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Original Article

^{18}F-FDG-PET/CT assessment of Takayasu arteritis and effect of time-of-flight reconstruction: an observational study

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Abstract

Background: To assess the impact of time-of-flight (TOF) positron emission tomography (PET)/computed tomography (CT) image reconstruction on assessment of Takayasu arteritis (TKA). We reviewed 14 patients (15 cases) who underwent TOF-PET/CT. PET images were reconstructed using ordered-subsets expectation maximisation ± TOF. Uptake in 10 vascular regions was assessed in each case using the four-point visual grading system (3, higher than liver uptake; 0, no uptake). Grades in the TOF-PET/CT and non-TOF-PET/CT groups were compared using the sign test. Relationships between visual grade and arterial FDG uptake pattern in the 10 regions and clinical findings were assessed. Additionally, qualitative summary score (PETVAS) and maximum standard uptake value (SUVmax) were compared between 2 groups using Wilcoxon signed rank test.

Results: Except for the highest visual grade, the grades in all 150 regions were significantly higher in the TOF-PET/CT group ($p=0.003$). FDG uptake pattern and region were not significant determinants of the effect of TOF reconstruction. PETVAS and SUVmax were significantly higher in the TOF-PET/CT group ($p=0.02$, $p<0.001$ respectively).

Conclusions: Visual grades, PETVAS, and SUVmax were significantly higher when assessed by TOF-PET/CT. The use of the same reconstruction algorithm before and after treatment is recommended when evaluating the response to treatment.

Keywords: Takayasu arteritis, ^{18}F-FDG-PET/CT, time-of-flight, large-vessel vasculitis

Introduction

Takayasu arteritis (TKA) is a chronic granulomatous large-vessel vasculitis that is rare and has severe potentially lethal complications, including aortic dissection/rupture, refractory hypertension, and myocardial infarction.[1, 2] Early diagnosis and detection of inflammation in the arterial wall is essential for improvement of the short-term and long-term outcomes in patients with TKA. However, the disease is difficult to evaluate because it has no specific symptoms and there are no laboratory biomarkers that accurately reflect its activity or progression.

^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) is a functional imaging modality that has an important role in the management of patients with cancer. Moreover, FDG-PET/CT has been demonstrated to be an effective imaging modality for assessment of TKA.[3, 4, 5, 6, 7, 8, 9]

Time-of-flight (TOF) reconstruction uses the time difference between the arrival of two photons and localises the emission point with much higher precision than non-TOF detection.[10] Previous studies have demonstrated the effects of TOF on PET/CT imaging in the fields of oncology and cardiology.[11, 12, 13, 14] However, to the best of our knowledge, the impact of TOF reconstruction on evaluation of TKA has not been reported previously. Therefore, the aim of this study was to investigate how TOF reconstruction affects PET/CT assessment of patients with TKA.

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Materials and methods

Patients

Consecutive patients who underwent TOF-FDG-PET/CT at Tokyo Medical and Dental University for assessment of large-vessel vasculitis between July 2018 and January 2019 were retrospectively reviewed. Patients who were under the age of 20 years and those who had undergone aortic surgery before FDG-PET/CT were excluded. The study was approved by the institutional ethics review committee of Tokyo Medical and Dental University (M2019-013). The need for written informed consent was waived in view of the retrospective nature of the study and the anonymity of the data.

We evaluated disease activity using the following four National Institutes of Health (NIH) criteria devised by Kerr et al.[15] : 1, systemic features; 2, features of vascular ischemia or inflammation; 3, laboratory data; and 4, typical angiographic features. Cases with new occurrence or aggravation of at least two of these four features were defined as active. Our assessment of laboratory parameters included the C-reactive protein or matrix metalloproteinase-3 level measured within 3 weeks before or after PET/CT in addition to the erythrocyte sedimentation rate. Angiographic features were assessed on CT or magnetic resonance images acquired 2 months before or after PET/CT scanning.

PET/CT protocol

All FDG-PET/CT images were obtained using a Celesteion scanner (Canon Medical Systems, Otawara, Japan). After fasting for at least 4 h, all patients received an intravenous injection of 3.7 MBq/kg of FDG. Whole-body CT data were obtained for attenuation correction and anatomical co-registration with free breathing. The technical CT scan parameters were as follows: tube voltage, 120 kV; field of view, 550 mm; pitch, 16.0; and slice thickness, 2.0 mm. After CT, whole-body PET scanning was started about 60 min after the injection of FDG. PET emission scans were acquired in 3D mode using the following parameters: 2 min per bed position, a pixel size of 4 mm, and a Gaussian filter size of 6 mm. The PET images were reconstructed using two algorithms, i.e., ordered-subsets expectation maximisation (OSEM) and OSEM + TOF. The reconstruction parameters were two iterations and 10 subsets for both algorithms.

Imaging analysis

All PET/CT images were analysed and scored by two nuclear medicine radiologists working independently. The four-point grading system was used for visual assessment of vascular FDG uptake (3, vascular uptake higher than liver uptake; 2, vascular uptake similar to liver uptake; 1, vascular uptake lower than liver uptake; 0, no vascular uptake).[3, 4, 5] Ten vascular regions, i.e., the ascending aorta, aortic arch, innominate artery, right and left common carotid arteries, right and left subclavian arteries, descending aorta, abdominal aorta, and pulmonary artery, were visually assessed in each patient. When FDG uptake was detected in a specific vascular region, we evaluated whether it was diffuse or patchy. When there was a discrepancy, the final decisions on visual grade and uptake pattern were reached by consensus. In each patient, the highest visual grade in the 10 vascular regions was defined as the final visual grade. In all 150 regions, a difference in visual grade was identified by subtraction of the grade for non-TOF (OSEM)-PET/CT from that for TOF (OSEM + TOF)-PET/CT. Additionally, a qualitative summary score (hereafter termed PET Vascular Activity Score - PETVAS) was created by adding the visual grades of 10 vascular regions in each case.[9] For the semiquantitative analysis of FDG uptake, we obtained the maximum standard uptake value (SUVmax) of arterial regions. In an axial view, Regions of interest with a diameter of 1cm were placed on the vascular regions with attention to anatomic location on CT by one observer. Regions of interest were placed on the same position between non-TOF and TOF-PET/CT. The vascular regions in which both the visual grades of TOF-PET/CT and non-TOF-PET/CT were 0 were excluded from semiquantitative analysis.

Statistical analysis

The sign test was used to compare the visual grades between the TOF and non-TOF groups. Agreement between the visual grade of TOF and non-TOF-PET/CT was assessed by weighted kappa coefficient. Fisher's exact test was used to compare the diffuse pattern with the patchy pattern and to compare the 10 vascular regions. Wilcoxon signed rank test was used to compare the PETVAS and SUVmax between the TOF and non-TOF groups. All statistical analyses were performed using R 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered statistically significant.

Results

Eighteen patients (19 cases) met the study inclusion criteria. Four patients (4 cases) were excluded (3 because of previous aortic surgery and 1 who was below the age limit). The characteristics of the 14 patients (15 cases)

Table 1. Patient demographic and clinical characteristics

Case	Sex	Age, years	BMI	Final visual grade (non-TOF)*	Final visual grade (TOF)*	PETVAS (non-TOF)‡	PETVAS (TOF)‡	Diagnosis	Activity	CRP (mg/dl)	ESR (mm/hr)	MMP-3 (ng/ml)	Medication
†1	F	39	22.6	3	3	24	26	TKA	+	0.1	14	67.6	TCZ, MTX
2	F	26	19.5	2	3	4	5	TKA	+	0.03	NA	157.7	IFX, PSL, MTX
3	F	32	19.4	0	1	0	2	BD s/o	+	0.02	9	NA	
†4	F	39	23.8	2	2	5	11	TKA	+	0.22	21	46.5	IFX, MTX
5	F	46	17.8	1	1	2	2	TKA	NA	NA	NA	NA	PSL
6	F	36	20.5	1	0	1	0	TKA	–	0.03	NA	NA	PSL, TCZ
7	F	30	19.9	1	1	1	2	TKA	–	0.04	10	NA	PSL, TAC
8	F	41	20.7	3	3	7	8	TKA	NA	NA	NA	NA	PSL
9	F	32	21.9	0	0	0	0	TKA	NA	NA	NA	NA	
10	M	48	22.4	1	1	1	1	TKA + IgG4RD	–	0.2	21	211.1	PSL
11	F	43	19.3	1	1	2	1	TKA	NA	NA	NA	NA	PSL
12	F	67	16.4	0	0	0	0	TKA	–	0.07	26	56.2	
13	F	29	16.7	3	3	7	9	TKA	NA	NA	NA	NA	
14	M	21	18.1	2	2	8	11	TKA	–	0.02	NA	NA	PSL, TCZ, MTX
15	F	60	22.7	1	1	4	5	TKA	–	0.02	10	NA	MTX

*There was no significant difference in the final visual grade between the non-TOF and TOF groups (p=1.0).

‡ There was significant difference in PETVAS between the non-TOF and TOF groups (p=0.02). The final visual grade is the highest visual grade recorded for each patient. PETVAS is the summary score of visual grade for each patients.

† Cases 1 and 4 are for the same patient. BD, Behcet's disease; BMI, body mass index; IgG4RD, IgG4-related disease; NA, not available; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MMP-3, matrix metalloproteinase-3; TCZ, Tocilizumab; MTX, Methotrexate; IFX, Infliximab; PSL, Prednisolone, PET, positron emission tomography; TKA, Takayasu arteritis; TOF, time-of-flight

Table 2. Comparison of visual grades recorded in 150 regions between the TOF-PET/CT group and the non-TOF-PET/CT group

	TOF-PET/CT visual grade			
Non-TOF-PET/CT visual grade	0	1	2	3
0	101	9	1	0
1	3	13	5	0
2	0	0	5	4
3	0	0	1	8

The visual grade value was significantly higher in the TOF group than in the non-TOF group (p=0.003). CT, computed tomography; PET, positron emission tomography; TOF, time-of-flight

Table 3. Relationship between changes in visual grade and symptoms

Visual grade (non-TOF/TOF)	Case	Region	Symptomatology
0/2 or 1/2	4	Arch, Innom A, rt Ca, lt subcl A	New-onset bruit in right subclavian region
	14	lt CA, Innom A	No symptoms (slight dilation of aortic arch)
2/3	1	A abd, rt subcl A	Right neck and shoulder pain
	2	lt CA	Vascular pain in lt CA
	13	rt CA	Vascular pain in rt CA

A abd, abdominal aorta; Arch, aortic arch; Innom A, Innominate artery; lt/rt subcl A, left/right subclavian artery; lt/rt CA, left/right common carotid artery; TOF, time-of-flight

included in the analysis are shown in Table 1. The mean blood glucose level was 102.2 ± 10.8 mg/dl. The mean fasting duration was 391 ± 85 min (data for 4 patients were excluded from the calculation because their fasting duration was over 4 h but their last mealtime was uncertain). We did not assess disease activity in 5 cases because of lack of laboratory and angiographic data; in 7 of 10 cases, we were able to assess disease activity but not necessarily accurately because of lack of angiographic data. The final visual grades were not significantly different between the non-TOF and TOF-PET/CT groups (p=1.0, the sign test). PETVAS was significantly different between the non-TOF and TOF-PET/CT groups (p=0.02, Wilcoxon signed rank test).

The visual grades for the 10 vascular regions in all patients are shown in Table 2. The visual grades for all 150 regions were significantly higher in the TOF-PET/CT group than in the non TOF-PET/CT group (p=0.003, the sign test). Weighted kappa coefficient between non-TOF and TOF-PET/CT groups was calculated as 0.89.

The relationship between change in visual grade and symptoms is shown in Table 3. The visual grade was elevated from 0 or 1 (non-TOF-PET/CT) to 2 (TOF-PET/CT) for 6 regions in 2 cases and from 2 to 3 for 4 regions in 3 cases.

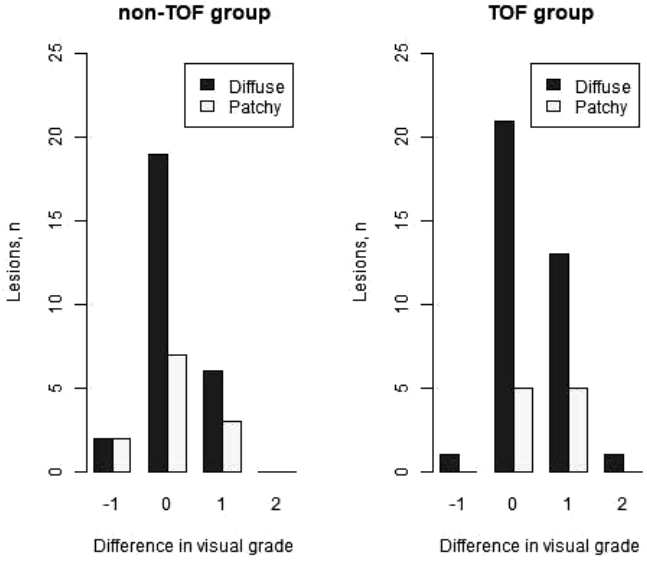

Figure 1. Bar plots showing the difference in visual grade value according to FDG uptake pattern.

The difference in visual grade was obtained by subtracting the visual grade of non-TOF-PET/CT from that of TOF-PET/CT. CT, computed tomography; PET, positron emission tomography; TOF, time-of-flight

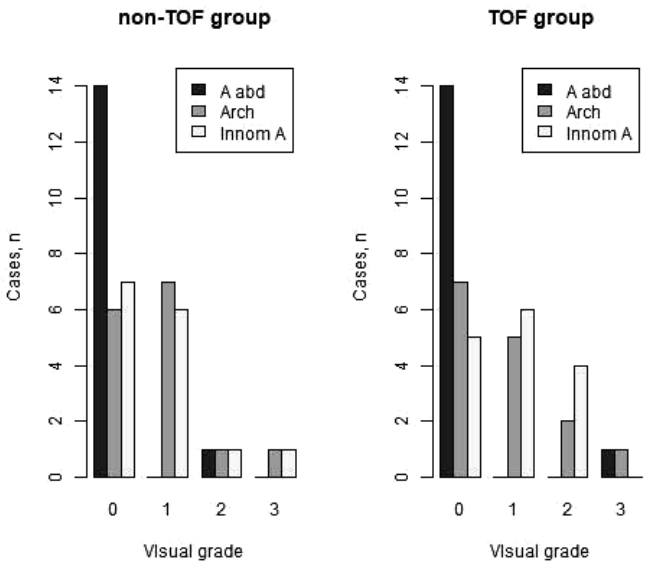

Figure 2. Bar plots showing the visual grades for 10 vascular regions.

A Abd, abdominal aorta; Arch, aortic arch; Innom A, innominate artery; TOF, time-of-flight

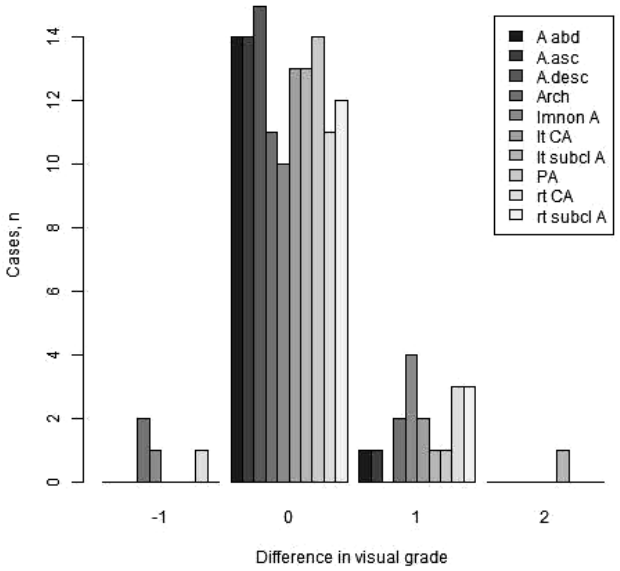

Figure 3. Bar plot showing the difference in visual grade values for 10 vascular regions.

The difference in visual grade was obtained by subtracting the visual grade of non-TOF-PET/CT from that of TOF-PET/CT. A Asc, ascending aorta; A desc, descending aorta; A abd, abdominal aorta; Arch, aortic arch; CT, computed tomography; Innom A, innominate artery, lt/rt subcl A, left/right subclavian artery; lt/rt CA, left/right common carotid artery; PA, pulmonary artery; PET, positron emission tomography; TOF, time-of-flight

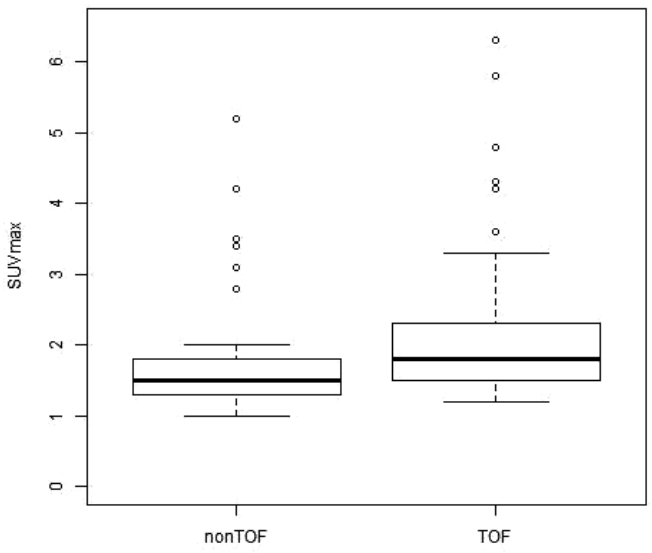

Figure 4. SUVmax distributions with non-TOF and TOF-PET/CT.

SUVmax from TOF-PET/CT is significantly higher than non-TOF-PET/CT ($p<0.001$, Wilcoxon signed rank test). TOF, time-of-flight; SUVmax, maximum Standard Uptake Value

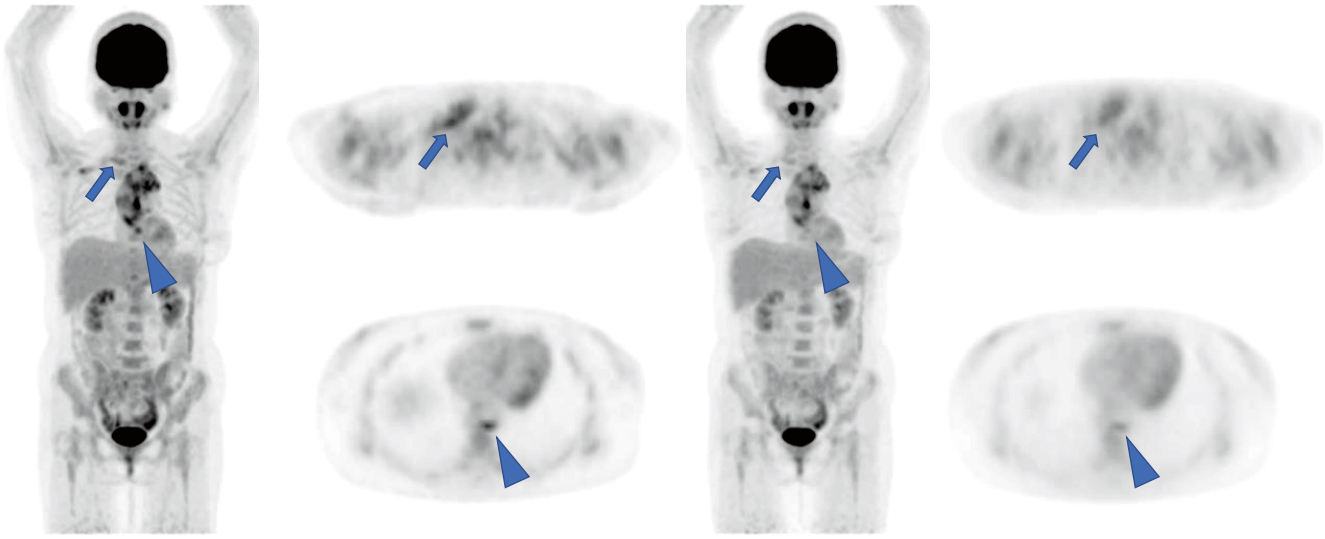

Figure 5. FDG-PET/CT images from a 39-year-old woman with Takayasu arteritis showing FDG uptake in right subclavian artery (arrow) and descending aorta (arrowhead).

FDG uptake is shown more clearly in the TOF-PET/CT image than in the non-TOF-PET/CT image. The visual grade of right subclavian artery was assessed to be 2 on the non-TOF-PET/CT image and to be 3 on the TOF-PET/CT image. The visual grade of descending aorta was assessed to be 3 on the non-TOF-PET/CT and TOF-PET/CT images. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; TOF, time-of-flight

There was no significant difference in the distribution of differences in visual grade between the patchy and diffuse uptake patterns (p=0.66 in the non-TOF group and p=0.83 in the TOF group, Fisher's exact test; Figure 1).

There were significant between-group differences in the distribution of visual grades in the 10 vascular regions (p=0.002 in the non-TOF group and p=0.011 in the TOF group, Fisher's exact test). The presence of FDG uptake was markedly more common at the aortic arch and innominate artery in both the TOF and non-TOF groups (Figure 2).

There was no significant difference in the distribution of differences in the visual grade between the 10 vascular regions (p=0.37, Fisher's exact test; Figure 3). SUVmax of the arterial regions were obtained in 49 regions and 101 regions were excluded from semiquantitative analysis because the visual grades of these regions were 0 in TOF and non-TOF-PET/CT. SUVmax from 49 regions were significantly higher in TOF-PET/CT group than non-TOF-PET/CT group (p<0.001, Wilcoxon signed rank test; Figure 4). A representative case (case 1) is shown in Figure 5.

Discussion

This study investigated the effect of PET/CT reconstruction using TOF on assessment of patients with TKA when using the established four-point visual grading system. Although TOF reconstruction had no significant impact on the final visual grade, we found that the visual grade for all regions assessed and PETVAS were significantly higher in the TOF-PET/CT group than in the non-TOF-PET/CT group. An earlier study demonstrated the effect of TOF reconstruction on uptake in the normal aorta[16]; however, subjects with suspected large-vessel vasculitis were excluded in that study. Therefore, this study is the first to investigate the effect of TOF reconstruction on assessment of TKA.

Weighted kappa coefficient between the visual grade of non-TOF and TOF-PET/CT group was 0.89, and this value means that the visual grades by two methods were in good agreement with each other. This is the reason the final visual grade between non-TOF and TOF was not significantly different while the visual grade assessed for all regions was significantly different. Although the highest score in each case was not significantly different

between non-TOF and TOF-PET/CT groups, PETVAS between two groups were significantly different. It has been reported that PETVAS was valuable for the assessment of TKA.[9, 17] Therefore, the slight but significant difference of visual grade between non-TOF and TOF-PET/CT was important for the assessment of TKA.

An earlier review showed that a visual grade of 2 was possibly indicative and that a grade of 3 was positive when assessing disease activity in large-vessel vasculitis.[3] In our study, assessment of disease activity by non-TOF-PET/CT and TOF-PET/CT was inconsistent for 6 (4%) of 150 regions when grade 2 or 3 was considered as active (Table 2). These regions were shown in case 4 (4 regions) and case 14 (2 regions). In these cases, TOF reconstruction had no effect on the final visual grade. Furthermore, when we defined grade 3 uptake as active, there was inconsistency between non-TOF-PET/CT and TOF-PET/CT in 5 (3.3%) of 150 regions. These 5 inconsistencies were in cases 1 (3 regions), 2 (1 region), and 13 (1 region). In case 2, there was a difference in the final grade between non-TOF-PET/CT and TOF-PET/CT; however, the disease activity based on the final visual grade assessed by TOF-PET/CT and by the NIH criteria were consistent (Table 1). Although the visual grade evaluated by two methods were in good agreement with each other, these findings indicate that the use of different reconstruction algorithms before and after treatment may lead to incorrect evaluation of the response to therapy in patients with TKA. Therefore, we recommend the use of the same reconstruction algorithm when evaluating their response to treatment.

As shown in Table 3, the visual grade increased from 0/1 to 2 in 2 cases (4 and 14) when TOF-PET/CT was used. In case 4, new-onset bruit and vascular obstruction were detected in the right subclavian region and the visual grade was elevated near the right subclavian artery (innominate and right common carotid arteries). In case 14, aortic surgery was performed 37 days after PET/CT. Infiltration of focal lymphocytes and neutrophils with disruption of elastic fibres and broad adventitial fibrosis was observed in the left common carotid artery and ascending aorta, indicating coexistence of acute and chronic inflammation,[18] and the visual grade was elevated near the left common carotid artery (Innominate and left common carotid arteries). Elevation of the visual grade may reflect mild chronic inflammation in these regions. Moreover, the visual grade was elevated from 2 to 3 on TOF-PET/CT in 4 regions (Table 3). Vascular pain was observed in 3 of these 4 regions (the right subclavian artery in case 1, left common carotid artery in case 2, and right common carotid artery in case 13). The symptomatology suggested acute inflammation in these regions, and TOF-PET/CT may reflect acute inflammation more accurately. TOF reconstruction has been reported to increase the standard uptake value for lymph node metastases,[12, 19] and this finding is compatible with our present results. Furthermore, Daube-Witherspoon et al. demonstrated that TOF reconstruction improved the accuracy and precision of measurement of FDG uptake using clinical whole-body patient data with embedded artificial lesions that had known activity uptake.[20] Therefore, based on the above findings, elevation of the visual grade from non-TOF-PET/CT to TOF-PET/CT may reflect a more accurate assessment of FDG uptake in the arterial wall.

There was no significant difference in the effect of TOF reconstruction on visual grade between the patchy and diffuse uptake patterns. As shown in an earlier phantom study, TOF reconstruction improved the contrast of hot lesions, particularly if they were small.[11] Therefore, we expected that the difference in visual grade for the patchy uptake pattern would be higher than that for the diffuse uptake pattern because the patchy uptake pattern was smaller. We speculate that the arterial wall lesions were so small that there was no significant difference between the patchy and diffuse uptake pattern.

In most cases, FDG uptake was detected at the aortic arch and innominate artery. This finding is consistent with previous studies showing that TKA involves predominantly the thoracic and cervical arteries in the Japanese population.[21, 22]

As shown in Figure 3, the effect of TOF reconstruction was not significantly different between the 10 vascular regions assessed. This is in contrast with an earlier study that found a difference in the gain in the signal-to-noise ratio because of TOF reconstruction in three body regions, i.e., the head and neck, abdomen, and lung.[23] In that study, the gain in the abdominal lesions showed a clear increase as a function of body mass index (BMI) in the range of 1.1–1.8. In contrast, the gain in the head and neck lesions showed a slight increase as a function of BMI in the range of 1.1–1.4. In our study, the effect of TOF on assessment of TKA was not significantly different between the 10 vascular regions, which included the abdominal aorta and carotid arteries. This finding may reflect the relatively low mean BMI (20.1 $\pm$ 2.3) in our cohort.

Finally, SUVmax on TOF-PET/CT was significantly higher than non-TOF-PET/CT. This result was consistent with previous studies.[12, 19] Several studies demonstrated the effectiveness of SUV for the assessment of TKA,[7, 8] but little is known regarding the effect of TOF on SUVmax

for the assessment of TKA. Therefore, this study was the first to investigate the effect of TOF on SUVmax for the assessment of TKA, and we should be careful for the assessment of the disease activity of TKA when using another reconstruction algorithm.

This study has several limitations. First, the sample size was small, which was inevitable given the rarity of TKA. Although the final visual grades were not significantly different between the non-TOF and TOF-PET/CT groups, the small sample size may have contributed to this result. Therefore, studies in larger cohorts may be needed. Second, patients with types of vasculitis other than TKA were included. Third, our investigation of the association between visual grade and clinical findings was inadequate because of the small sample size and our lack of ability to assess disease activity fully using the NIH criteria. A further prospective study would be required to investigate the relationship between the findings of TOF-FDG-PET/CT and the activity of TKA. Fourth, this study was performed at a single centre in a Japanese population. Therefore, studies in other populations may be needed. Fifth, we excluded 101 regions when we compared SUVmax between 2 methods because visual grades of these regions were zero in TOF and non-TOF-PET/CT. However, the aim of this study was to evaluate the TOF impact on the TKA and these 101 regions were considered as normal regions. Therefore, we suggest that exclusion of these regions was not important for the assessment of TOF impact on SUVmax of the TKA regions.

In conclusion, we found in this study that the visual grades for all 150 regions and PETVAS and SUVmax observed by TOF-PET/CT were significantly higher than those observed by non-TOF-PET/CT in patients with TKA. Although evaluation of the activity of TKA does not change markedly when TOF-PET/CT is used, we recommend that the same reconstruction algorithm be used before and after treatment when possible to assess the response to therapy in patients with TKA.

Conflicts of Interest: none

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