases. We evaluated its effect on several parameters: lesion volume, standardized uptake value (SUV), diagnostic performance, and image quality.

MATERIALS AND METHODS

Patients

Patients who were initially diagnosed as having squamous cell carcinoma in the head and neck were recruited into our study after giving their written informed consent. Children and women who might be pregnant—rare in HNSCC patient groups—were excluded. Seventy-four patients were included at first, but 35 patients dropped out because there were no final histologic reports for correlation. A total of 39 patients (30 men and 9 women; mean age, 61 y; age range, 44–84 y) who underwent surgery immediately after the PET/CT examination were evaluated for TOF technique. For anatomic correlation between imaging findings and the neck dissection report, the specimens were divided into individual cervical lymph node regions (17). Histopathologic analysis of lymph nodes served as the gold standard for diagnostic decision

TABLE 1
Reconstruction Parameters for the 4 Sequences

Parameter	HD PET		TOF PET	
	1	2	3	4
Matrix	200	400	200	400
Iterations	3	3	3	3
Subsets	24	24	21	21
Zoom	1.0	1.0	1.0	1.0
Filter	Gaussian (3 mm in FWHM)	Gaussian (3 mm in FWHM)	Gaussian (3 mm in FWHM)	Gaussian (3 mm in FWHM)

FWHM = full width at half maximum.

making. The prospective study was approved by our hospital institutional ethics committee.

¹⁸F-FDG PET/CT Protocol and Image Interpretation

The imaging protocol, established by us for dedicated head and neck imaging, was similar to that in a recent study published by our group (16). Patients were imaged on a Biograph mCT PET/CT scanner (Siemens Healthcare) with a high-counting-rate lutetium oxyorthosilicate detector and a 64-slice CT scanner. The coincidence time window was 4.1–4.5 ns, with an energy resolution of 435–650 keV. For TOF imaging, the time resolution was 555 ps. After at least a 6-h fasting period, weight-adapted ¹⁸F-FDG with activity between 300 and 350 MBq was intravenously administered, followed by an approximately 1-h uptake phase.

At first, an anterior–posterior topogram was obtained for imaging planning. Then, a low-dose CT scan for attenuation correction was acquired (Siemens CARE Dose4D: 120 kV, 50 mAs, pitch of 0.8) with a slice thickness of 5 mm and a 3-mm increment from the skull base to the proximal femur. PET imaging of the same area was then performed in 3-dimensional mode with 8–10 bed positions at 3 min each. Finally, all patients underwent contrast-enhanced diagnostic CT (120 kV, 50–120 mAs, pitch of 0.8, collimator slice width of 1.2 mm) from the skull base to the thorax after intravenous injection of weight-adapted iodinated contrast medium (Imeron 320; Bracco).

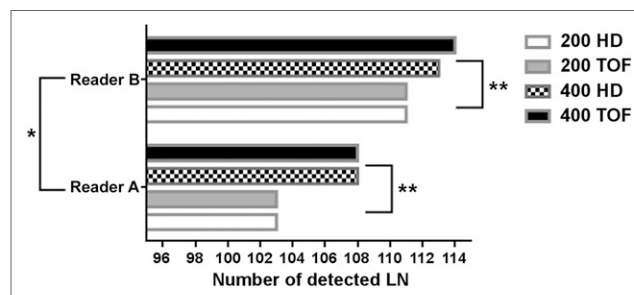


FIGURE 1. In total, 124 lymph nodes were assessed on PET images and correlated with histologic reports. Readers A and B detected different numbers of lymph nodes. Reader B performed better and missed fewer lesions (reader B, 47 undetected lymph nodes; reader A, 74 undetected lymph nodes; * $P = 0.0111$). Additionally, matrix 400 enabled detection of more lesions than matrix 200 (** $P = 0.0137$). No significant difference between TOF PET and standard HD PET could be shown.

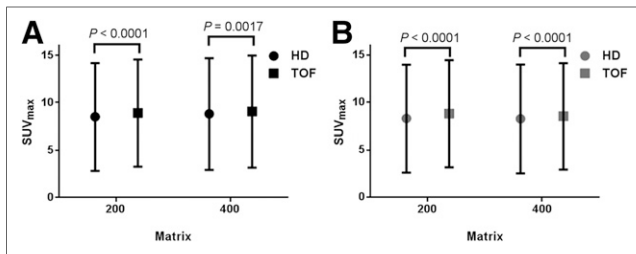


FIGURE 2. For both reader A (A) and reader B (B), SUV_{max} was significantly higher on TOF PET than on HD PET for matrix 200 and matrix 400 ($P < 0.05$).

After acquisition, all PET/CT raw data of the 39 patients were reconstructed at the Syngo workstation (Siemens Healthcare). For each patient, first the CT data were reconstructed for the purpose of scatter and attenuation correction. Then, PET raw data were reconstructed in 4 different sequences for each patient. The TOF PET sequences (reconstructed using the TOF method) and high-definition (HD) PET sequences (reconstructed using the standard TrueX method [Siemens Healthcare]) were reconstructed with 2 different matrices: 200×200 and 400×400 . HD PET sequences used 3 iterations and 24 subsets combined with 3-dimensional gaussian postfiltering at 3 mm in full width at half maximum, which renders high diagnostic output for HNSCC lymph node staging (16). For TOF PET sequences, 3 iterations and 21 subsets were recommended by the manufacturer for clinical routine imaging of the head and neck region. The details of the reconstruction parameters are listed in Table 1.

Image reading and reporting were performed on a workstation equipped with fusion software displaying CT, PET, and PET/CT images (TrueD software, multimodality workplace; Siemens Healthcare). All PET/CT images were evaluated in a masked manner by 2 board-certified radiologists with long-term experience in nuclear medicine. The results were correlated with the postsurgical histologic findings for the lymph nodes.

The TrueD software was used to build the volume of interest and determine the volume and maximal SUV (SUV_{max}) of suspected lymph nodes. These data were then documented on an evaluation sheet individually for the left and right sides of the

neck, according to the established neck lymph node classification. For both readers, their diagnostic judgment on the character of the detected lymph nodes (benign or malignant) was based entirely on the PET information, not on the correlating CT images. The CT images were viewed for anatomic localization of the suspected lymph node levels.

Image quality was visually scored on a 4-level scale as follows: 1, excellent; 2, good; 3, satisfactory; 4, not assessable. The quality scoring was based predominantly on the individual reader's perception of blurring and quality of lesion demarcation on the image.

Through a comparison between PET findings and postoperative histologic findings for the dissected lymph nodes, sensitivity and specificity for lymph node detection were determined for each method.

Statistics

Paired *t* testing was performed to compare lesion volumes and SUV_{max} . For comparison of PET lymph node character, image quality, sensitivity, and specificity between different sequences and different readers, the McNemar test and κ values were used (weighted κ value if there were more than 2 levels involved).

RESULTS

Patients and Lesions

The diagnosis of HNSCC was confirmed by histologic evaluation in all 39 patients. Despite PET/CT, a primary tumor location could not be identified in 2 patients, who were therefore given a diagnosis of cancer of unknown primary (CUP). The primary tumor location in the other 37 patients was hypopharynx ($n = 3$), larynx ($n = 8$), oral cavity ($n = 2$), oropharynx ($n = 17$), tongue ($n = 6$), and tonsil ($n = 1$).

In total, 124 lymph nodes were assessed on PET images and were clearly correlated with histologic reports: 86 malignant and 38 benign. Because there were 4 different sequences (200 HD PET, 200 TOF PET, 400 HD PET, and 400 TOF PET) and 2 readers evaluating each lymph node, our data volume included 992 imaging units. Among them, 871 imaging units (87.8%) were detected. Readers A and B

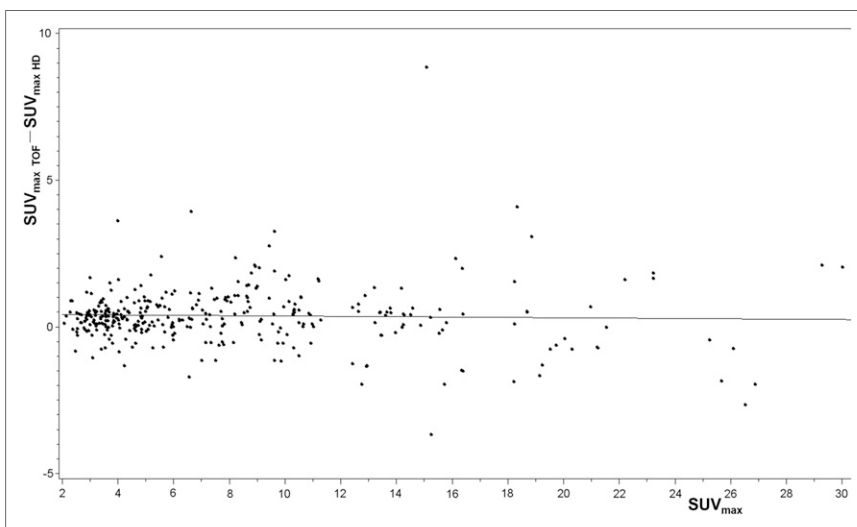


FIGURE 3. Bland–Altman analysis demonstrates that differences in SUV_{max} between TOF PET and HD PET were independent of SUV_{max} range ($P = 0.4683$). Data were included if SUV_{max} was greater than 2.5.

TABLE 2
Intersequence Agreement on Lesion Character for Both Readers

Sequence	Reader A		Reader B	
	κ	Intersequence agreement	κ	Intersequence agreement
200 HD vs. 200 TOF	0.94	Very good	0.95	Very good
400 HD vs. 400 TOF	0.85	Very good	0.85	Very good
200 HD vs. 400 HD	0.68	Good	0.79	Good
200 TOF vs. 400 TOF	0.79	Good	0.74	Good

detected a different number of lymph nodes (Fig. 1). Reader B performed better and missed fewer lesions (reader B, 47 undetected lymph nodes; reader A, 74 undetected lymph nodes; $P = 0.0111$). Additionally, matrix 400 enabled detection of more lesions than matrix 200 ($P = 0.0137$). However, no significant difference could be demonstrated when TOF PET and HD PET sequences were compared ($P > 0.05$).

Lesion Volume

The lesion volumes for reader A were 3.90 ± 5.83 (mean \pm SD) cm^3 , $3.85 \pm 5.69 \text{ cm}^3$, $3.52 \pm 5.54 \text{ cm}^3$, and $3.61 \pm 5.56 \text{ cm}^3$ for 200 HD PET, 200 TOF PET, 400 HD PET, and 400 TOF PET, respectively. For reader B, the respective lesion volumes were $3.39 \pm 4.62 \text{ cm}^3$, $3.43 \pm 4.40 \text{ cm}^3$, $3.16 \pm 4.89 \text{ cm}^3$, and $3.27 \pm 4.93 \text{ cm}^3$. Neither reader showed a significant difference in comparing reconstruction methods or matrices ($P > 0.05$).

SUV_{max}

For both readers, SUV_{max} was significantly higher in TOF PET sequences than in HD PET sequences ($P < 0.05$) for matrix 200 and matrix 400 (Fig. 2). SUV_{max} for reader A was 8.50 ± 5.67 , 8.91 ± 5.63 , 8.80 ± 5.88 , and 9.07 ± 5.90 for 200 HD PET, 200 TOF PET, 400 HD PET, and 400 TOF PET, respectively. For reader B, the respective values were 8.31 ± 5.68 , 8.83 ± 5.65 , 8.27 ± 5.73 , and 8.55 ± 5.60 . Furthermore, the Bland–Altman analysis demonstrated that the differences between 2 reconstruction methods were independent of SUV_{max} range ($P = 0.4683$, Fig. 3), reader ($P = 0.6614$), and matrix ($P = 0.5601$), which means that the SUV_{max} for TOF PET was always higher than that for HD PET, regardless of the SUV_{max} range, reader, or matrix.

PET Character

The influence of different sequences on the reader's diagnostic judgment of the character (benign or malignant) of detected lymph nodes on PET was assessed. For both readers, κ values showed good to very good agreement on le-

sion character in comparisons of different reconstruction methods and matrices (Table 2), indicating that different sequences have no significant effect on lesion characterization. The agreement between the 2 readers was moderate to good (Table 3). McNemar testing confirmed that there was no significant difference ($P > 0.05$).

Sensitivity and Specificity

The sensitivity and specificity of the 4 sequences for both readers are summarized in Table 4. Diagnostic sensitivity was slightly higher for TOF PET than for HD PET but not significantly so. There was only a weakly significant difference between 200 TOF PET and 400 TOF PET (Fig. 4, $P = 0.0588$). For both readers, TOF PET was slightly less specific than HD PET with both matrix 200 and matrix 400. However, statistical analysis revealed no significant difference in specificity between different reconstruction methods or different matrices (Fig. 5).

Image Quality

The images of all 4 sequences were scored by both readers. TOF images were considered to have sharper boundaries and better delineation, especially for small lesions with mild uptake (Fig. 6). The relative frequency of each score range was calculated and is shown in Figure 7. 400 TOF PET (very good, 11.53%; good, 65.38%; satisfactory, 23.07%) and 400 HD PET (very good, 6.41%; good, 66.66%; satisfactory, 26.92%) definitely revealed better image quality than 200 TOF PET (good, 37.17%; satisfactory, 55.12%; not assessable, 7.69%) and 200 HD PET (good, 34.61%; satisfactory, 58.97%; not assessable, 6.41%) ($P < 0.05$, $\kappa = 0.01$ – 0.03). TOF PET had a higher frequency of score 1 (very good) than did HD PET, but the difference between TOF PET and HD PET was not significant ($P < 0.05$, $\kappa = 0.29$ – 0.51 , showing fair to moderate agreement between the 2 sequences).

DISCUSSION

The incidence of HNSCC is increasing, with approximately 650,000 newly diagnosed cases annually around the world, among which 60% are in an advanced stage. Lymph node infiltration is the most important adverse prognostic factor for HNSCC patients. In addition, good postsurgical outcome depends largely on complete resection of all tumor tissue. Therefore, precise preoperative nodal staging is critical for optimal treatment planning and the long-term survival of patients (19). However, despite rapid advances

TABLE 3
Interreader Agreement on Lesion Character

Sequence	κ	Interreader agreement
200 HD	0.58	Moderate
200 TOF	0.44	Moderate
400 HD	0.66	Good
400 TOF	0.68	Good

TABLE 4
Sensitivity and Specificity of the 4 Sequences for Readers A and B

Parameter	200 HD		200 TOF		400 HD		400 TOF	
	A	B	A	B	A	B	A	B
Sensitivity (%)	84.21	88.61	85.53	87.34	85.71	88.61	87.01	90.00
Specificity (%)	40.74	59.38	37.04	56.25	38.71	58.82	38.71	58.82

in different imaging modalities, lymph node staging can still be challenging because of the presence of complex structures in an anatomically small region. One possibility for improving the diagnostic output of PET/CT might be the integration of TOF technique. Yet, few data on TOF technique in the head and neck region are available. With the intention of further optimizing reconstruction parameters in PET/CT and increasing diagnostic output, it was our aim to analyze the effect of TOF technique on the diagnostic performance of ^{18}F -FDG PET/CT for assessment of HNSCC lymph node metastases.

In studies using phantoms, TOF technique in PET/CT has been reported to show superior performance regarding small-lesion detection, signal-to-noise ratio (SNR), and contrast resolution (18,20,21). However, quantifying and transferring these improvements to the clinical setting is complex. Kadrmas et al. (22) presented 2 illustrative case examples, a patient with colon cancer and a patient with esophageal cancer, in which a visually lower noise level and improved SNR could be demonstrated. Karp et al. (14) showed, in 3 cases of large patients (1 with colon cancer, body mass index of 46.5; 1 with an abdominal tumor, body mass index of 38; 1 with non-Hodgkin lymphoma, body mass index of 46), that TOF reconstruction revealed higher lesion uptake and a higher contrast recovery than non-TOF reconstruction at a matched noise level. In their study, Lois et al. (23) enrolled 100 oncologic patients with lesions in various body regions (upper and lower abdomen, lungs, and head and neck) and confirmed that TOF technique better defined small lesions, improved uniformity, and reduced noise for most lesions in the thorax

and abdomen. Furthermore, their study demonstrated a clear correlation between TOF SNR gain and patient body mass index for abdominal lesions but no correlation and only a slight SNR increase in the head and neck region. Hausmann et al. (24) demonstrated additional value for TOF technique in ^{18}F -choline PET/CT for detecting small metastatic lesions in 32 patients with prostate cancer and biochemical recurrence.

In our study, we investigated the effect of TOF technique on the diagnostic outcome of ^{18}F -FDG PET/CT with regard to preoperative lymph node staging in HNSCC. We could demonstrate that TOF PET images always show significantly higher SUV_{max} than HD PET images regardless of SUV_{max} range, matrix, and reader. This finding is consistent with previous results (24,25). But unexpectedly, in our study a higher SUV_{max} on TOF PET did not result in significantly increased lesion detection in the head and neck region when compared with HD PET. Sensitivity was slightly higher in TOF PET than in HD PET but not significantly so. In addition, TOF PET images more clearly delineated lesions and were more frequently given a high score for image quality. Yet, comparison of image quality scores by the 2 experienced readers did not indicate a significant improvement resulting from TOF PET. Also, TOF PET and HD PET had no significant effect on the assessment of whether lymph nodes were malignant or benign.

All these results suggest that in the head and neck region, the performance of TOF PET does not equal that found previously for abdominal imaging (14,23,24). One explanation might be the fact that 2 completely different anatomic regions are involved and that the results of abdominal imaging cannot be directly transferred to head and neck imaging. According to a previous finding by Budinger (12), variance between different body regions exists because a SNR improvement is proportionate to the square root of the object size and inversely related to the square root of the system timing resolution. Therefore, there may not be so significant an SNR improvement in the head and neck region as in body parts with a larger diameter, such as the abdomen and pelvis. This is consistent with the only available research involving TOF application in the head and neck region (23). The authors explained that the slight SNR improvement in lesions of the head and neck region was the result of patients being in the arms-up position during examination, which increased the effective diameter of the region.

Although it did not result in significantly higher lesion detection rates, a higher SUV_{max} could still be considered

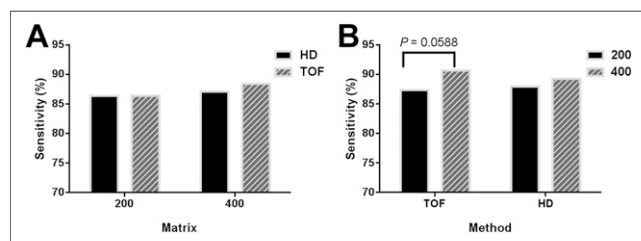


FIGURE 4. (A) Comparison of sensitivity between HD PET and TOF PET for both readers. TOF PET showed slightly higher sensitivity than HD PET but without a significant difference ($P > 0.05$). (B) Comparison of sensitivity between matrix 200 and matrix 400 for both readers. There was a weak significant difference between 200 TOF PET and 400 TOF PET ($P = 0.0588$).

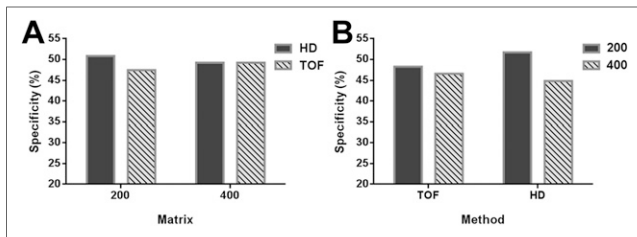


FIGURE 5. (A) Comparison of specificity between HD PET and TOF PET for both readers. For matrix 200, TOF PET showed slightly lower specificity than HD PET. (B) In comparison of specificity between matrices, matrix 400 showed slightly lower specificity than matrix 200. However, statistical analysis demonstrated no significant difference in specificity between different reconstruction methods or different matrices.

useful. TOF technique can achieve similar SUV_{max} levels in less acquisition time and with less ^{18}F -FDG activity, the latter of which, in particular, has practical potential in clinical applications. A patient with cancer commonly requires several sequential PET/CT scans over the course of treatment, including a staging scan before treatment and usually at least 2 scans for posttherapeutic monitoring at certain intervals. Moreover, there are difficult cases that may involve the use of multiple tracers. Therefore, the problem of radiation exposure could raise concern among patients and referring doctors. According to the results of Murray et al. (26), it was feasible to provide images without a significant lesion-uptake bias using TOF PET technique with a short acquisition time and reduced activity, which could be translated into clinical protocols.

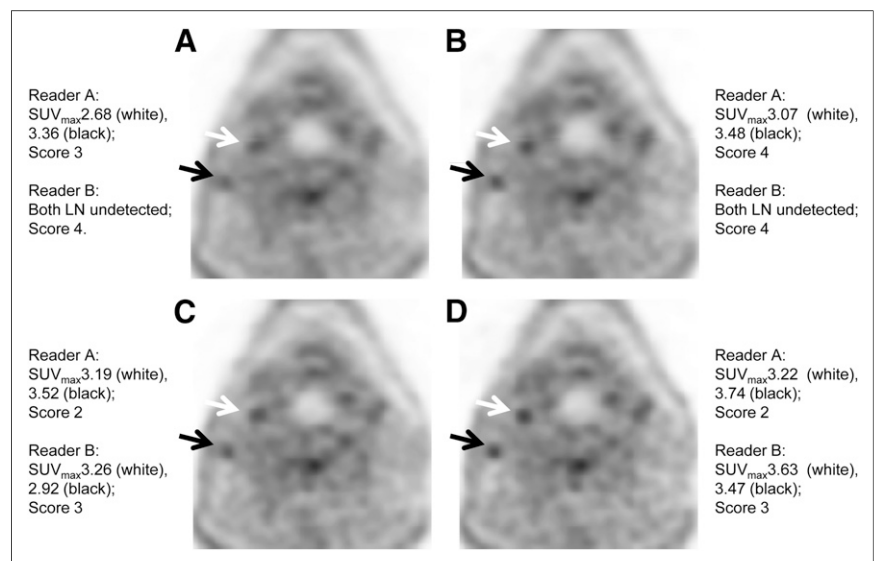
On the other hand, when comparing different scans, especially in clinical practice, we should bear in mind the dependence of SUV_{max} on the reconstruction method. As the most widely used semiquantitative parameter, SUV_{max} plays an essential role in the clinical setting, such as in characterizing a lesion as benign or malignant and in

assessing treatment response and long-term follow-up. However, with the introduction of an increasing number of new reconstruction techniques, the question of intercomparability is raised. According to a European procedure guideline for tumor imaging with PET, it is not yet possible to specify rational reconstruction settings for each new technique (27). With the maturation of these techniques over time, there should be a standardized protocol to ensure comparability of SUVs between multiple PET scans, especially in the setting of treatment response assessment (28).

Our study also found matrix selection to be an important factor influencing lesion detectability. Compared with matrix 200, matrix 400 detected more lymph nodes, had a higher sensitivity for lesion detection, and had better image-quality output. Although it was not the main concern of our study, this result can be helpful in further clinical applications of TOF technique. Lois et al. (23) found in a phantom study that TOF images perform better in visualizing lesions than non-TOF images at a large pixel size (image matrix of 168×168 , 4-mm pixel size). Also, the intrinsic noise reduction of TOF technique can compensate for the higher noise level caused by smaller pixel size (image matrix of 336×336 , 2-mm pixel size), which made the use of higher-spatial-resolution mode possible in the clinical setting. However, there was no direct comparison of matrix in the study of Lois et al., nor has there been a relevant clinical study until now. Further research is required to investigate the effect of matrix selection on the diagnostic performance of PET/CT with the TOF algorithm.

We have to mention certain limitations of our study. First, in order to focus on a comparison between different PET reconstruction methods, only PET information was made available to the 2 readers. The valuable contribution of the CT information, such as regarding the size of the lymph node, was not considered during the reading. This

FIGURE 6. Axial PET images reconstructed using different methods in 55-year-old man with oropharyngeal carcinoma (T2N2bM0). Two suspected lymph nodes in right level 2 were proved to be malignant by histologic examination. For both anterior (white arrow) and posterior (black arrow) lymph nodes, SUV_{max} measured on TOF PET (B and D) was consistently higher than SUV_{max} measured on HD PET (A and C). Lesions on TOF PET images had sharper boundaries and better contrast, especially on 400 TOF PET (D). However, both readers classified the lesions as benign lymph nodes, considering their mild uptake. SUV_{max} and image quality score as assessed by the 2 readers are shown individually on each sequence: 200 HD PET (A); 200 TOF PET (B), 400 HD PET (C), and 400 TOF PET [D].



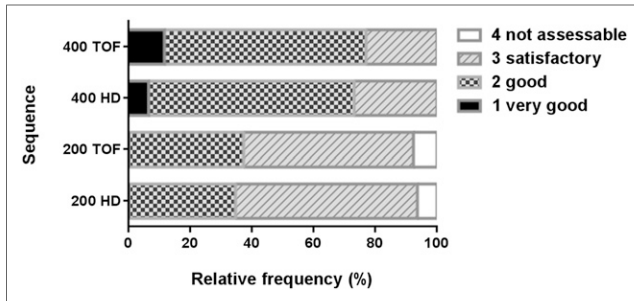


FIGURE 7. Image quality scores for the 4 sequences. Matrix 400 definitely provided better image quality than matrix 200 ($P < 0.05$, $\kappa = 0.01$ – 0.03). TOF PET had a higher frequency of score 1 (very good) than did HD PET, but the difference between TOF PET and HD PET was not significant ($P < 0.05$, $\kappa = 0.29$ – 0.51).

factor may explain the decreased sensitivity and specificity compared with the diagnostic performance of PET/CT in clinical practice. Moreover, the number of patients for whom histologic confirmation of the PET diagnosis could serve as the gold standard was limited. Further studies on large cohorts need to be performed to confirm these findings and to integrate them in optimized PET/CT scanning protocols.

CONCLUSION

For diagnostic assessment of lymph node metastases in patients with an initial diagnosis of HNSCC, ^{18}F -FDG PET/CT using TOF technique increases SUV_{max} and results in better image quality but has no significant effect on small-lesion detectability. The selection of the matrix plays an important role in precise lesion detectability, sensitivity, and image quality and in the potential of TOF technique for the clinical management of patients with HNSCC.

DISCLOSURE

The Institute of Clinical Radiology and Nuclear Medicine has research agreements with Siemens Healthcare Sector. No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Sadick M, Schoenberg SO, Hoermann K, Sadick H. Current oncologic concepts and emerging techniques for imaging of head and neck squamous cell cancer. *GMS Curr Top Otorhinolaryngol Head Neck Surg.* 2012;11:Doc08.
- Kapoor V, Fukui MB, McCook BM. Role of ^{18}F FDG PET/CT in the treatment of head and neck cancers: principles, technique, normal distribution, and initial staging. *AJR.* 2005;184:579–587.
- Vandecaveye V, De Keyser F, Vander Poorten V, et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. *Radiology.* 2009;251:134–146.

- Riffel P, Michaely HJ, Morelli JN, et al. Zoomed EPI-DWI of the pancreas using two-dimensional spatially-selective radiofrequency excitation pulses. *PLoS ONE.* 2014;9:e89468.
- Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the use of ^{18}F -FDG PET in oncology. *J Nucl Med.* 2008;49:480–508.
- Schöder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. *Semin Nucl Med.* 2004;34:180–197.
- Yoon DY, Hwang HS, Chang SK, et al. CT, MR, US, ^{18}F -FDG PET/CT, and their combined use for the assessment of cervical lymph node metastases in squamous cell carcinoma of the head and neck. *Eur Radiol.* 2009;19:634–642.
- Rodrigues RS, Bozza FA, Christian PE, et al. Comparison of whole-body PET/CT, dedicated high-resolution head and neck PET/CT, and contrast-enhanced CT in preoperative staging of clinically M0 squamous cell carcinoma of the head and neck. *J Nucl Med.* 2009;50:1205–1213.
- Menda Y, Graham MM. Update on ^{18}F -fluorodeoxyglucose/positron emission tomography and positron emission tomography/computed tomography imaging of squamous head and neck cancers. *Semin Nucl Med.* 2005;35:214–219.
- Conti M. Focus on time-of-flight PET: the benefits of improved time resolution. *Eur J Nucl Med Mol Imaging.* 2011;38:1147–1157.
- Mullani NA, Markham J, Ter-Pogossian MM. Feasibility of time-of-flight reconstruction in positron emission tomography. *J Nucl Med.* 1980;21:1095–1097.
- Budinger TF. Time-of-flight positron emission tomography: status relative to conventional PET. *J Nucl Med.* 1983;24:73–78.
- Conti M, Eriksson L, Rothfuss H, Melcher CL. Comparison of fast scintillators with TOF PET potential. *IEEE Trans Nucl Sci.* 2009;56:926–933.
- Karp JS, Surti S, Daube-Witherspoon ME, Muehllehner G. Benefit of time-of-flight in PET: experimental and clinical results. *J Nucl Med.* 2008;49:462–470.
- Jakoby BW, Bercier Y, Conti M, Casey ME, Bendriem B, Townsend DW. Physical and clinical performance of the mCT time-of-flight PET/CT scanner. *Phys Med Biol.* 2011;56:2375–2389.
- Sadick M, Molina F, Frey S, et al. Effect of reconstruction parameters in high-definition PET/CT on assessment of lymph node metastases in head and neck squamous cell carcinoma. *J Nucl Med Technol.* 2013;41:19–25.
- Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg.* 2002;128:751–758.
- Bettinardi V, Presotto L, Rapisarda E, Picchio M, Gianolli L, Gilardi MC. Physical performance of the new hybrid PETCT Discovery-690. *Med Phys.* 2011;38:5394–5411.
- Mamelle G, Pampurik J, Luboinski B, Lancar R, Lusinch A, Bosq J. Lymph node prognostic factors in head and neck squamous cell carcinomas. *Am J Surg.* 1994;168:494–498.
- Conti M, Bendriem B, Casey M, et al. First experimental results of time-of-flight reconstruction on an LSO PET scanner. *Phys Med Biol.* 2005;50:4507–4526.
- Surti S, Karp JS. Experimental evaluation of a simple lesion detection task with time-of-flight PET. *Phys Med Biol.* 2009;54:373–384.
- Kadrmas DJ, Casey ME, Conti M, Jakoby BW, Lois C, Townsend DW. Impact of time-of-flight on PET tumor detection. *J Nucl Med.* 2009;50:1315–1323.
- Lois C, Jakoby BW, Long MJ, et al. An assessment of the impact of incorporating time-of-flight information into clinical PET/CT imaging. *J Nucl Med.* 2010;51:237–245.
- Hausmann D, Bittencourt LK, Attenberger UI, et al. Diagnostic accuracy of ^{18}F choline PET/CT using time-of-flight reconstruction algorithm in prostate cancer patients with biochemical recurrence. *Clin Nucl Med.* 2014;39:e197–e201.
- Akamatsu G, Mitsumoto K, Taniguchi T, Tsutsui Y, Baba S, Sasaki M. Influences of point-spread function and time-of-flight reconstructions on standardized uptake value of lymph node metastases in FDG-PET. *Eur J Radiol.* 2014;83:226–230.
- Murray I, Kalemis A, Glennon J, et al. Time-of-flight PET/CT using low-activity protocols: potential implications for cancer therapy monitoring. *Eur J Nucl Med Mol Imaging.* 2010;37:1643–1653.
- Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2010;37:181–200.
- Boellaard R. Need for standardization of ^{18}F -FDG PET/CT for treatment response assessments. *J Nucl Med.* 2011;52(suppl 2):93S–100S.