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Diagnostic Accuracy of Positron Emission Tomography/Computed Tomography of the Head, Neck, and Chest for Giant Cell Arteritis: A Prospective, Double-Blind, Cross-Sectional Study

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Objective. Positron emission tomography/computed tomography (PET/CT) has not been well studied as a first-line test for giant cell arteritis (GCA), due, in part, to historical limitations in visualizing the cranial arteries. The Giant Cell Arteritis and PET Scan (GAPS) study was therefore carried out to assess the accuracy of a newer generation PET/CT of the head, neck, and chest for determining a diagnosis of GCA.

Methods. In the GAPS study cohort, 64 patients with newly suspected GCA underwent time-of-flight PET/CT (1-mm slice thickness from the vertex to diaphragm) within 72 hours of starting glucocorticoids and before undergoing temporal artery biopsy (TAB). Two physicians with experience in PET reviewed the patients' scans in a blinded manner and reported the scans as globally positive or negative for GCA. Tracer uptake was graded across 18 artery segments. The clinical diagnosis was confirmed at 6 months' follow-up.

Results. In total, 58 of 64 patients underwent TAB, and 12 (21%) of the biopsies were considered positive for GCA. Twenty-one patients had a clinical diagnosis of GCA. Compared to TAB, the sensitivity of PET/CT for a diagnosis of GCA was 92% (95% confidence interval [95% CI] 62–100%) and specificity was 85% (95% CI 71–94%). The negative predictive value (NPV) was 98% (95% CI 87–100%). Compared to clinical diagnosis, PET/CT had a sensitivity of 71% (95% CI 48–89%) and specificity of 91% (95% CI 78–97%). Interobserver reliability was moderate ($\kappa = 0.65$). Among the enrolled patients, 20% had a clinically relevant incidental finding, including 7 with an infection and 5 with a malignancy. Furthermore, 5 (42%) of 12 TAB-positive GCA patients had moderate or marked aortitis.

Conclusion. The high diagnostic accuracy of this PET/CT protocol would support its use as a first-line test for GCA. The NPV of 98% indicates the particular utility of this test in ruling out the condition in patients considered to be at lower risk of GCA. PET/CT had benefit over TAB in detecting vasculitis mimics and aortitis.

INTRODUCTION

Giant cell arteritis (GCA), also known as temporal arteritis, is a medium-to-large vessel vasculitis of the elderly that can cause acute irreversible vision loss, aortic aneurysm, and peripheral artery stenosis. Rapid and accurate diagnosis is critical to allow the urgent introduction of glucocorticoid-based therapy in those with the disease and prevent morbidity resulting from inappropriate treatment in those with alternative diagnoses.

Temporal artery biopsy (TAB) is the traditional test to confirm the diagnosis of GCA and remains widely used in clinical practice (1). Although a positive finding of GCA on TAB definitively confirms the diagnosis, a negative finding on biopsy does not

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exclude it, since the disease has a propensity to skip artery segments or primarily affect large vessels (2–6). In the absence of a better gold standard, the true sensitivity of TAB is unknown, but it is likely to be 85–90% at best (1,4).

Positron emission tomography (PET)/computed tomography (CT) scans can detect large vessel vasculitis in the aorta and subclavian, carotid, iliac, and/or femoral arteries in ~80% of patients with TAB-positive GCA (7,8). Its diagnostic accuracy, however, has not been robustly studied in unselected cohorts of patients with newly suspected GCA (9,10).

Recent studies have provided better guidance as to how to use PET/CT in GCA. Scans should ideally be performed within 72 hours from the initiation of glucocorticoid treatment, as the intensity and distribution of vascular tracer uptake decreases with treatment duration. A study published in 2018 demonstrated that the diagnostic sensitivity of PET/CT for large vessel vasculitis was maintained at 3 days after the commencement of glucocorticoids, but was decreased at 10 days (11). Newer generation time-of-flight PET/CT scanners can more precisely calculate the arrival time of photons and provide improved image resolution compared to conventional scanners. Time-of-flight PET/CT has recently been shown to detect arteritis in the smaller temporal, occipital, maxillary, and vertebral arteries, all of which are typically involved in GCA but have not been well visualized on older PET/CT scanners (12–14). A retrospective case–control study demonstrated that PET/CT scans of these vessels provided good discrimination between GCA patients and controls, with a sensitivity of 82% and specificity of 100% (14).

In the present study, we hypothesized that a newer generation time-of-flight PET/CT scan of the head, neck, and chest would be able to detect the presence of inflammation in vascular sites typically affected by GCA, including both the cranial and large arteries, and thus provide high diagnostic accuracy for the condition.

PATIENTS AND METHODS

Study design and participants. The Giant Cell Arteritis and PET Scan (GAPS) study was designed as a prospective, double-blind, cross-sectional study conducted at Royal North Shore Hospital, a tertiary referral center in Sydney, Australia, between May 2016 and July 2018. Ethics approval was granted by the Northern Sydney Local Health District Human Research Ethics Committee (approval no. HREC/16/HAWKE/68).

Patients who were newly suspected of having GCA were referred by specialist rheumatologists, ophthalmologists, neurologists, or clinical immunologists. Hospitalized and ambulatory clinic patients were eligible for inclusion. Consecutively referred patients were screened and enrolled, after provision of informed consent, if they met the following prespecified inclusion criteria: 1) age >50 years, 2) having fulfilled at least 2 of the 5 American College of Rheumatology (ACR) 1990 classification criteria for GCA (15), 3) having been scheduled for, but not yet undergone, TAB, and 4) having received glucocorticoids for <72 hours at the time of the PET/CT scan. Patients were excluded if they had known active malignancy, had a history of connective tissue disease or vasculitis, or had been taking glucocorticoids for a single period of >1 week during the preceding 6 months.

Clinical information was prospectively recorded at enrollment by means of a standardized data collection template. Responses were entered after conducting a detailed patient history review and physical examination. Results from ancillary ophthalmologic examinations and vascular imaging studies (performed at the discretion of the treating clinician and not standardized for this study) were also recorded at that time, along with determination of the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) at a time point most closely corresponding to the commencement of glucocorticoids.

Test methods. *PET/CT scan as the index test*. PET/CT scans were performed prior to TAB on a single Siemens Biograph mCT time-of-flight scanner. Patients fasted for at least 4 hours before they received an intravenous injection of 100 MBq fluorine-18 fluoro-2-deoxyglucose (FDG). At 60 minutes after the infusion of the FDG tracer, patients were scanned from the vertex of the head to the diaphragm with 1-mm CT reconstruction. Arms were positioned by the side to allow better visualization of the head and neck vessels.

The full set of scans was independently read between July and August 2018 by 2 nuclear medicine physicians (EH and GS) who were experienced in PET scans. These physician readers were blinded with regard to all clinical, imaging, and biopsy data. To calibrate reporting parameters, the physicians co-read 6 unblinded training scans from non–study patients at 14 months prior to the scan readings. In addition, at that time, they performed a limited blinded reading of 20 study scans to ensure that the study protocol was providing interpretable results.

The primary reporting outcome was a subjective global assessment of the scan as being positive or negative for GCA. Specific criteria were not provided to the readers, and the assessment was made based on the intensity and distribution of FDG vascular uptake. In general, the readers were more confident in reporting a scan as being positive for GCA in the following circumstances: 1) artery wall FDG uptake markedly increased compared to the blood pool, 2) artery wall FDG uptake increased diffusely along its length (in contrast to focal uptake in regions such as the carotid bifurcation, which are known to have a high atherosclerotic burden), or 3) cranial artery involvement (as these vessels are less likely to demonstrate the mild physiologic uptake that can be seen in the aorta and primary branches).

The 2 physician readers also reported the intensity of FDG uptake in 18 artery segments: the bilateral temporal, occipital, maxillary, vertebral, carotid, subclavian, and axillary arteries, the brachiocephalic artery, and the ascending, arch, and descending aorta. Vascular wall FDG uptake was compared to the background intensity of the blood pool in the superior vena cava (16).

The grading system for vascular tracer uptake was based on established definitions (17) as follows: 0 = no FDG uptake (less than or equal to the blood pool), 1 = minimal/equivocally increased uptake, 2 = moderate/clearly increased uptake, and 3 = very marked uptake. The FDG grading schema for the right superficial temporal artery are illustrated in Figure 1. These results were used for an exploratory analysis of the diagnostic accuracy of PET/CT, using a cutoff value of either grade 1 or grade 2 uptake in any vessel to define a GCA-positive scan. Comparison of vascular to liver FDG uptake was not performed because the scan field did not routinely include liver parenchyma.

Discordant results relating to each patient's global scan assessment and the maximum FDG uptake grade in any artery segment were resolved by a consensus reading by the 2 nuclear medicine physicians. A consensus FDG uptake grade was not determined for all artery segments.

Clinically guided unilateral TAB as the reference standard. Clinically guided unilateral TAB was the prespecified reference

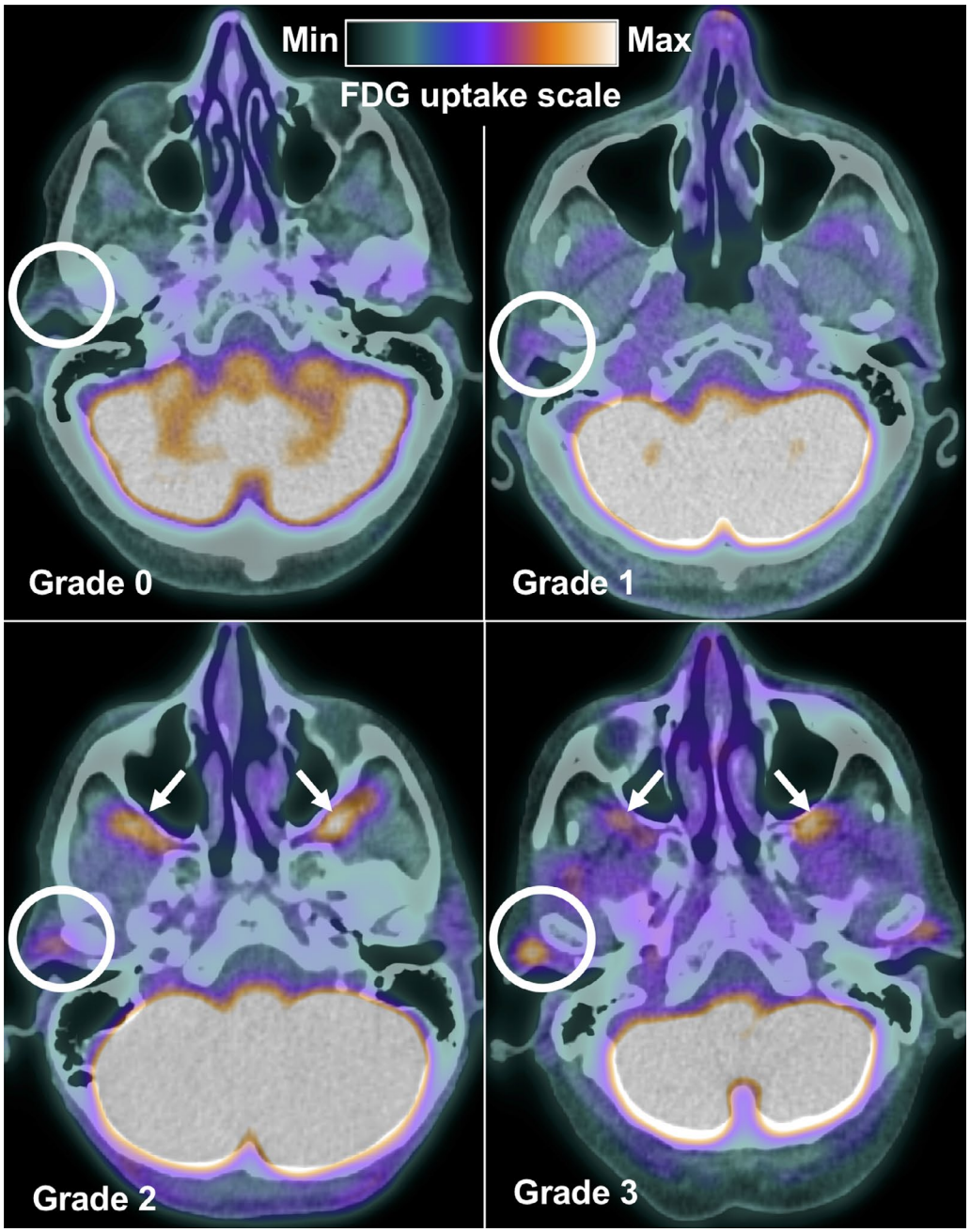


Figure 1. Axial head positron emission tomography/computed tomography scans illustrating the grading system for fluorine-18 fluoro-2-deoxyglucose (FDG) uptake in the right superficial temporal artery (marked by **circles**). **Arrows** point to FDG uptake in the maxillary arteries. Grade 0 = no uptake (less than or equal to the blood pool); grade 1 = minimal/equivocally increased uptake; grade 2 = moderate/clearly increased uptake; grade 3 = very marked uptake.

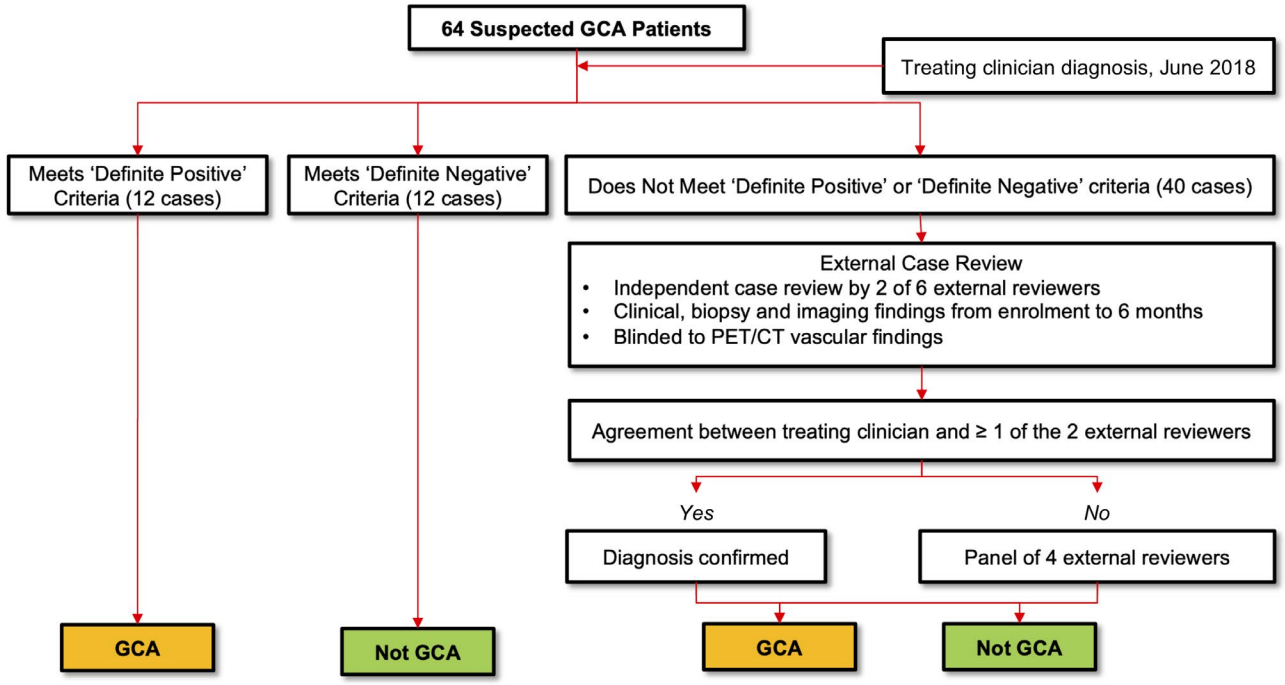
standard. In order to minimize the chance of missing skip lesions, we cut through each temporal artery specimen at 0.25-mm increments. One of 2 anatomic pathologists reviewed all sections for inflammation. The pathologists were blinded with regard to the PET/CT vascular findings but not to clinical details. In accordance with the majority of published literature, we defined a positive biopsy finding for GCA as having evidence of inflammation through one or more layers of the main artery wall (intima, media, and/or adventitia) (18). The presence of isolated vasa vasorum or periadventitial small vessel vasculitis (19) was noted but classified as a negative biopsy finding for GCA. A sequential contralateral biopsy was performed in a small number of patients at the discretion of the treating clinician.

Clinical diagnosis as the secondary reference test. Given that TAB has imperfect sensitivity for GCA, we also compared PET/CT to a secondary reference test, the 6-month clinical diagnosis. This time point was chosen to allow time for clinicians to judge the response to steroid weaning and to confirm relevant alternative diagnoses. The 2016 TABUL ultrasound study (The Role of Ultrasound compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis) also used this time point for confirmation of the final clinical diagnosis (5). Clinical follow-up data were prospectively obtained at 2 weeks and 3 and 6 months after diagnosis by means of a standardized phone survey, and by testing CRP and ESR levels. GCA disease flares were determined by the treating clinician.

Patients, treating clinicians, and reviewers were blinded with regard to the PET/CT vascular findings, to ensure that the clinical diagnosis was independent from the index test. They were, however, made aware of PET/CT detection of incidental findings, such as infection or cancer, to allow the timely confirmation and management of vasculitis mimics.

Patient diagnoses were confirmed according to the protocol shown in Figure 2. Treating clinicians were contacted in writing in June 2018 and asked if they thought their patient had GCA. They were also asked to choose the "most likely diagnosis for the clinical presentation leading to suspicion of GCA/temporal biopsy" from a prepopulated list of 28 options. Diagnosis by the treating clinician as well as the biopsy result and the level of glucocorticoid dosing at 3 months' follow-up were used to define "definite positive" or "definite negative" cases of GCA, in accordance with the criteria for a definite diagnosis (as listed in Figure 2).

Twenty-four patients were given a "definite positive" or "definite negative" diagnosis of GCA, and the remaining 40 underwent external case review. The reviewer panel comprised 5 rheumatologists and 1 neuro-ophthalmologist who were not involved in the patients' clinical care. Reviewers were provided a standardized set of data from enrollment to 6 months for each



Criteria for 'Definite' Diagnosis

Criteria	Definite Positive	Definite Negative
Biopsy	Mural inflammation	No inflammation
Treatment at 3 months	Taking corticosteroids	Not on treatment
Treating clinician diagnosis	GCA	Not GCA

Figure 2. Protocol to arrive at the clinical diagnosis (top), and criteria for a definite diagnosis of giant cell arteritis (GCA) (bottom). PET/CT = positron emission tomography/computed tomography.

patient. Enrollment data included details of symptoms, examination findings, glucocorticoid dosing, inflammation markers, results of vascular imaging when performed (not including PET/CT), biopsy results, incidental PET/CT findings, and ophthalmologic assessments. Follow-up data for the 2-week, 3-month, and 6-month time points included prednisone dose, use of steroid-sparing agents, active GCA symptoms, inflammation markers, details of GCA flares, and other objective clinical, imaging, histopathology, and serology findings that were available to the treating clinician, such as a histologically confirmed malignancy. The final diagnosis required consensus between the treating clinician and at least 1 of 2 reviewers. For the 8 patients for whom consensus was not reached, a panel of 4 rheumatologist reviewers decided on the diagnosis.

Statistical analysis. Data analysis was performed using IBM SPSS version 25. The 95% confidence intervals (95% CIs) were calculated using the exact Clopper-Pearson method. Patients who did not undergo TAB were excluded from the analysis comparing PET/CT to TAB but were included in the assessment comparing PET/CT to clinical diagnosis. Interobserver reliability was assessed using the kappa statistic.

The initial target sample size was 69 patients, calculated to achieve a 10% CI around the anticipated test sensitivity of 90% (20). This assumed a 50% rate of TAB-positive GCA. We expected our cohort to have a higher rate of TAB-positive GCA compared to recent cohorts of patients with "suspected GCA," given that we required the presence of 2 or more of the ACR 1990 classification criteria for GCA to be met for enrollment (1,17,21,22). After reaching 60 patients, we recalculated our required sample size as 170 based on our actual rate of TAB-positive GCA of 20%. This was beyond the resources of our study, and we closed enrollment at the end of 2017 with 64 patients enrolled.

RESULTS

In total, 96 patients were referred to the study from 13 sites in Sydney, Australia, of whom 64 met the inclusion criteria and underwent PET/CT. Of the 64 patients, 58 underwent TAB at a median of 4 days (range 0–21 days) after the PET/CT scan, and 95% of patients completed 6 months of follow-up. The distribution of the study participants is presented in Figure 3.

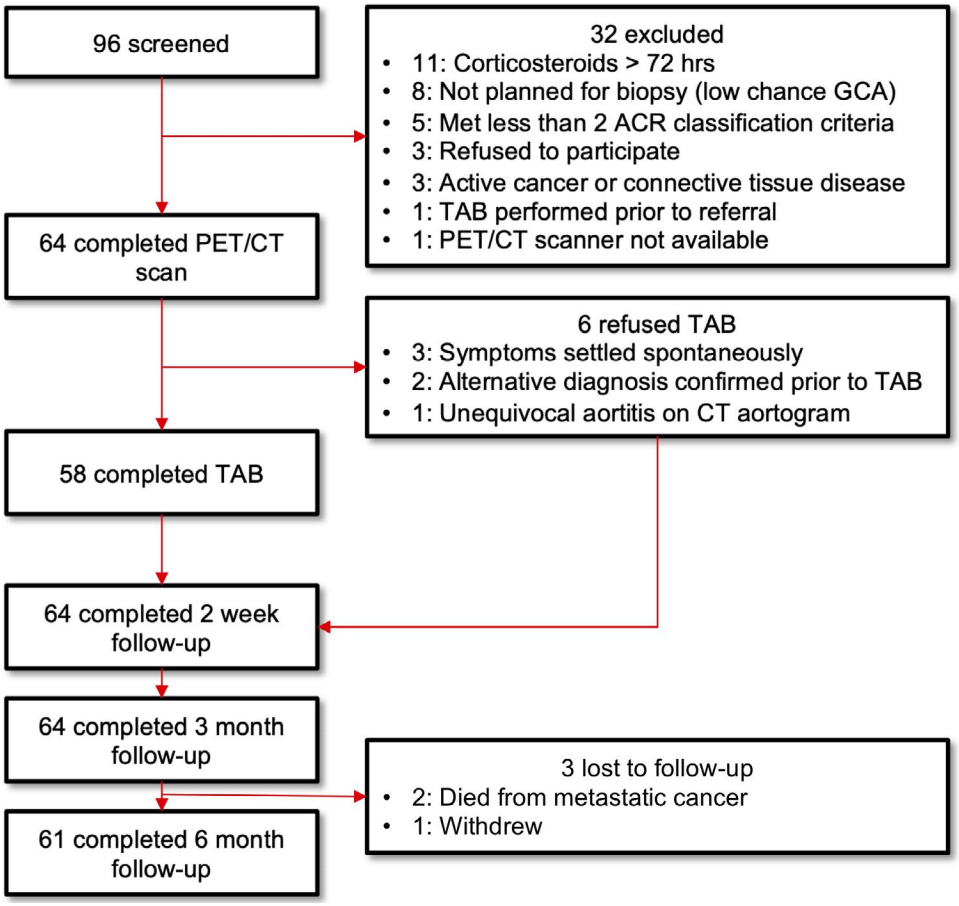


Figure 3. Flow chart showing the distribution of the study participants. GCA = giant cell arteritis; ACR = American College of Rheumatology; TAB = temporal artery biopsy; PET/CT = positron emission tomography/computed tomography.

Table 1. Baseline characteristics and temporal artery biopsy (TAB) results in the 64 enrolled study patients*

Age, median (range) years	69 (50–90)
Sex, female	45 (70)
Jaw claudication	18 (28)
Polymyalgia rheumatica	21 (33)
Headache	58 (91)
Vision disturbance	21 (33)
Temporal arteries, tender or reduced pulse	35 (55)
Occipital artery tenderness	12 (19)
CRP, median (range) mg/liter	21 (1–280)
ESR, median (range) mm/hour	41 (2–130)
Meeting the ACR criteria for GCA†	42 (66)
Undergoing TAB	58 (91)
Days between PET/CT and TAB, median (range)	4 (0–21)
TAB length, median (range) mm	19 (7–32)
Positive for GCA by TAB among those undergoing TAB	12 (21)
Negative for GCA by TAB among those undergoing TAB	46 (79)
No inflammation	35 (60)
Limited VV or periadventitial SVV	11 (19)

* Except where indicated otherwise, values are the number (%) of patients. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PET/CT = positron emission tomography/computed tomography; VV = vasa vasorum; SVV = small vessel vasculitis.
† The American College of Rheumatology (ACR) 1990 classification criteria for giant cell arteritis (GCA) (15).

The median age of enrolled patients was 69 years, and 70% were female. At enrollment, 91% of patients had headache, 33% had polymyalgia rheumatica (PMR) symptoms, 33% had vision disturbance, and 28% had jaw claudication. The median CRP level was 21 mg/liter (mean 46 mg/ liter), and the median ESR was 41 mm/hour (mean 48 mm/hour). In total, 56 patients had a clinically guided unilateral TAB, and 2 had sequential bilateral biopsies. The median length of the first biopsy was 19 mm.

In total, 12 (21%) of the 58 patients who underwent TAB had evidence of mural inflammation consistent with GCA. Of the 46 patients with a negative biopsy finding, 35 (60%) had no significant inflammation and 11 (19%) had limited vasa vasorum or periadventitial small vessel vasculitis. The baseline demographic and clinical characteristics of the patients and the TAB results are presented in Table 1.

Among the 64 enrolled patients, 21 (33%) had a clinical diagnosis of GCA, and 43 were diagnosed as having other conditions. In total, 42 patients (66%) met the ACR 1990 classification criteria for GCA, with the caveat that these are not diagnostic criteria (15). A list of the final clinical diagnoses for the 64 enrolled patients is presented in Table 2. Among the 5 patients who were ultimately diagnosed as having PMR, all 5 reported having headache and/or scalp tenderness at enrollment and 2 reported having transient visual disturbance. Their mean CRP level was 11 mg/liter and the mean ESR was 29 mm/hour. None of these patients had evidence of inflammatory change on unilateral TAB. Only 1 patient underwent dedicated large vessel vascular imaging (by ultrasound), the findings of which were negative for arteritis 2 weeks after commencement of glucocorticoids.

Levels of inflammation markers were highest in the biopsy-positive GCA cohort. The mean CRP level and ESR was 98 mg/liter and 72 mm/hour, respectively, in TAB-positive GCA patients (n = 12), 71 mg/liter and 62 mm/hour, respectively, in patients with clinically diagnosed GCA (n = 21), and 33 mg/liter and 41 mm/hour, respectively, in patients with alternative diagnoses (n = 43).

Among the enrolled patients, 11 of 12 with TAB-positive GCA were positive for GCA by PET/CT, and 39 of 46 patients with a negative TAB were negative for GCA by PET/CT. For a diagnosis of GCA, this indicated that the PET/CT protocol had a sensitivity of 92%, specificity of 85%, positive predictive value (PPV) of 61%, negative predictive value (NPV) of 98%, and area under the receiver operating

Table 2. Final clinical diagnosis accounting for the GCA presentation*

Clinical diagnosis	No. (%) of patients
GCA	21 (33)
Cervicogenic headache	9 (24)
PMR	5 (8)
Self-limited ophthalmologic disease, other	4 (6)
Infection, other	3 (5)
Malignancy	3 (5)
Pneumonia	3 (5)
Dental abscess	2 (3)
Headache, not otherwise specified	2 (3)
Herpes zoster	2 (3)
Inflammatory ocular disease (uveitis, scleritis)	2 (3)
Rheumatic disease†	2 (3)
Chronic ophthalmologic disease, other	1 (2)
Neurologic disease, other	1 (2)
Sinusitis	1 (2)
Stroke/TIA	1 (2)
Thyroiditis	1 (2)
Unknown	1 (2)

* GCA = giant cell arteritis; PMR = polymyalgia rheumatica; TIA = transient ischemic attack.
† Rheumatic disease was defined as rheumatoid arthritis, connective tissue disease, spondyloarthropathy, or sarcoidosis. No other definitions were provided to treating clinicians.

Table 3. Diagnostic performance of PET/CT compared to TAB and clinical diagnosis

	Reference test			
	TAB		Clinical diagnosis	
PET/CT index test	Positive for GCA	Negative for GCA	Positive for GCA	Negative for GCA
No. of patients				
Positive for GCA	11	7	15	4
Negative for GCA	1	39	6	39
Total assessed	12	46	21	43
Performance*				
Sensitivity	92 (62–100)		71 (48–89)	
Specificity	85 (71–94)		91 (78–97)	
PPV	61 (36–83)		79 (54–94)	
NPV	98 (87–100)		87 (73–95)	
AUC	0.88 (0.79–0.98)		0.81 (0.70–0.92)	

* Values for the performance of positron emission tomography/computed tomography (PET/CT), compared to temporal artery biopsy (TAB) and clinical diagnosis, in the diagnosis of giant cell arteritis (GCA), including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC), are the percentage (95% confidence interval).

characteristic curve (AUC) of 0.88. Three of the 7 TAB-negative, PET/CT-positive GCA patients had a clinical diagnosis of GCA. Two of these patients had convincing GCA disease flares when treatment was withdrawn, with recrudescence of headache and elevated inflammation markers. These symptoms as well as the exacerbation of inflammation markers resolved with the reintroduction of glucocorticoid treatment. The third patient had hypoechoic wall thickening in the bilateral temporal and left axillary arteries on ultrasound, suggestive of arteritis. Details of the 8 discordant TAB and PET/CT cases are presented in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40864/abstract). Patient-level data (with 95% CIs) assessing the diagnostic performance of PET/CT compared to both TAB and the 6-month clinical diagnosis are presented in Table 3.

The 2 readers disagreed on the PET/CT diagnosis for 9 patients on their initial scan review. These cases were subsequently co-read to arrive at the consensus diagnosis, with 6 of 9 scans being judged as positive for GCA. The clinical diagnoses of these 9 patients were as follows: biopsy-positive GCA (3 patients), biopsy-negative GCA (1 patient), PMR (1 patient), zoster ophthalmicus (1 patient), cervical osteomyelitis (1 patient), cervicogenic headache (1 patient), and headache not otherwise specified (1 patient). The diagnostic accuracy of the initial scan assessment was higher for reader 1 (EH) (sensitivity 83%, specificity 87%) than for reader 2 (GS) (sensitivity 75%, specificity 85%). Interobserver reliability was moderate ($\kappa = 0.65$).

Global PET/CT assessment provided higher overall diagnostic accuracy compared to use of an FDG uptake grade cutoff to define a positive scan. When grade 1 or higher FDG uptake in any vessel was used for the GCA-positive scan cutoff, the sensitivity was 100% and specificity was 46%. Interobserver reliability was poor ($\kappa = 0.19$). When grade 2 or higher FDG uptake in any vessel was used for the GCA-positive scan cutoff, the sensitivity was 83% and specificity 83%, and interobserver reliability was moderate ($\kappa = 0.65$).

The distribution of FDG vascular uptake differed between patients. Some patients had predominantly cranial involvement, while others had predominantly large vessel involvement. Both readers noted that 3 (25%) of 12 TAB-positive GCA patients had moderate FDG uptake limited to the head and neck (temporal, occipital, maxillary, and vertebral arteries), and 2 (17%) of 12 had moderate FDG uptake limited to the larger thoracic and/or carotid vessels. The distribution of vascular uptake by vascular territory for those with biopsy-positive GCA, those with clinically positive GCA, and those with alternative diagnoses is presented in Supplementary Table 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40864/abstract).

Six patients underwent a dedicated vascular ultrasound study for GCA within 1 week of PET/CT scan. For the 2 patients who had negative findings on ultrasound, 1 had a negative TAB finding and the other did not undergo biopsy. Both patients had negative findings for GCA on their PET/CT scans, and both were given a final clinical diagnosis of cervicogenic headache. Four patients had positive findings of GCA on ultrasound, with hypoechoic temporal artery wall thickening. All 4 had globally positive findings on their PET/CT scans and had grade 1 or higher FDG uptake in at least one temporal artery. Three of the 4 patients were positive for GCA on biopsy, and 1 had a negative biopsy finding (limited periadventitial small vessel vasculitis). All 4 of these patients had a final clinical diagnosis of GCA.

In addition to the vascular findings, 13 (20%) of 64 patients had a clinically relevant incidental finding on PET/CT. This included 7 patients with an acute infection (3 cases of pneumonia, 3 cases of sinusitis, and 1 case of cervical osteomyelitis), 5 with a malignancy (4 with lung cancer and 1 with thyroid cancer), and 1 with subacute thyroiditis. None of these patients had a positive biopsy finding for GCA, while 1 of the 13 patients had a clinical diagnosis of GCA in addition to acute sinusitis that was detected on the PET/CT scan.

Moderate or marked FDG uptake was detected by at least one reader in the aorta of 11 (17%) of 64 patients. Eight of these patients had a clinical diagnosis of GCA and 5 had a positive TAB finding of GCA. The remaining 3 patients had other clinical diagnoses, including PMR (n = 1), zoster ophthalmicus (n = 1), and metastatic lung cancer (n = 1).

There were no reported adverse events from either the TAB or PET/CT scan. The mean ionizing radiation exposure for the PET/CT scan was 3.4 mSv (range 2.8–4.6 mSv).

DISCUSSION

This is the first study to assess the diagnostic accuracy of time-of-flight PET/CT scan of the head, neck, and chest in patients having newly suspected GCA. The technique had high diagnostic accuracy against both TAB (sensitivity 92%, specificity 85%) and the 6-month clinical diagnosis (sensitivity 71%, specificity 91%). The NPV of PET/CT compared to TAB was particularly high, at 98%.

In contrast to previous PET/CT studies, which have generally included preselected patients with positive findings of GCA on TAB or with suspected large vessel disease (7,17), we included a real-world, heterogenous cohort of consecutive patients who required confirmation of GCA or an alternative diagnosis. The positive biopsy rate of 21% and modest baseline elevations in the CRP level and ESR are in keeping with the data from contemporary cohorts in Canada and the UK (5,18).

Our study is also unique in that it utilized a time-of-flight scanner with 1-mm CT reconstruction. This allowed more detailed assessment of the smaller temporal, maxillary, occipital, and vertebral arteries, which are known to be involved in GCA but have previously been considered beyond the resolution of PET/CT. We prespecified a 72-hour window from the commencement of glucocorticoids to PET/CT. Given the imperative to commence therapy immediately in high-risk patients (23), this provided a clinically practical window to arrange a scan while minimizing the diagnostic impact of glucocorticoid-related attenuation of FDG vessel wall uptake (11).

While TAB remains the traditional gold standard test for GCA, there has been a trend toward the use of imaging to support the diagnosis. In 2018, a European League Against Rheumatism group released recommendations on imaging in large vessel vasculitis (24). Ultrasound and high-resolution scalp magnetic resonance imaging (MRI) were listed as suitable first-line tests to confirm a diagnosis of GCA. PET was recommended for evaluating large vessel extracranial arteritis but not for the assessment of cranial arteries or for use as a general first-line imaging modality. Our study challenges this view. The diagnostic performance of PET/CT of the head, neck, and chest compares well with recent large, high-resolution scalp MRI and ultrasound studies. Our protocol, when compared against TAB, performed similarly to that shown in a 2016 study of high-resolution scalp MRI (18) for the diagnosis of GCA (MRI versus TAB, sensitivity 94%, specificity 78%). The performance of our PET/CT protocol (relative to both TAB and clinical diagnosis) was superior to that in the TABUL ultrasound study (5) (ultrasound versus TAB, sensitivity 73%, specificity 69%); ultrasound versus clinical diagnosis, sensitivity 54%, specificity 81%). It is important to note that the TABUL study had a lower diagnostic accuracy than many other ultrasound studies in GCA (25,26). While only 6 of our patients underwent dedicated cranial ultrasound as part of their diagnostic workup, all cases had diagnostic agreement between the ultrasound and PET/CT scan.

This study also clarifies how best to report PET/CT scans in GCA. We found that the global scan assessment by a PET-experienced nuclear medicine physician provided better accuracy than using a predefined vascular FDG uptake grade cutoff. In part, this may be a reflection of the ability of readers to vary the diagnostic weight of FDG uptake by location, taking into consideration the particular vessels involved, the diffuse versus localized nature of vascular uptake, and the potential for inflammatory atheroma at particular vascular sites such as the carotid bifurcation.

PET/CT had utility in diagnosing vasculitis mimics. In this study, a clinically relevant incidental finding was present in 1 in 5 patients. One patient with cervical osteomyelitis may have had a serious adverse outcome if he had been treated with high-dose glucocorticoids while awaiting TAB.

Aortitis was a common finding in our biopsy-positive GCA cohort. Moderate or marked aortic wall FDG uptake was detected in 5 (42%) of 12 TAB-positive GCA patients. It was also detected in a further 3 patients with a clinical diagnosis of GCA. These patients may be at higher risk of developing aneurysms, with implications for the duration and frequency of aortic surveillance (27).

Despite the promising diagnostic performance and ability to detect mimicking conditions, PET/CT does have shortcomings, including its cost and availability. PET/CT is generally considered to be more expensive than ultrasound or MRI. The low-dose, 100-MBq FDG head, neck, and chest protocol used in this study was less costly than a standard full-body, 250–300-MBq PET/CT scan.

Our study has a number of limitations. First, due to the fact that the percentage of TAB-positive GCA cases was lower than predicted, the 95% CI around the sensitivity was wider than our desired CI of 10%. Second, our primary PET/CT reporting

measure, the global assessment for GCA, is subjective. Although we have specified some general principles that our physician readers used to increase their confidence in reporting a scan as being positive for GCA, accuracy ultimately requires the readers to be experienced in interpreting vessel wall changes on PET/CT. This includes an awareness that a high atheroma burden can result in increased FDG uptake and mimic arteritis (28). Diagnostic accuracy was higher with the final consensus diagnosis compared to that achieved by either of the 2 independent readers. This suggests the need for careful assessment of all artery segments and the potential benefit of dual reporting of equivocal scans. The moderate interobserver reliability ($\kappa = 0.65$) in our study is similar to that described in the TABUL study (5) for ultrasound and TAB reporting (intraclass correlation coefficient 0.61 and 0.62, respectively) and to that of superficial cranial MRI ($\kappa = 0.68$) (29).

Moving forward, we will consider testing a number of technical modifications that may improve scan resolution. These include increasing the dose of FDG to 150 mSv and delaying the scan to 90 minutes after FDG injection. A longer delay between injection and scan may reduce background blood pool FDG activity and potentially allow better determination between vessel wall and blood pool uptake.

In summary, time-of flight PET/CT scan of the head, neck, and chest with 1-mm CT reconstruction had high diagnostic accuracy compared to TAB for the diagnosis of GCA. The results compare well with recent ultrasound and MRI studies. This study would support a first-line role for PET/CT in the assessment of patients newly suspected of having GCA. The high NPV indicates particular value in excluding the diagnosis in lower risk patients. Given the significant morbidity associated with a misdiagnosis, we believe that TAB remains indicated when the scan is inconclusive or discordant with the pretest probability of GCA. PET/CT had additional benefits over TAB, including detection of clinically relevant incidental findings in 20% of patients, and identification of aortitis in more than 40% of biopsy-positive GCA patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sammel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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