Different Scoring Methods of FDG PET/CT in Giant Cell Arteritis

Need for Standardization

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Abstract: Giant cell arteritis (GCA) is the most frequent form of vasculitis in persons older than 50 years. Cranial and systemic large vessels can be involved. [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is increasingly used to diagnose inflammation of the large arteries in GCA. Unfortunately, no consensus exists on the preferred scoring method. In the present study, we aim to define the optimal FDG PET/CT scoring method for GCA diagnosis using temporal artery biopsy and clinical diagnosis as the reference method.

FDG PET/CT scans of GCA patients (12 glucocorticoid-naive, 6 on glucocorticoid treatment) and 3 control groups (inflammatory, atherosclerotic, and normal controls) were evaluated. We compared 2 qualitative visual methods (i.e. (1a) first impression and (1b) vascular uptake versus liver uptake) and 4 semiquantitative methods ((2a) SUVmax aorta, (2b) SUVmax aorta-to-liver ratio, (2c) SUVmax aorta-to-superior-caval-vein ratio, and (2d) SUVmax aorta-to-inferior-caval-vein ratio). FDG uptake pattern (diffuse or focal) and presence of arterial calcifications were also scored.

Diagnostic accuracy of the visual method vascular versus liver uptake (1b) was highest when the cut-off point ''vascular uptake higher than liver uptake'' (sensitivity 83%, specificity 91%) was used. Sensitivity increased to 92% when patients on glucocorticoids were excluded from the analysis. Regarding the semiquantitative methods, the aorta-to-liver ratio (2b) with a cutoff of 1.03 had the highest diagnostic accuracy, with a sensitivity and specificity of 69% and 92%, respectively. Sensitivity increased to 90% when patients on glucocorticoids were excluded. The number of vascular segments with

diffuse FDG uptake pattern was significantly higher in GCA patients without glucocorticoid use compared with all control patient groups. CRP was not significantly different between positive and negative FDG PET scans in the GCA group.

Visual vascular uptake higher than liver uptake resulted in the highest diagnostic accuracy for the detection of GCA, especially in combination with a diffuse FDG uptake pattern. Of the semiquantitative methods, the aorta-to-liver SUVmax ratio (cutoff point = 1.03) had the highest diagnostic accuracy. The diagnostic accuracy increased when patients using glucocorticoids were excluded from the analyses.

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Abbreviations: CRP = C-reactive protein, FDG PET LDCT = [^{18}F]fluorodeoxyglucose positron emission tomography low dose CT, GCA = giant cell arteritis, ICV = inferior caval vein, ROC = receiver-operating characteristic, ROI = region of interest, SCV = superior caval vein, SUV = standardized uptake value.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis in persons older than 50 years. The aorta and the main branches of the aorta are mostly affected. The name GCA is derived from the giant cells that are typically found in histological specimens.[1] GCA rarely occurs in people under the age of 50 and women are 2 to 3 times more often affected than men.[2] The incidence is highest in northern Europe and reaches 20–30 per 100,000 in the population older than 50 in Sweden.[3] In 40% of GCA cases, polymyalgia rheumatica coexists.[4]

In the past, GCA was often named temporal arteritis, due to the involvement of the temporal artery and the related typical cranial symptoms. In the last 2 decades, it became clear that 2 overlapping variants of the disease can be distinguished: cranial and systemic GCA.[5,6] In GCA, inflammation of the vessel walls results in intimal hyperplasia that can occlude blood vessels which might result in new headache, visual loss, stroke, and limb and jaw claudication.[2] In systemic GCA, the inflammatory state may cause fatigue, fever, weight loss, and malaise.[5] Longstanding undiagnosed GCA of the aorta predisposes patients to aneurysms and aortic dissection.[7] Standard treatment of GCA consists of high-dose glucocorticoids.[1]

GCA is diagnosed when patients fulfil 3 out of 5 ACR 1990 classification criteria.[8] A major drawback of these criteria is that they are mainly based on symptoms of cranial GCA. For cranial GCA, the temporal artery biopsy is often positive. This invasive diagnostic tool lacks sensitivity; only 43% of temporal artery biopsies are positive in GCA patients who present without specific cranial symptoms.[5] For systemic GCA a standardized,

TABLE 1. Characteristics of GCA Groups and Control Groups

	GCA[a] (n = 12)	GCA[b] (n = 6)	Inflammation (n = 18)	Atherosclerosis (n = 19)	Normal (n = 16)
Sex (female/male)	9/3	6/0	15/3	14/5	14/2
Age	69.6 ± 9.7	69.4 ± 3.9	67.7 ± 7.7	69.0 ± 8.8	58.8 ± 7.3
TAB (Pos/Neg/ND)	5/2/5	2/1/3	NA	NA	NA
ACR (Pos/Neg)	7/5	5/1	NA	NA	NA
CRP (range)	55 (20–147)	8 (5–59)	69 (18–176)	11 (9–14)	5 (5–16)
Glucose (mmol/L, range)	6.2 (5.3–7.1)	5.8 (4.5–8.6)	6.1 (2.9–10.8)	5.9 (4.9–9.8)	5.8 (5.0–8.0)
Use of statins	5	1	3	8	1
Liver/kidney disturbances	0/0	0/1	6/7	5/3	2/2
Visual FDG uptake compared with liver (range)	35 (19–40)	22 (11–37)	12 (6–16)	13 (5–27)	12 (10–17)
Number of diffuse segments (range)	13 (5–14)	4 (0–13)	0 (0–2)	0 (0–9)	0 (0–5)
Calcification score (range)	14 (0–33)	12 (3–21)	12 (2–46)	22 (6–34)	2 (0–8)

ACR = American Rheumatology Society criteria for the classification of GCA; Atherosclerosis = control group with calcifications on PET/CT; CI = 95% confidence interval. NA = not applicable, ND = not done, Neg = negative, Normal = control group without an elevated CRP, without calcifications on PET/CT, Pos = positive, TAB = temporal artery biopsy. GCA[a] = GCA patients without glucocorticoid treatment. GCA[b] = GCA patients on glucocorticoid treatment, inflammation = control group with an elevated CRP.

reproducible diagnostic tool is lacking. Histological specimens of the aorta are impossible to obtain unless a vascular calamity requires aortic surgery.[9]

With the use of [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET), it is possible to image glucose metabolism in the vessels.[10] FDG is taken up by cells with a high metabolic rate, which makes it possible to identify the focus of inflammation. FDG PET may therefore diagnose GCA at an earlier stage than MR angiography (MRA) or CT angiography (CTA).[1] In previously published studies, FDG-PET was found to have an added value for the initial diagnosis in patients with nonspecific symptoms (fever without known cause) to identify an area for biopsy, to evaluate the extent of the disease, and to evaluate the success or failure of therapy.[11–13] However, especially for the diagnosis of GCA based on FDG-PET both visual and semiquantitative methods have been published. In 2003, Meller et al[14] were the first to make the comparison between vascular uptake and liver uptake, using a 4-point scale (grade 0: no uptake, grade I: uptake lower than liver, grade II: similar to liver, and grade III: higher than liver). In several articles, vascular uptake similar to or higher than liver uptake was defined as a scan positive for GCA.[18–21] It has been shown that there is an association between arterial FDG uptake and computed tomography (CT) derived vascular calcification score.[22] This indicates that it is important to distinguish focal (atherosclerotic) and diffuse (vasculitis) FDG uptake.[23,24]

In 2008, Hautzel et al[15] proposed the use of the aorta-to-liver standardized uptake value (SUV) ratio. First, the FDG uptake in the aorta and in the liver is quantified by constructing regions of interest (ROIs) on the PET image, followed by the aorta-to-liver SUV ratio calculation. A ratio >1 supports the diagnosis of GCA.[15] Theoretically, this should make the PET/CT more suitable for clinical use, since only anatomical knowledge is needed. However, it is a time-consuming method and it is doubtful whether this method has added value to the 4-point scale.

In 2014, Besson et al[16] reported on a semiquantitative approach in GCA. They reported that the aortic to venous blood pool SUV max ratio outperformed the lung and liver ratios.[16]

Summarized, different methods for assessment of the inflamed aorta have been described and there is no preferred method yet. In a recent metaanalysis the different methods were compared for diagnostic performance and their advantages and limitations. A drawback of this metaanalysis was that the studies were very heterogeneous with respect to patients, methods, and healthy controls, and therefore hard to compare.[25]

The primary aim of our study was therefore to evaluate all relevant scoring methods for the diagnosis of GCA using FDG PET/CT in a group of well classified GCA patients compared with 3 different control groups. In order to increase the diagnostic yield, the FDG uptake pattern was also studied, and finally the FDG uptake was correlated with the degree of calcification on low-dose CT (LDCT).

METHODS

This retrospective study was performed at the University Medical Center of Groningen (UMCG). Since our study was performed retrospectively, we were relieved by the ethics committee of our hospital from obtaining informed consent.

Laboratory and clinical data were retrieved from the hospital's electronic patient system. C-reactive protein (CRP) was used as a marker of inflammation as erythrocyte sedimentation rate (ESR) was not always measured. The following clinical data were recorded: temporal artery biopsy findings, whether the patient met the ACR criteria for GCA, and the use and dose of glucocorticoids and/or statins.

Patient Group

All GCA patients who underwent a FDG PET/LDCT scan between November 2009 and December 2012 were retrospectively selected from the database of our hospital. Patients either: fulfilled the ACR classification criteria for GCA, had a positive temporal artery biopsy, or had a clinical diagnosis of GCA (typical clinical and laboratory picture, response to steroids, typical findings on ultrasound, anterior ischemic optic neuritis), which could not be explained otherwise and which held true during at least 1 year of follow-up. Patients that underwent vascular surgery (e.g., vascular endoprosthesis) or had focal
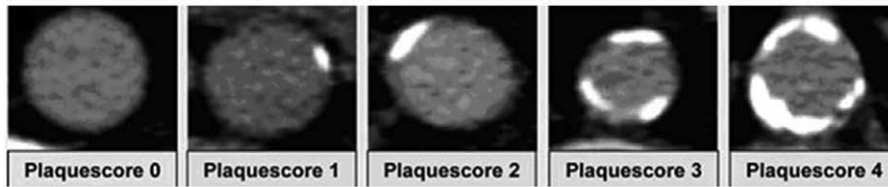
FIGURE 1. Calcification score.[22] Plaque score 0: no calcification, 1: <10%, 2: 10–25%, 3: 25–50%, and 4: >50% of the vessel affected by calcification.

instead of diffuse FDG uptake in the liver were excluded. Low-dose glucocorticoid treatment (<10 mg/day) initiated before the FDG PET/CT scan was allowed (6 out of 18 patients) (Table 1). Patients were regarded as steroid-naive when they had not received treatment for a period of 30 days before FDG PET/CT. The GCA group was divided into patients either using or not using glucocorticoids.

Control Groups

We chose controls to exclude the effect of inflammation and atherosclerosis on FDG uptake. CRP has a direct proinflammatory effect on endothelial cells[26] and hepatic cells, which may result in increased arterial FDG uptake. The presence of atherosclerotic plaques can also cause an increased arterial FDG uptake.[22]

Inflammatory Controls

The first control group existed of patients with an elevated CRP without being diagnosed as having GCA. We selected this group by searching the nuclear medicine department's database for ''fever of unknown origin'' as one of the primary reasons for FDG PET scanning. Out of 50 patients, 18 patients were selected who were matched for age, sex, and CRP with the GCA group.

Atherosclerotic Controls

Regarding the second control group, we selected patients with a vascular calcification score higher than 2[22] (methodology, see Figure 1) on the low-dose CT (LDCT). This was executed by randomly reviewing scans that were performed from 2010 and onward. Patients were matched for age and sex with the GCA group.

Normal Controls

As a final control group, patients without inflammation and no vascular calcifications on LDCT were selected. We randomly reviewed scans of patients older than 50 from 2010 and onward without any vascular calcifications. Due to difficulties in finding older patients without calcifications on the scan, this group was only matched for sex.

Scanning Procedure

All FDG PET LDCT scans were performed on a Biograph mCT camera system (Siemens Medical Systems, Knoxville, TN) and were performed according to a standardized protocol [EANM guidelines, 2010–2011]. In short, after fasting for at least 4 hours, whole-body (from head to knees) or total-body (from head to toes) PET scans were acquired 60 ($\pm$5) min after intravenous injection of 3 MBq/kg FDG. A low-dose CT scan was acquired prior to the PET-emission scan for attenuation correction and anatomic localization. FDG uptake was

quantified with the maximal standardised uptake value (SUVmax) using the EANM Research Limited (EARL) reconstruction techniques.[27]

Scoring Procedure

Two nuclear medicine physicians (AG, RS) were blinded to patient data when scans were visually interpreted.

FDG Uptake

We applied 2 qualitative visual methods. In method 1a, the PET/CT scan was judged on first impression (i.e., gestalt) as normal or vasculitis, depending on whether FDG uptake was found in the large arteries. This judgment was based on expert opinion of experienced nuclear medicine physicians.[10] In method 1b, 14 vascular segments (i.e., the aortic arch, the ascending, descending and abdominal aorta, and both vertebral, carotid, subclavian, iliac, and femoral arteries) were scored by the method as previously described by Meller et al[14] (see Table 2). Briefly, the visual scoring system is as follows: grade 0 is no vascular FDG uptake, grade I is vascular FDG uptake less than liver, grade II is vascular FDG uptake similar to liver, and grade III is vascular FDG uptake higher than liver FDG uptake. Median and range of the sum scores (max sum score is 42) on FDG uptake per patient are presented in the results section. Interobserver variability between both readers was evaluated.

With the semiquantitative methods (2a–d), ellipsoids were placed on the vascular branches to determine maximal standard uptake values (SUVmax) within the ROI by 1 observer. In method 2a (SUVmax aorta), the SUVmax of the aorta (subdivided in the SUVmax of the aortic arch, the ascending, descending, and abdominal aorta) was determined. In method 2b (SUVmax ratio aorta-to-liver), method 2c (SUVmax ratio aorta-to-superior-caval-vein (SCV)), and method 2d (SUVmax ratio aorta-to-inferior-caval-vein (ICV)), the SUVmax of the aorta was compared with background FDG uptake (SUVmax of the liver, SCV, and the ICV, respectively). We aimed to draw large ROIs around the majority of the target vascular structure, while the chance of including surrounding FDG uptake within the ROI was minimized. In the liver, we projected the ROI on the right lobe to reduce the chance of including the various veins and arteries running through the liver.

TABLE 2. Visual Grades of Vascular FDG Uptake[14]

Grade 0	No vascular FDG uptake
Grade I	Vascular FDG uptake less than liver FDG uptake
Grade II	Vascular FDG uptake equal to liver FDG uptake
Grade III	Vascular FDG uptake higher than liver FDG uptake

TABLE 3. Sensitivity and Specificity on Various Cut-Off Points for Visual Scoring

Grade II	Group	True Test	False Test	Sensitivity (%)	Specificity (%)
	GCA (steroid)	12 (6)	0 (0)	100 (100)	
	Inflammation	12	6		67
	Atherosclerosis	7	12		37
	Normal	8	8		50
Diffuse Grade II	**Group**	**True Test**	**False Test**	**Sensitivity (%)**	**Specificity (%)**
	GCA (steroid)	12 (4)	0 (2)	100 (89)	
	Inflammation	16	2		88
	Atherosclerosis	15	4		79
	Normal	12	4		75
Grade III	**Group**	**True Test**	**False Test**	**Sensitivity (%)**	**Specificity (%)**
	GCA (steroid)	11 (4)	1 (2)	92 (83)	
	Inflammation	17	1		94
	Atherosclerosis	15	4		79
	Normal	16	0		100
Diffuse Grade III	**Group**	**True Test**	**False Test**	**Sensitivity (%)**	**Specificity (%)**
	GCA (steroid)	10 (2)	2 (4)	83 (67)	
	Inflammation	18	0		100
	Atherosclerosis	18	1[*]		95
	Normal	16	0		100

True test is either true positive (for GCA group) or true negative (for control groups). False test is either false negative (for GCA group) or false positive (for control groups). Sensitivity is displayed for the glucocorticoid-naive GCA group and, between brackets, for both GCA groups combined. Specificity is displayed for all control groups separately. Grade II: FDG uptake in at least 1 vessel is similar to FDG uptake in the liver. Grade III: FDG uptake in at least 1 vessel is higher than FDG uptake in the liver. Diffuse: FDG uptake in the vascular segment of either grade II or grade III is diffuse.
[*] Patient presenting after chemotherapy for non-Hodgkin lymphoma.

Uptake Pattern

When FDG uptake was present in the vascular segment, we evaluated whether the uptake was diffuse (homogeneous) in the vessels or focal (heterogeneous). Median and range of the number of segments with diffuse uptake were quantified (max score is 14). Interobserver variability between both readers was evaluated.

Calcification on Low-Dose CT

The degree of calcification was visually scored according to the classification system of Rominger[22] (see Figure 1). Briefly, vascular score was 0: no calcification, 1: <10%, 2: 10−25%, 3: 25−50%, and 4: >50% of the vessel affected by calcification. Median and range of the sum scores on calcification (max sum score is 56) per patient were quantified. Interobserver variability between both readers was evaluated.

Statistics

Data are presented as mean ($\pm$ SD) or as median (range) for normally distributed and nonnormally distributed data, respectively. Interobserver reliability between both readers was evaluated using Cohen's Kappa for categorical data and intraclass correlation coefficient (ICC; 2-way mixed effects model, single measures, absolute agreement) for continuous

data. Values of <0.4, between 0.4 and 0.75, and >0.75 were considered to represent poor, fair to good, and excellent agreement, respectively.

Background FDG uptake (SUVmax of the liver, SCV, or the ICV) was compared between groups. Subsequently, the ratios between the SUVmax in the vessel wall and background were compared. ROC curves were reconstructed and analyzed to determine the optimal cutoff points and corresponding sensitivity (GCA group) and specificity (control groups) for each method. Diagnostic accuracy is defined as the average of the sensitivity and specificity of each method. Subanalyses for GC-treated and nontreated GCA patients were performed to determine the influence of glucocorticoid treatment in GCA patients on diagnostic performance. Statistical analysis was performed using IBM SPSS Statistics 20 (SPSS Inc, Chicago, IL).

RESULTS

A total of 71 scans were analyzed. Patient characteristics and sum scores on FDG uptake grade, uptake pattern, and calcification score are presented in Table 1.

Visual Methods of FDG Uptake

The uptake of the vascular regions was significantly higher in both GCA groups compared with the control groups

TABLE 4. SUVmax $\pm$ SD of the Various Backgrounds and the Segments of the Aorta

	GCA[a] (10)	GCA[b] (6)	Inflammation (18)	Atherosclerosis (19)	Normal (16)
Liver	3.01 $\pm$ 0.52	4.20 $\pm$ 1.32	3.33 $\pm$ 1.13	3.28 $\pm$ 0.80	2.98 $\pm$ 0.74
ICV	2.26 $\pm$ 0.73	2.55 $\pm$ 0.95	2.21 $\pm$ 0.76	2.01 $\pm$ 0.54	1.86 $\pm$ 0.48
SCV	2.13 $\pm$ 0.45	2.27 $\pm$ 0.67	2.06 $\pm$ 0.72[*]	1.93 $\pm$ 0.47	1.88 $\pm$ 0.48
Ascendens	3.17 $\pm$ 0.64	3.39 $\pm$ 0.57	2.41 $\pm$ 0.63	2.33 $\pm$ 0.48	2.19 $\pm$ 0.50
Arcus	2.87 $\pm$ 0.62	3.37 $\pm$ 0.27	2.40 $\pm$ 0.71	2.52 $\pm$ 0.66	2.16 $\pm$ 0.57
Descendens	3.32 $\pm$ 0.77	3.74 $\pm$ 0.40	2.63 $\pm$ 0.72	2.50 $\pm$ 0.65	2.37 $\pm$ 0.55
Abdominal	3.67 $\pm$ 1.21	3.97 $\pm$ 0.82	2.69 $\pm$ 0.77	2.64 $\pm$ 0.73	2.27 $\pm$ 0.59
MaxAorta	3.83 $\pm$ 1.10	4.04 $\pm$ 0.77	2.89 $\pm$ 0.79	2.82 $\pm$ 0.76	2.45 $\pm$ 0.57

GCA[a] = GCA patients without glucocorticoid treatment; GCA[b] = GCA patients on glucocorticoid treatment; ICV = inferior caval vein; Max-Aorta = highest SUVmax of the segments of the aorta; SCV = superior caval vein; SD = standard deviation; SUVmax = maximal standard FDG uptake value in a region of interest.

[*] Missing value due to port-a-cath.

($P < 0.05$). The uptake of vascular regions did not differ significantly between the various control groups.

For method 1a, overall judgement based on expert opinion, sensitivity was 56% and specificity was 98%. Sensitivity increased to 75% when excluding patients with glucocorticoid treatment from the analysis. The interobserver agreement for this method was very high (Cohen's kappa = 0.94).

The highest diagnostic accuracy in method 1b was achieved by defining a scan positive when an arterial structure revealed a higher visual uptake than liver (grade III) (sensitivity 83%, specificity 91%, sensitivity raised to 92% when patients on glucocorticoid treatment were excluded, specificity remained 91%). When FDG uptake similar to liver (Grade II) was also judged as positive, sensitivity was 100%, but specificity dropped to 51%. In Table 3, the occurrence of vascular FDG uptake similar to and higher than liver FDG uptake of the various control groups is shown. The interobserver agreement on the sum scores of visual FDG uptake was very high (ICC = 0.99).

Semiquantitative Analysis

The FDG uptake of the vascular regions was significantly higher in both GCA groups than the control groups ($P < 0.05$). The FDG uptake of vascular regions did not differ significantly between the various control groups. The background FDG uptake did not significantly differ between the GCA and control groups (see Table 4). Table 5 shows the average SUVmax ratio per semiquantitative method and patient group. All semiquantitative methods had good diagnostic accuracy (see Table 6). The FDG uptake in all ROIs was higher in GCA patients receiving glucocorticoids than in those not receiving glucocorticoids; however, the differences were not significant.

Method 2a (SUVmax Aorta)

When only taking the FDG uptake in the aorta into account, the optimal cutoff value was a SUVmax of 3.12. As presented in Table 6, this yields a sensitivity of 83% and a specificity of 73%. In the subanalysis, the diagnostic accuracy was higher in GCA patients with glucocorticoid treatment (sensitivity 100%, specificity 83%) than in those without (sensitivity 83%, specificity 62%).

Method 2b (SUVmax Aorta-to-Liver Ratio)

When dividing the FDG uptake in the aorta with the background FDG uptake in the liver, the optimal cutoff value was a SUVmax ratio of 1.03. As presented in Table 6, this yields a sensitivity of 72% and a specificity of 92%. In the subanalysis, the diagnostic accuracy was lower in the GCA patients with glucocorticoid treatment (sensitivity 67%, specificity 62%) than in those without (sensitivity 92%, specificity 92%).

Method 2c (SUVmax Aorta-to-SCV Ratio)

When dividing the FDG uptake in the aorta with the FDG uptake in the SCV, the optimal cut-off value was a SUVmax ratio of 1.65. As presented in Table 6, this yields a sensitivity of 72% and a specificity of 92%. When looking at the subanalysis, the diagnostic accuracy was lower in the GCA patients with glucocorticoid treatment (sensitivity 67%, specificity 92%) than in those without (sensitivity 75%, specificity 96%).

Method 2d (SUVmax Aorta-to-ICV Ratio)

When dividing the FDG uptake in the aorta with the FDG uptake in the ICV, the optimal cutoff value was a SUVmax ratio of 1.60. As presented in Table 6, this yields a sensitivity of 67%

TABLE 5. SUVmax Ratios $\pm$ SD. SUVmax Aorta Compared With SUVmax of the Background

SUV Ratio (n)	GCA[a] (10)	GCA[b] (10)	Inflammation (18)	Atherosclerosis (19)	Normal (16)
Liver	1.25 $\pm$ 0.21	1.00 $\pm$ 0.17	0.90 $\pm$ 0.18	0.85 $\pm$ 0.14	0.83 $\pm$ 0.12
ICV	1.72 $\pm$ 0.23	1.69 $\pm$ 0.39	1.35 $\pm$ 0.24	1.39 $\pm$ 0.25	1.33 $\pm$ 0.24
SCV	1.79 $\pm$ 0.26	1.90 $\pm$ 0.56	1.45 $\pm$ .028[*]	1.43 $\pm$ 0.16	1.32 $\pm$ 0.16

GCA[a] = GCA patients without glucocorticoid treatment; GCA[b] = GCA patients on glucocorticoid treatment; ICV = inferior caval vein; SCV = superior caval vein; SD = standard deviation.

[*] Missing value due to port-a-cath.

TABLE 6. AUCs, Optimal Cut-Off Values and Corresponding Sensitivity and Specificity of the Semiquantitative Methods

All Patients	AUC (CI)	Cut-Off Value	Sensitivity	Specificity
Method 2a (no background)	0.82 (0.71–0.93)	3.12	83%	73%
Method 2b (liver)	0.88 (0.79–0.97)	1.03	72%	92%
Method 2c (ICV)	0.83 (0.72–0.94)	1.60	67%	86%
Method 2d (SCV)	0.82 (0.69–0.96)	1.65	72%	92%
Without GC Treated	**AUC (CI)**	**Cut-Off Value**	**Sensitivity**	**Specificity**
Method 2a (no background)	0.79 (0.65–0.93)	2.75	83%	62%
Method 2b (liver)	0.94 (0.88–1.00)	1.03	92%	92%
Method 2c (ICV)	0.87 (0.78–0.96)	1.48	92%	73%
Method 2d (SCV)	0.85 (0.71–1.00)	1.72	75%	96%
Only GC Treated	**AUC (CI)**	**Cut-Off Value**	**Sensitivity**	**Specificity**
Method 2a (no background)	0.88 (0.79–0.97)	3.58	100%	83%
Method 2b (liver)	0.75 (0.59–0.92)	0.85	67%	62%
Method 2c (ICV)	0.75 (0.51–0.99)	1.62	67%	88%
Method 2d (SCV)	0.76 (0.50–1.00)	1.65	67%	92%

AUC = area under the curve; CI = 95% confidence interval; ICV = inferior caval vein; Only GC treated = GCA group not receiving glucocorticoid treatment excluded; SCV = superior caval vein; Without GC treated = GCA group receiving glucocorticoid treatment excluded.

and a specificity of 86%. When looking at the subanalysis, the diagnostic accuracy was lower in the GCA patients with glucocorticoid treatment (sensitivity 67%, specificity 88%) than in those without (sensitivity 92%, specificity 73%).

When comparing the 4 above-mentioned semiquantitative methods, the SUVmax aorta-to-liver ratio had the highest AUC value and therefore the highest diagnostic accuracy (Figure 2, Table 6). The diagnostic accuracy was higher when patients on glucocorticoid treatment were excluded, except in Method 2a (SUVmax aorta). Optimal cutoff point for the aorta-to-liver ratio was 1.03, with a specificity of 92%. Sensitivity is 69%, or 90% when patients on glucocorticoid treatment were excluded.

FDG Uptake Pattern

As illustrated in Table 1, the number of vascular segments with diffuse FDG uptake pattern was significantly higher in GCA patients without glucocorticoid use compared with all control patient groups ($P < 0.05$). The interobserver reliability on the number of diffuse segments was very high (ICC = 0.99). Examples are given in Figures 3 and 4.

Calcification on Low-Dose CT

Table 3 shows that the majority of patients from the atherosclerosis control group were assigned as false positive, especially when diagnosed only on the visual arterial FDG uptake versus liver FDG uptake (Grade II: 12 out of 19, Grade III: 4 out of 19), without taking the FDG uptake pattern into account. When the FDG uptake pattern is taken into account, few patients are regarded false positive (Grade II: 4 out of 19, Grade III: 1 out of 19). The interobserver reliability on the calcification sum score was very high (ICC = 0.99).
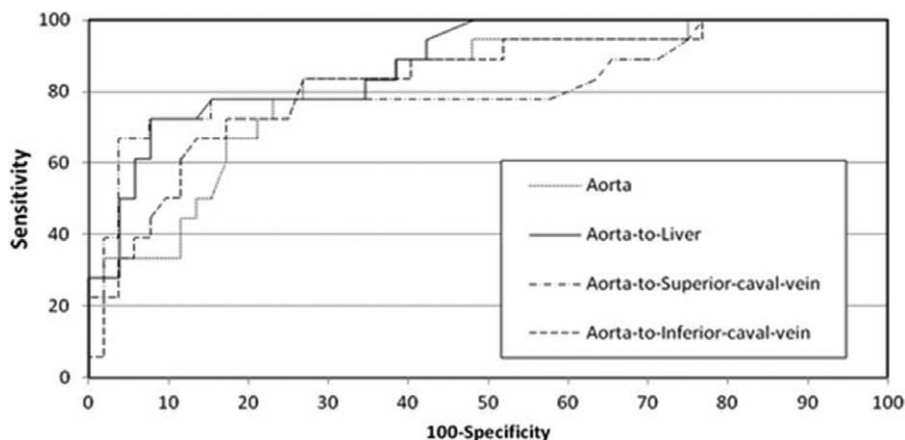

FIGURE 2. ROC curve on the SUVmax of the aorta (dotted), aorta-to-liver (solid), aorta-to-superior-caval-vein (dash-dot), and aorta-to-inferior-caval-vein (dashed).
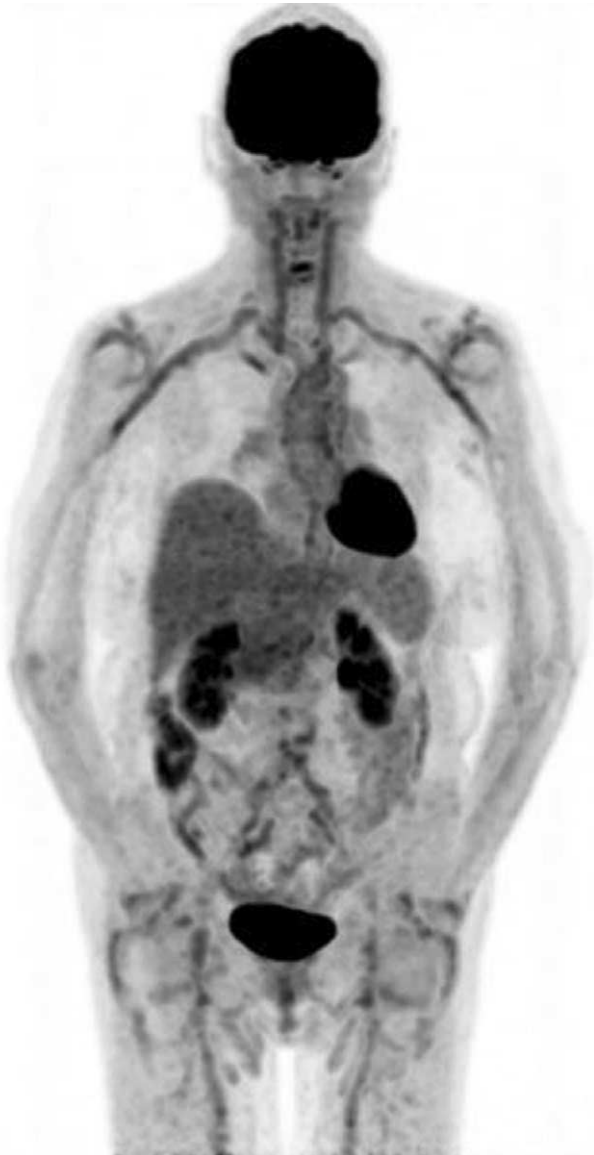
FIGURE 3. PET scan of a patient with large vessel vasculitis. Diffuse FDG uptake higher than liver FDG uptake (grade III) is visible in the carotid arteries, the subclavian arteries, and the ascending aorta.

FIGURE 4. PET scan of a patient with a malignancy in the left hemi-thorax and without large vessel vasculitis. Minimal (blood pool) FDG uptake is seen in the large arteries.

DISCUSSION

This is the first study to compare both visual as semi-quantitative methods in judging FDG PET/CT scans in defined groups of GCA patients. In addition, the vascular FDG uptake on FDG PET/CT scans of GCA patients was compared with 3 different control groups, including an atherosclerosis control group, using the same methods. Main findings were that visual vascular FDG uptake higher than liver resulted in the highest diagnostic accuracy for the detection of GCA, especially in combination with a diffuse FDG uptake pattern. An aorta-to-liver SUVmax ratio higher than 1.03 revealed the highest diagnostic accuracy as the semiquantitative method. The diagnostic accuracy increased when patients using glucocorticoids were excluded from analysis.

The highest diagnostic power to diagnose GCA is achieved when arterial wall FDG uptake is higher than liver by visual evaluation.

Several methods have been described to quantify FDG uptake in large vessel vasculitis. In 2003, Meller et al[14] were one of the first to use the comparison between liver FDG uptake and arterial FDG uptake, using a 4-point scale. In several other publications, arterial FDG uptake equal to liver FDG uptake and also higher than liver FDG uptake was assigned as positive for GCA.[18–20,28] Our results indicate that specificity will drop to 51% when grade II FDG uptake (i.e., equal to liver) is qualified as positive. Based on our results, only scans showing higher arterial FDG uptake than liver FDG uptake (grade III) should be assigned as positive for GCA. More recently, 3 studies were published investigating different quantitative scoring methods. Hautzel et al[15] used the method SUVmax aorta-to-liver ratio and a ratio >1 supported the diagnosis of GCA. Our results are in line with the findings of this study, since our highest diagnostic power was found for a cutoff SUVmax ratio value of 1.03. Besson et al[16] found that the caval vein was superior to the liver and the lung as background for the vascular FDG uptake. Prieto-Gonzalez et al[17] studied 32 GCA patients

positive on temporal artery biopsy, of whom 17 were on glucocorticoid treatment (<4 days), and used 20 controls. In that study the authors used the arterial SUVmax without taking the background FDG uptake into account.[17]

In the literature, the diagnostic power of FDG PET/CT in GCA has often been discussed. In various studies, a low sensitivity was found ranging from 60 to 73%.[29,30] However, this could be due to the inclusion of patients on glucocorticoid treatment. In a study of Lehmann et al,[29] 8 out of 20 patients were on glucocorticoids, and in a study of Walter et al,[30] 17 out of 26 patients were on glucocorticoids. In a metaanalysis of 6 studies in 2005, an overall sensitivity of 80% and specificity of 89% was shown which lowered when patients on immunosuppressive therapy were included.[31] This is in line with our results; we found that GCA patients on glucocorticoid treatment are comparable to control patients. In the SUVmax aorta-to-liver ratio, sensitivity increased from 69% to 90% when excluding patients on glucocorticoid treatment. With the visual scoring method, sensitivity increased from 83% to 92%.

We noticed that there was a trend to higher FDG uptake in the liver in GCA patients receiving glucocorticoid treatment compared with GCA patients not receiving glucocorticoids. Recently, Besson et al[16] reported that the aortic-to-blood-pool ratio outperformed the aorta-to-liver ratios and Prieto-Gonzalez et al[17] found that the aorta-to-liver ratio had a much lower discriminatory performance than the aorta SUVmax. They concluded that the liver is not reliable to use as a background, since FDG uptake was higher in GCA patients. However, both studies included a relative large number of patients receiving glucocorticoids (Besson: 9 out of 12 (75%), Prieto-Gonzalez: 17 out of 32 (53%)). In our study 33% (n = 6) of GCA patients were on glucocorticoids and we clearly showed an increased liver FDG uptake in these patients comparedwith GCA patients not on steroid treatment (n = 12). This higher liver FDG uptake in GCA patients on glucocorticoids (see Table 6) results in a lower diagnostic accuracy of the SUVmax aorta-to-liver ratio.

It has been shown that a correlation exists between arterial FDG uptake and arterial calcification score.[22] Therefore, it is important to distinguish focal (atherosclerosis) from diffuse (vasculitis) FDG uptake.[23,24] The use of statins may reduce the FDG uptake in the atherosclerotic process[32] and this could therefore be a confounder in our study. However, the use of statins between the atherosclerotic patient group and the GCA group was not significantly different in our study (see Table 1).

The main difficulty in performing a study to evaluate the diagnostic accuracy of the PET/CT scan in GCA is the lack of a gold standard. Some studies take a positive temporal artery biopsy as a gold standard, but not all TAB-positive patients have aortic involvement. Other studies based the gold standard solely on clinical findings. Differences in clinical findings could have interfered with the outcome and comparability of these studies. The advantage of our study is that we used the same group of GCA patients and several different control groups to compare the different scoring methods. A limitation of our study is that we retrospectively selected the groups. A better way to test the diagnostic accuracy of the FDG PET/CT would be to perform a prospective study including patients suspected of having GCA.

Of interest, we found that the CRP level was not related to FDG PET uptake, and that glucocorticoids increased both the vessel wall and liver FDG uptake.

CONCLUSION

FDG-PET/CT is an important imaging technique for diagnosing systemic GCA. Based on our results, a visual grading method with an arterial FDG uptake higher than the liver FDG uptake has the highest diagnostic accuracy for GCA. It is also important to score the pattern of FDG uptake (focal vs. diffuse) and to correct for the presence of atherosclerosis. When using the semiquantitative methods, the best method is to calculate the aorta-to-liver SUVmax ratio. Furthermore, the use of glucocorticoids results in a less reliable aorta-to-liver SUVmax ratio.

REFERENCES

1. Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. *Autoimmun Rev.* 2012;11:A544–A554.

2. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet.* 2008;372:234–245.

3. Petursdottir V, Johansson H, Nordborg E, et al. The epidemiology of biopsy-positive giant cell arteritis: special reference to cyclic fluctuations. *Rheumatology (Oxford).* 1999;38:1208–1212.

4. Cantini F, Niccoli L, Storri L, et al. Are polymyalgia rheumatica and giant cell arteritis the same disease? *Semin Arthritis Rheum.* 2004;33:294–301.

5. Brack A, Martinez-Taboada V, Stanson A, et al. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum.* 1999;42:311–317.

6. Kermani TA, Warrington KJ. Recent advances in diagnostic strategies for giant cell arteritis. *Curr Neurol Neurosci Rep.* 2012;12:138–144.

7. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Ann Intern Med.* 1995;122:502–507.

8. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* 1990;33:1122–1128.

9. Janssen SP, Comans EH, Voskuyl AE, et al. Giant cell arteritis: heterogeneity in clinical presentation and imaging results. *J Vasc Surg.* 2008;48:1025–1031.

10. Blockmans D, Maes A, Stroobants S, et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. *Rheumatology (Oxford).* 1999;38:444–447.

11. Blockmans D, de Ceuninck L, Vanderschueren S, et al. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum.* 2006;55:131–137.

12. Bertagna F, Bosio G, Caobelli F, et al. Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography for therapy evaluation of patients with large-vessel vasculitis. *Jpn J Radiol.* 2010;28:199–204.

13. Lensen KJ, Voskuyl AE, van der Laken CJ, et al. 18F-Fluorodeoxyglucose positron emission tomography in elderly patients with an elevated erythrocyte sedimentation rate of unknown origin. *PLoS One.* 2013;8:e58917.

14. Meller J, Strutz F, Siefker U, et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. *Eur J Nucl Med Mol Imaging.* 2003;30:730–736.

15. Hautzel H, Sander O, Heinzel A, et al. Assessment of large-vessel involvement in giant cell arteritis with 18F-FDG PET: introducing an ROC-analysis-based cutoff ratio. *J Nucl Med.* 2008;49:1107–1113.

16. Besson FL, de Boysson H, Parienti JJ, et al. Towards an optimal semiquantitative approach in giant cell arteritis: an (18)F-FDG PET/CT case-control study. *Eur J Nucl Med Mol Imaging.* 2014;41:155–166.

17. Prieto-Gonzalez S, Depetris M, Garcia-Martinez A, et al. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis:

a prospective, case-control study. *Ann Rheum Dis.* 2014;73: 1388–1392.

18. Fuchs M, Briel M, Daikeler T, et al. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. *Eur J Nucl Med Mol Imaging.* 2012;39:344–353.

19. Papathanasiou ND, Du Y, Menezes LJ, et al. 18F-Fludeoxyglucose PET/CT in the evaluation of large-vessel vasculitis: diagnostic performance and correlation with clinical and laboratory parameters. *Br J Radiol.* 2012;85:e188–e194.

20. Czihal M, Forster S, Hoffmann U. Imaging diagnostics of large vessel vasculitis. *Radiologe.* 2010;50:855–860.

21. Forster S, Tato F, Weiss M, et al. Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. *Vasa.* 2011;40:219–227.

22. Rominger A, Saam T, Wolpers S, et al. 18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med.* 2009;50: 1611–1620.

23. Belhocine T, Blockmans D, Hustinx R, et al. Imaging of large vessel vasculitis with (18)FDG PET: illusion or reality? A critical review of the literature data. *Eur J Nucl Med Mol Imaging.* 2003;30: 1305–1313.

24. Tahara N, Imaizumi T, Virmani R, et al. Clinical feasibility of molecular imaging of plaque inflammation in atherosclerosis. *J Nucl Med.* 2009;50:331–334.

25. Puppo C, Massollo M, Paparo F, et al. Giant cell arteritis: a systematic review of the qualitative and semiquantitative methods to assess vasculitis with 18F-fluorodeoxyglucose positron emission tomography. *Biomed Res Int.* 2014;2014:574248.

26. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation.* 2000;102:2165–2168.

27. 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.

28. Forster S, Tato F, Weiss M, et al. Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. *Vasa.* 2011;40:219–227.

29. Lehmann P, Buchtala S, Achajew N, et al. 18F-FDG PET as a diagnostic procedure in large vessel vasculitis-a controlled, blinded re-examination of routine PET scans. *Clin Rheumatol.* 2011;30:37–42.

30. Walter MA, Melzer RA, Schindler C, et al. The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. *Eur J Nucl Med Mol Imaging.* 2005;32:674–681.

31. Besson FL, Parienti JJ, Bienvenu B, et al. Diagnostic performance of (1)(8)F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* 2011;38:1764–1772.

32. Tawakol A, Fayad ZA, Mogg R, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol.* 2013;62:909–917.