FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: Joint procedural recommendation of the EANM, SNMMI, the PET Interest Group (PIG), and endorsed by the ASNC

Writing group*:

Riemer H.J.A. Slart[a,d], Andor W.J.M. Glaudemans[b,d], Panithaya Chareonthaitawee[c,e], Giorgio Treglia[b,d], Florent L. Besson[d], Thorsten A. Bley[d], Daniel Blockmans[d], Ronald Boellaard[d], Jan Bucerius[a], José Manuel Carril[d], Wengen Chen[c], Maria C Cid[d], Bhaskar Dagupta[d], Sharmila Dorbala[c,e] , Olivier Gheysens[b,d], Fabien Hyafil[a,d], Shaifali Jain[d] , Thorsten Klink[d], Conny J. van der Laken[d], Francisco Lomeña[d], Michela Massollo[d], Sergio Prieto-González[d], Raashid Luqmani[d], Anna Roivainen[d], Carlo Salvarani[d], Antti Saraste[d], Michael Schirmer[d], Hein J. Verberne[a], Annibale Versari[b,d], Alexandre E. Voskuyl[d], Martin A. Walter[d], Dario Camellino[d], Elisabeth Brouwer[d], Marco A. Cimmino[d]

Reviewer group*:

Aiden Abidove[e], Denis Agostini[a], Rob S. Beanlands[e], Roberto C. Delgado-Bolton[f], Andrew J.Einstein[e], Alessia Gimelli[a], Edward J. Miller[e], Roberto Sciagrà[a], Alberto Signore[b]

*Members of EANM Cardiovascular[a], EANM Infection & Inflammation[b] Committees, SNMMI Cardiovascular[c] Council, PET Interest Group[d], and ASNC[e], EANM Committee Coordinator[f].

Address for correspondence:
Riemer H.J.A. Slart, MD, PhD
Medical Imaging Center, Department of Nuclear Medicine & Molecular Imaging
University of Groningen, University Medical Center Groningen,
Hanzeplein 1, P.O. Box 30001
9700 RB Groningen, The Netherlands
Telephone: +31-50-3613541
Fax: +31-50-3611687
Email: r.h.j.a.slart@umcg.nl

Abstract

Large vessel vasculitis (LVV) is defined as a disease affecting mainly large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA). GCA often coexists together with PMR in the same patient, since both belong to the same disease spectrum. FDG-PET/CT is a functional imaging technique, which is an established tool in oncology, and has also demonstrated to have a role in the field of inflammatory diseases. Functional FDG-PET combined with anatomical CT angiography, FDG-PET/CT(A), may be of synergistic value for optimal diagnosis, disease activity monitoring, and evaluation of damage development of LVV. There are currently no guidelines regarding PET imaging acquisition for LVV and PMR, even though standardization is of utmost importance to facilitate clinical studies and for daily clinical practice.

This is a joint procedural recommendation on FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica from the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the PET Interest Group (PIG), and endorsed by the American Society of Nuclear Cardiology (ASNC)

The aim of this joint paper is to provide recommendations and statements, based on the available evidence in the literature and consensus of experts in the field, for patient preparation, FDG-PET/CT(A) acquisition and interpretation for the diagnosis and follow up of patients with suspected or diagnosed LVV and/or PMR. This position paper aims to set an internationally accepted standard for FDG-PET/CT(A) imaging and reporting of LVV and PMR.

Key words: large vessel vasculitis; polymyalgia rheumatica; FDG PET/CT(A); imaging procedure.

Preamble

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine.

The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question. The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine includes both the art and the science of the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make

it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

This joint procedural recommendation paper on 2-[18F]-Fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT) or PET/CT(A) (with angiography) imaging in large vessel vasculitis (LVV) and polymyalgia rheumatica (PMR) has been developed under the auspices of the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the PET Interest Group (PIG). The purpose of this procedural recommendation paper is to assist imaging specialists and clinicians in recommending, performing and interpreting the results of FDG-PET in patients with suspected LVV and PMR. Furthermore, this paper highlights the importance of standardization and optimal procedural performance of FDG-PET/CT(A) imaging in LVV and PMR, and emphasizes the importance of bridging imaging specialists and clinicians working in this field.

INTRODUCTION

Large vessel vasculitis (LVV) is defined as a disease affecting mainly large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA) [1]. Vasculitis can be distributed locally in the branches of the internal and external carotid artery or the aorta and its main branches more central in the thorax. TA and GCA are different diseases with different onset age, ethnic distribution, immunogenic background [2], distribution and therapy response [3,4] of the affected arteries. GCA and TA also show some overlap, regarding histopathology of arterial lesions reflecting shared pathways in tissue inflammation[5,6]. Clinically GCA and polymyalgia rheumatica (PMR) belong to a disease spectrum, and both often coexist in the same patient. Nearly half of the patients with GCA have evidence of PMR, while approximately 20% of patients with PMR have concomitant GCA [7,8], however the frequency of GCA in PMR (either by biopsy or imaging) may vary, depending on the selection criteria applied to the cohorts.

FDG-PET/CT is a functional imaging technique, which is an established tool in oncology, and has also demonstrated to have a role in the field of inflammatory diseases. FDG-PET is based on the ability to detect enhanced glucose uptake, from high glycolytic activity of inflammatory cells, in inflamed arterial walls and synovia/bursa [9]. Thereby, it can identify the presence of systemic LVV in patients with GCA and TA, while it can also show inflammation of peri-articular and extra-articular synovial structures in case of PMR. Approximately 20% of patients with apparently isolated PMR show LVV on FDG-PET/CT [10], which percentage can even be higher, depending on the presence of LVV symptoms [11-13]. It is important to realize that a negative temporal artery biopsy, an ultrasonography without a halo sign, or a magnetic resonance imaging (MRI) without aortic wall thickening or edema does not definitively exclude the presence of LVV and should therefore not limit the use of FDG-PET/CT when LVV is clinically suspected [14,15]. Furthermore, there is substantial variation in the type of vessels involved (i.e. aortic and cranial large vessels) [16], which can be detected by FDG-PET given its whole body scan nature, with exception of the temporal artery, due to the high physiological FDG uptake in the brain and limited resolution of the camera system. In addition, FDG-PET may assist in the differential diagnosis between PMR and elderly onset rheumatoid arthritis (EORA) or -spondyloarthritis [8], according to the location of inflammation (articular, capsular or extracapsular). In patients with fever of unknown origin when the diagnosis of systemic LVV is ruled out, PET/CT results allow to identify other causes of the inflammatory process, including oncological diseases, in the majority of cases. Functional FDG-PET combined with anatomical CT angiography, FDG-PET/CT(A), may be of synergistic value for optimal diagnosis, disease activity monitoring, and evaluation of damage development of LVV [17]. The main limitation of FDG-PET/CT(A) to become a standardized diagnostic tool is the lack of an internationally accepted definition of vascular inflammation and/or PMR, based on the intensity and pattern of the glucose analogue uptake. Also, FDG-PET/CT is not disease specific and is primarily developed to diagnose malignant and infectious diseases. Results have to be interpreted with caution as inflammatory/metabolic changes in the arterial wall usually precede anatomic changes [18-23]. Furthermore, whereas increased FDG uptake is mainly seen in active disease processes, information of advanced stages, for example calcification in chronic or past inflammation, is mainly provided by morphological imaging [24]. Atherosclerosis activity may also interfere with the FDG-PET signal in patients with LVV [25]. Finally, the instigating inflammatory

process may have subsided, leaving residual arterial stenosis or aortic aneurysms for which FDG-PET is not the best imaging option.

In nuclear medicine, procedural guidelines for FDG-PET have been published for both cancer [26] and infection/inflammation imaging [27]. However, LVV and PMR are distinct disease entities, which need a specific technical approach. The interpretation of FDG-PET images for LVV can be challenging, and currently there is no consensus on how to interpret the images in the setting of LVV. Furthermore, as previously published, FDG uptake has been demonstrated to respond to glucocorticoid therapy, which reduces metabolic cell activity. In this setting aortic/arterial wall thickening (visible on CT or MRI) is still present due to a delayed morphologic vascular response [28].

There are currently no guidelines regarding PET imaging acquisition for LVV and PMR, even though standardization is of utmost importance to facilitate clinical studies and for daily clinical practice.

The aim of this joint paper is to provide recommendations and statements, based on the available evidence in the literature and consensus of experts in the field, for patient preparation, FDG-PET/CT(A) acquisition and interpretation for the diagnosis and follow up of patients with suspected or diagnosed LVV and/or PMR. This position paper aims to set an internationally accepted standard for FDG-PET/CT(A) imaging and reporting of LVV and PMR. An additional aim is to facilitate prospective clinical studies and pooling of future multi-center data. Other imaging modalities applied in LVV diagnostics such as MRI angiography and ultrasound are beyond the scope of this document.

FDG-PET/CT(A) PROCEDURES IN LVV & PMR

Patient Preparation and Image Acquisition of FDG PET/CT (A)

Patient preparation

The main goal of adequate patient preparation is to reduce physiologic tracer uptake in normal tissues (myocardium, skeletal muscle, urinary tract and brown adipose tissue) while maintaining uptake in diseased tissues and organs. Patients are instructed to fast for at least 6 hours prior to FDG administration although intake of non-caloric beverages is allowed during that period [27]. In addition, strenuous physical activities should be avoided within 24 hours

before FDG administration. At the moment and after administration of FDG, patients should relax in an adequately temperature-controlled room (20-22°C (68-71.6 °F)) to minimize physiologic uptake in muscles and brown fat [29]. In some cases, FDG uptake in brown fat can be reduced by beta-blocking drugs, e.g. oral administration 20 mg propranolol one hour before FDG injection [30]. Prior to positioning on the table, patients are asked to void urine. Patients with fever of unknown origin (FUO), and suspicion of cardiac involvement (e.g. endocarditis, sarcoidosis) need to be prepared with a special diet, to reduce physiological myocardial uptake of FDG. Patient preparation for cardiac FDG-PET imaging is based on increasing the provision of fatty acids to the heart and decreasing physiological uptake of glucose by the myocardium. The SNMMI/ASNC/SCCT guidelines and SNMMI/ASNC consensus document recommend preparation with a fat-enriched diet lacking carbohydrates for 12-24 hours prior to the scan, a 12-18 hour fast, and/or the use of intravenous unfractionated heparin approximately 15 min prior to FDG injection [31,32].

Serum glucose levels before FDG administration

For oncological imaging, studies have shown that FDG uptake is reduced if serum glucose levels exceed 11 mmol/L (200 mg/dL) [26,33,34], thereby rapidly and efficiently shunting FDG to organs with a high density of insulin receptors (e.g., skeletal and cardiac muscles), resulting in altered FDG biodistribution and suboptimal image quality [35].

The impact of glucose levels on FDG uptake in inflammatory lesions is less well investigated. A study by Rabkin et al., in 123 patients with suspected infection demonstrated that hyperglycemia at the time of study did not have any significant impact on the false negative rate [33]. However, a prospective study in 195 patients evaluating the impact of fasting glucose levels on arterial uptake showed a negative correlation between uptake in the arterial wall and pre-scan glucose levels as well as increased blood pool activity with increased glucose levels [36]. In general, efforts should be made to decrease blood glucose levels to the lowest possible level, but glucose levels below 11 mmol/L (200 mg/dL) are acceptable.

Glucocorticoids & FDG administration

Glucocorticoids (GC) may reduce vascular wall uptake of FDG: scarce data is available yet on the effect of GC withdrawal on FDG uptake. Nielsen et al., confirmed recently that the diagnostic accuracy of LVV with FDG-PET remains till 3 days after initiation of GC, thereafter

the signal decreases significantly [37-39]. So there may be a diagnostic window of opportunity within 3 days of initiation of GC.

A brief withdrawal of GC could "restore" pathological FDG uptake and reduce the likelihood of a false negative result, but this is not known. At the same time, GC withdrawal may pose risks to the patient. In case of GCA, especially if temporal artery or ocular involvement is suspected, administration of GC cannot be delayed or withdrawn due to possible ischemic complications. In other conditions, such as PMR or Takayasu arteritis, withdrawing or delaying therapy until after PET can be accepted, unless there is risk of ischemic complications (Table 1).

The use of GC may also increase the FDG uptake in the liver, resulting in underestimation and/or underscoring of vascular FDG uptake [40].

Acquisition time after FDG administration

A minimum interval of 60 minutes between intravenous FDG administration and acquisition has been recommended for adequate tracer biodistribution [27]. Delayed acquisitions increase the vascular to blood pool ratio, hence increase contrast resolution [36], and could make the measured vascular uptake more accurate [41]. However, as the majority of LVV studies were performed at 60 minutes, PET positive criteria at delayed time points have not been evaluated yet in this setting and may slightly differ from those defined at the standard time interval. In contrast to FDG-PET studies evaluating metabolic activity of atherosclerotic lesions, studies are scarce that have compared early (1 hour) versus delayed (3 hours) imaging in LVV [42]. A small prospective study in 23 patients with suspicion of LVV concluded that delayed imaging at 3 hours yielded a more detailed image of the arterial wall mainly due to decreased blood pool activity [43]. The recently published EANM position paper on the use of FDG-PET in atherosclerosis recommends a two-hour time interval between FDG administration and acquisition [44]. Currently, there is not enough evidence to apply the same time window for LVV. At the present time, we recommend an uptake interval of at least 60 minutes. It is essential to standardize the time interval especially when using semi-quantitative analyses and when comparing FDG uptake on follow up studies and between institutes.

Patient positioning and acquisition parameters

There are currently no guidelines for image acquisition in LVV or PMR, but whole-body acquisition from head to knee (optional including the feet) in the supine position with the arms next to the body is recommended, because (PMR) patients are in general not able to hold their arms above their head. For FDG-PET/CT imaging, a low-dose non-contrast CT must be performed for attenuation correction and anatomical localization. Alternatively, a diagnostic contrast-enhanced CT may be performed according to applicable local or national protocols and guidelines. A contrast-enhanced CTA is useful for identifying stenotic lesions in TA, but data are insufficient to support its routine use for GCA LVV [45]. When using a contrast-enhanced CTA, a low-dose CT scan should be performed prior to intravenous contrast injection for attenuation correction and subsequent standardized uptake value (SUV) calculations. The impact of intravenous contrast agents on the accuracy of attenuation correction is only considered acceptable when CT data are collected in the equilibrium or venous phase (i.e. delayed acquisition), with the advantage of radiation dose reduction [26]. Detection of smaller vascular structures in the head and neck region can be improved by increasing the acquisition time (~ doubled) per bed position to improve image quality, and applying larger image matrices (thus smaller voxels) [46]. This will reduce the partial volume effect of smaller structures provided appropriate high resolution image reconstruction settings are chosen, e.g. minimal image filtering during reconstruction and appropriate number of iterations/subsets to assure sufficient convergence and/or contrast recovery by the iterative reconstruction process.

Consensus recommendations (see supplement 1)

- Recommend fasting the patient for at least 6 hours prior to FDG administration although intake of non-caloric beverages is allowed during that period (evidence level II, grade B).
- Normal blood glucose levels are desirable, but glucose levels below 11 mmol/L (200 mg/dL) are acceptable (evidence level II, grade B).
- Withdraw or delay GC therapy until after PET, unless there is risk of ischemic complications, as in the case of GCA with temporal artery involvement. FDG/PET within three days after start of GC is optional as a possible alternative (evidence level III, grade B).
- A minimum interval of 60 minutes is recommended between FDG administration and acquisition for adequate biodistribution (evidence level III, grade B).

Interpretation criteria

Several factors may significantly influence the arterial wall FDG uptake, and must be taken into consideration for interpretation of FDG-PET in LVV and PMR. For clinical routine,

interpretation criteria must be uniform, reproducible, and easy to use. Many PET interpretation criteria have been proposed (Table 2), and evidence from the last 15 years supports the use of a visual grading scale (vascular to liver uptake) (Figure 1). We propose the use of a standardized 0-to-3 grading system as follow: 0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver), with grade 2 possibly indicative and 3 surely being considered positive for active LVV (Table 3) [25,47]. A total vascular score (TVS) can be determined, for instance, at 7 different vascular regions (thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries, and femoral arteries) as negative (0) or positive, further scored semi-quantitatively as 1 (minimal but not negligible FDG uptake), 2 (clearly increased FDG uptake), or 3 (very marked FDG uptake). Therefore, a TVS could be calculated, ranging from 0 (no vascular FDG uptake in any of the 7 vascular regions) to 21 (vascular FDG uptake scored 3 in all 7 territories).

As PMR and GCA frequently overlap, typical FDG joint uptake patterns should be reported, including uptake in glenohumeral synovia, subacromio-subdeltoid bursa, supraspinatus tendinitis and biceps synovitis (shoulder), trochanteric/ischiatic bursa, hip synovia, interspinous regions of the cervical and lumbar vertebrae or the synovial tissue of the knees if present, including the use of a standardized 0-to-3 grading system [48,49] (Figure 2).

Atherosclerotic vascular uptake [50,51], frequent with aging, may be a source of false positivity for LVV evaluation, despite a classical “patchy” uptake pattern. Uptake in ilio-femoral arteries should be interpreted with caution, because this is a frequent site of atherosclerosis. Taking these considerations into account, vascular inflammation in LVV on FDG-PET classically appears as a smooth linear pattern, involving the aorta and its main branches (subclavian, carotid or vertebral arteries, pulmonary arteries specifically in TA), but not all main branches have to be involved.

Quantification issues requiring further clarification

Several semi-quantitative methods have also been proposed, from simple SUV metrics to target to background ratios (TBR) (Table 2). The clinical utility of SUV or TBR for initial diagnosis of LVV or PMR is currently unknown, and their use is not recommended. However, their relevance for recurrence or follow-up evaluation may be of interest. Simple SUV metrics do not appear relevant in initial diagnosis, due to the high overlap between patients and controls

[52] and the potential loss of specificity [53]. TBR methods using lung [12], liver [54] or blood pool [52,55] as a reference have been proposed, mainly in GCA studies. Recently, a target-to-blood pool method was successfully applied in LVV, was highly reproducible in atheroma [56], and is currently recommended by the cardiovascular committee of the EANM for the assessment of vascular wall inflammation in this setting [44]. Based on the few promising results in LVV [40,52], we encourage the use of this target-to-blood pool method in LVV for research studies. It is recommended to use TBR instead of SUV as the use of a ratio between two measurements limits the effects on signal quantification of errors in patient weight, injected radiotracer dose, and imaging time-point [44].

The normalization of the arterial wall uptake to the background activity of venous blood pool provides a good reference to assess vascular inflammation [40]. Also, grading of arterial inflammation against the liver background is an established method [25,40].

Regions of interests (ROIs) are drawn around the majority of the target arterial structure, while the chance of including surrounding FDG uptake within the ROI needs to be minimized [40]. For background quantification, the ROI is projected on the right lobe of the liver to reduce the chance of including the various veins and arteries running through the liver. For blood pool, a ROI is drawn central in the blood pool of the (inferior or superior) caval vein.

TBR varies as a function of blood-pool activity. Blood-pool activity can be affected by many factors including: (a) FDG uptake in circulating blood cells, (b) chronic renal insufficiency, and (c) blood glucose levels [79,80]. A study of Lensen et al, in patients with atherosclerosis showed that results are affected by several data acquisition parameters, i.e. FDG uptake time and SUV normalization [81]. Although the individual factors may not have a large impact by themselves, the cumulative effects of these factors may result in substantial differences in reported SUV's throughout studies and within multi-center trials. Repeated PET/CT examinations should be performed using the same protocol as compared with the previous studies. Semiquantitative analysis should be done in the same way as well (in order to compare PET/CT results). For treatment response evaluation it is important to have basic (prior to therapy) PET/CT results, as the detection of even slight FDG uptake in the region of initial lesion should be considered as residual inflammatory process.

Consensus recommendations

- We propose the use of a standardized grading system: 0 = no uptake (≤ mediastinum); 1 = low-grade uptake (< liver); 2 = intermediate-grade uptake (= liver), 3 = high-grade uptake (> liver), with grade 2 considered possible positive, and 3 being positive for active LVV (evidence level II, grade B).
- Typical FDG joint uptake patterns including scapular and pelvic girdles,

Diagnostic accuracy of FDG-PET/CT(A) for LVV and PMR

The diagnostic performance of FDG-PET for the detection of LVV is overall good; individual studies are summarized in Table 4, and meta-analyses are summarized in Table 5. A recent meta-analysis of eight studies including 170 LVV patients with GCA or TA and 230 controls confirmed that FDG-PET offers good diagnostic performance for the identification of LVV [82]. The diagnostic performance of FDG-PET was higher for the detection of GCA than TA (87% vs. 58%, respectively; $p < 0.0001$) [47,82], but impaired in patients under glucocorticoids and/or immunosuppressive treatment at the time of imaging [47]. Of note, patients with TA are more frequently long-term treated at the time of imaging than patients with GCA. For the diagnosis of patients with GCA, FDG-PET demonstrated high pooled sensitivity (90%) and specificity (98%) without significant heterogeneity in a meta-analysis of 4 pooled studies including 57 patients with giant cell arteritis and 176 controls [47]. These findings are in line with a previous meta-analysis including GCA patients evaluated by FDG-PET, showing pooled sensitivity and specificity of 80% and 89%, respectively [83]. In TA, FDG-PET demonstrated a pooled sensitivity of 87% and specificity of 73% for the assessment of disease activity in a recent meta-analysis pooling 7 studies, including 191 patients with TA with significant heterogeneity [47]. These findings are in line with a previous meta-analysis including TA patients evaluated by FDG-PET, showing pooled sensitivity and specificity of 70% and 77%, respectively [84]. The specificity of FDG-PET increased up to 84% when considering studies using National Institutes of Health (NIH) criteria [85] as the disease activity assessment scale [47]. Visual analysis showed that high FDG uptake was well correlated with the presence of markers of disease

activity in TA, but vascular uptake could be observed in up to 67% of TA patients without markers of activity [47].

The precise evaluation of diagnostic accuracy of FDG-PET for the diagnosis of LVV faces several hurdles. First, in some patients FDG-PET represents the only modality that allows for the diagnosis of LVV and can therefore not be compared to a gold standard. For GCA, the diagnosis is usually classified according to the American Collage of Rheumatology (ACR) criteria [86] that include cranial symptoms, the presence of elevated erythrocyte sedimentation rate (ESR) and a positive superficial temporal artery biopsy (TAB). Arterial wall inflammation in GCA is, however, characterized by a segmental distribution, and can be absent in the excised segment of the superficial temporal artery. The presence of aortitis in patients with PMR is even more difficult to confirm as FDG uptake is most often the only modality that allows for the detection of inflammatory activity in large vessels. The diagnosis of TA is usually based on the NIH score [85] that integrates clinical, biological and radiological criteria. Several studies have, however, found that there might be discrepancies between the activity of TA evaluated with the NIH score and the results of FDG-PET imaging [47]. This raises the question of whether FDG-PET is more sensitive than the NIH score to detect and assess TA or if this vascular signal has no relation with active progressive disease. Secondly, patients with suspected GCA often immediately receive high-dose glucocorticoids before imaging, which has an impact on the intensity of arterial FDG uptake subsequently measured with PET. The accuracy of FDG-PET can therefore vary in relation to the delay between the initiation of glucocorticotherapy and imaging. Thirdly, the accuracy of a diagnostic test is influenced by the criteria used to define the presence of the disease. To date, no definite consensus criteria exist to define the presence of vascular inflammation with FDG-PET in LVV and/or PMR. In summary, based on the available evidence, FDG-PET imaging has high diagnostic value for the detection of LVV or PMR. Future studies are needed to select the most clinically-relevant and reproducible criteria for defining the presence of LVV with FDG-PET, as well as test the clinical impact of FDG-PET imaging on the management of patients with suspected LVV.

Consensus statement

- Based on the available evidence, FDG-PET imaging has high diagnostic performance for the detection of LVV and PMR (evidence level II, grade B).
- Further studies are needed to select the most clinically-relevant and reproducible criteria for defining the presence of LVV with FDG-PET, as well as test the clinical impact of FDG-PET imaging on the management of patients with suspected LVV.

CT Angiography in LVV and PMR

Image acquisition

Little data has been published concerning the additional value of CTA for the diagnosis of LVV. Such evaluation could be of interest by providing morphological information on the vasculature in a "one stop shop" procedure when using hybrid PET/CTA imaging (Figure 3). In acute disease stages, CTA can focus on the vascular lumen for both detection and characterization of stenosis and for assessing acute complications of a critical stenosis. In chronic disease stages, CTA is an alternative to MRI for detecting late complications such as aneurysm formation and is helpful in planning percutaneous and surgical treatment. However, given the currently limited evidence supporting the use of contrast enhanced PET/CT in LVV, further studies are mandatory to assess its potential incremental value.

CTA scanning parameters should be adapted to the specific capabilities of the local scanner specifications. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC) has produced guidelines for CTA in the diagnosis of aortic disease in adults in 2014 [91]. The American College of Radiology (ACR), the North American Society for Cardiovascular Imaging (NASCI), the Society of Interventional Radiology (SIR), and the Society for Pediatric Radiology (SPR) have jointly revised their guidelines for performing body CTA in 2016 [92]. These guidelines provide general information regarding CTA scanning and image post-processing, as specific scanning parameters and image reconstruction settings differ substantially among CT vendors and machines.

Generally, these guidelines recommend, if available, the use of a multi-detector-row CT (MSCT) scanner with wide z-axis or volume coverage. The scans should be performed with ECG-triggering to avoid motion or pulsation artifacts of the ascending aorta [93].

Contrast material is administered through a venous catheter using an automated contrast material injector. The contrast material dose depends on the body weight, body mass index and the kidney function (recent estimated glomerular filtration rate) of the patients [26].

CTA images should be reconstructed in thin slices, e.g. 1 mm thick, to allow for additional multi-planar reformations (MPR) and 3D image post-processing. Preferably, isotropic voxels should be achieved. Both filtered back projection and iterative reconstruction algorithms can be used, with the latter providing improved image quality due to noise removal and offers dose-saving potential [94]. Medium-sharp or vascular reconstruction kernels can be recommended with a reconstruction matrix of 512 × 512 pixels and angiographic window setting using a level 100 Hounsfield units (HU) and width of 700 HU.

Interpretation and reporting

CTA is indicated to "diagnose and localize diseases with primary manifestations in the arterial wall, including vasculitis, infection, and degenerative disorders" according to American College of Radiology guidelines [92]. Arterial vessel wall thickening is the typical sign of vascular inflammation on contrast enhanced CT images (Figure 4). In vasculitis, mural thickening usually involves the complete circumference of the vessel wall, whereas in atherosclerosis plaque formation starts from a focal point rather than circumferentially. CTA-based diagnosis is considerably facilitated in the absence of atherosclerotic plaques and when the thickening is not concentric. A circumferential aortic wall thickness of more than 2-3 mm with adventitial and peri-adventitial contrast enhancement is suggestive of aortitis [95,96]. It is assumed that the degree of mural contrast enhancement is associated with the inflammatory activity, as studies have shown that aortic wall contrast enhancement can resolve during glucocorticoid therapy while the wall thickening may persist [39].

Diagnostic accuracy of CTA

Although CTA itself is helpful for diagnosing LVV, the diagnostic accuracy of combined FDG-PET/CTA scans remains undefined. While the inflammatory activity within the vessel wall is displayed on FDG-PET images with high sensitivity, combining FDG-PET with CTA enhances the specificity by providing high-resolution anatomical details.

CTA also helps to differentiate different pathologic FDG-PET findings, as both vasculitis and atherosclerosis can demonstrate increased FDG wall uptake. Equally important to the

contribution of CTA to the diagnostic accuracy of combined FDG-PET/CTA is its role for detecting structural changes and potential complications of vasculitis [96]. During the primary diagnostic work-up, CTA often helps to find or exclude acute or symptomatic manifestations that require immediate therapy. For example, inflammatory vascular stenoses can lead to serious sequelae, such as brain infarction or mesenteric ischemia with bowel necrosis. Furthermore, initial CTA may provide information on current disease stage, distribution, and duration. During disease follow-up, CTA plays a particular role in the detection and monitoring of complications such as aortic aneurysm and dissection. While stenoses are frequently observed in TA, GCA may lead to aortic or arterial dilatations. These dilated arteries might enlarge to aneurysms during the disease course, even though inflammatory activity is absent or sufficiently suppressed.

Consensus recommendation

- CTA and FDG-PET have complementary roles in the diagnosis of LVV (evidence level III, grade B).
- CTA has incremental value in detecting structural vascular changes and potential complications of vasculitis (evidence level II, grade A).

Monitoring the efficacy of immunosuppressive therapy with FDG-PET/CT(A)

To monitor LVV activity during and after treatment, related biomarker measurements would be helpful. Unfortunately both the cranial GCA and the extra-cranial large vessel form type GCA or TA lack disease specific serum biomarkers.

Although FDG-PET/CT(A) has proven to be an important imaging modality for making the diagnosis of non-temporal GCA, very limited data are available on the role of FDG-PET/CT(A) for patient management once treatment has started. The results of the utility of FDG-PET to assess changes in arterial wall inflammation in response to GC and methotrexate are mixed and include only small patient cohorts.

In the only prospective study by Blockmans et al., (Table 7) whole body FDG-PET/CT images were acquired at baseline and after 3 and 6 months of GC therapy [68]. Total vascular score (TVS) decreased from a mean ± SD score of 7.9 ± 5.5 at baseline to 2.4 ± 3.5 on repeat PET scan at 3 months ($p < 0.0005$), but did not further decrease at 6 months. In patients who experienced a relapse (recurrent signs and symptoms together with an increase in acute phase

reactants), FDG-PET was performed within 5 days. The authors found no difference in the predicting value of FDG uptake between relapsing and non-relapsing patients.

A retrospective study by Bertagna et al. (Table 7) included a total of nine patients, with eight GCA patients having a normalized FDG-PET at follow-up after GC therapy, and one patient without any change of the FDG-PET [97]. Despite the small number of patients enrolled, they concluded that FDG-PET/CT might be a useful and accurate tool for evaluating disease progression.

In a small study of 5 patients by Camellino et al., (Table 7) FDG-PET uptake decreased after addition of methotrexate to the traditional GC treatment [98]. Whether GCA disease activity can be monitored by FDG-PET/CT in patients on GC-sparing drugs such as tumor necrotic factor (TNF) blocking agents for TA and Interleukin-6- receptor blockade (tocilizumab) for GCA has not been studied.

Interestingly, a recent abstract by Nielsen et al. [37] reported that the FDG-PET/CT score, based on the semi-quantitative approach by Meller et al. [64] (score < 3), remained positive for vasculitis after 3 days of GC treatment , but became negative after 10 days.

Recently, studies showed that at the temporal artery level, infiltrates can persist even up to one year following the start of glucocorticoid treatment [28,99]. Macrophages and granulomatous inflammation decrease with glucocorticoid treatment in experimental models [100] and diminish in a time-dependent manner from 78 to 100% at initial biopsy to 50% at 9 months and 25% at 12 months in sequential temporal artery biopsies. Lymphocytes may persist longer [100] and remain present in GCA patients treated for up to 1 year [28]. Granulomatous inflammation decreased in a time-dependent manner at initial biopsy to 50% at 9 months and 25% at 12 months. This is in agreement with a study by Brack et al., in which macrophages persisted in the vessel wall of severe combined immunodeficiency (SCID) mice engrafted with TAB after one week of GC treatment [101]. These findings are also in line with the fact that the FDG-PET/CT(A) shows arterial wall uptake after 6 months in treated patients although the uptake is no longer diagnostic for vasculitis.

Prieto-González et al., prospectively assessed GC-induced changes in CTA findings of LVV in patients with GCA [39]. Forty biopsy-proven GCA patients evaluated by CTA at diagnosis were prospectively followed and scheduled for a new CTA approximately after 1 year of treatment. Vessel wall thickening, diameter, and contrast enhancement of the aorta and its tributaries were evaluated. Results were compared to those obtained at the time of diagnosis. CTA was

repeated to 35 patients after a median follow-up of 13.5 months (IQ25-75% 12.4-15.8). Arterial wall thickening was still present in 17 patients (68% of the patients who initially had LVV). The number of affected segments and wall thickness at various aortic segments significantly decreased and no patients developed new lesions, new aortic dilation or increase in previous dilation. Contrast enhancement disappeared in 15 (93.75%) of 16 patients in whom this finding could be assessed. Signs of LVV improve with treatment. While contrast enhancement resolves in the majority of patients, vessel wall thickening persists in two thirds. However, the number of affected aortic segments as well as aortic wall thickness significantly decreases.

For PMR there is one study by Blockmans et al., with sequential PET/CT's (Table 7) with the same methodology as for GCA. They found that vascular FDG uptake was present in 11 patients and was slight or moderate at diagnosis in nine out of 35 patients and that the uptake decreased after 3 and 6 months [69]. At baseline, FDG uptake in the shoulders was present in all but two patients and after 3 months and 6 months of GC therapy uptake was still present, although to a lower extent. The same holds true for the hips and the spinous processes. No difference in the predicting value of FDG uptake at baseline and after 3 months at the shoulders, hips or spinous processes was found between patients who experienced a relapse and those who did not have a relapse.

The optimal time window between performing FDG-PET in PMR after treatment with GC is unclear. A recent study of Palard-Novello et al., evaluated the use of FDG-PET/CT(A) for the assessment of tocilizumab as first-line treatment in patients with polymyalgia rheumatica (PMR) [102]. They found that FDG uptake decreased significantly but moderately after TCZ therapy in PMR patients, and might reflect disease activity.

Consensus statement
FDG-PET/CT(A) may be of value to evaluate response to treatment by monitoring functional metabolic information and detecting structural vascular changes (evidence level III, grade C), but additional prospective FDG-PET/CT(A) studies are warranted.

CONSENSUS STATEMENTS ON OPEN ISSUES FOR FUTURE RESEARCH AGENDA

Clinical issues

- Further establish the role of FDG-PET/CT in patient management and evaluate its role in treatment monitoring. When to use FDG-PET/CT in the diagnosis, in the follow-up and how often?
- Development of guidelines in LVV and PMR imaging with FDG-PET/CT(A) similar to those previously developed for FDG-PET/CT in oncology (EARL) criteria [26]. Randomized prospective studies are needed for more evidence.
- Including imaging biomarkers to the current diagnostic criteria to be considered for TA, GCA and/or PMR.
- Finding a consensus in the clinical support to perform imaging as early as possible and before starting GC therapy if treatment delay can be justified due to non-critical symptoms.
- Further investigation of the GC effect on vascular FDG uptake.
- Theranostics (diagnostics for selected therapy) for LVV/PMR, which may open more ways to targeted therapy, resulting in personal/precision medicine. Radiolabeled tocilizumab, or other monoclonal antibody PET tracers are potential candidates for this.
- Circumstances of when there may be myocardial involvement in patients with LVV should be further investigated (additional myocardial perfusion imaging, CT coronary calcium assessment & CT angiography maybe needed), including the risk of cardiovascular events due to drugs therapy in LVV [105].

<u>Methodological issues</u>

- Standardization of visual scoring and (semi)quantification in FDG-PET in LVV and PMR is essential for interpretation, for optimal comparison among centers especially for future multicenter trials.
- Decide how much thickening is mild, moderate or severe (not established in literature). Based on our expertise, we think that ≥ 2 mm (up to 2.9) may be mild, ≥ 3 mm (up to 3.9) moderate, and ≥ 4 mm severe.
- Consensus needed on which quantification method to apply in LVV.
- An uptake interval of 60 minutes after FDG injection is recommended, but 90-120 minutes interval can be evaluated for better image quality.

- Dual time point imaging may improve the target to background ratio, resulting in better image quality, due to greater FDG blood pool clearance, particularly in patients with reduced kidney function. However evidence based data is lacking.
- New imaging and reconstruction techniques of the skull, that allow visualizing the superficial temporal artery, which will result in better comparison of local LVV with TAB.
- Value of combining FDG-PET with CTA as a standard procedure in LVV and PMR, single modalities or hybrid.
- Value of FDG-PET/MRI in monitoring LVV and PMR, i.e. reduction of radiation dose [106].
- Development of online training modalities for interpretation.

Technical issues

- Optimization of the application of hybrid imaging in monitoring (residual) vascular wall disease in LVV.
- The use of vasculitis-specific tracers, directed against cells/proteins involved in and unique for the pathophysiology of LVV and PMR, should be investigated.
- New developments in camera systems, such as PET/MRI, allows us to combine metabolism or other molecular targets (PET) with vascular tissue layer characterization (MRI), including a reduction in radiation dose and improved cranial visualization. The value of these new multimodality imaging systems may be of interest for LVV assessment and monitoring.
- Optimal use of (low-dose) CT to distinguish active atherosclerosis from active vasculitis by pattern recognition, visually as well as by using dedicated software methodologies (textural feature).

CONCLUSION

The present procedural recommendation paper provides recommendations to assist imaging specialists and clinicians in requesting, performing and interpreting the results of FDG-PET in patients with suspected LVV and PMR.

Based on the present clinical data, FDG-PET/CT(A) has an important role in the

diagnosis of extra-cranial vascular involvement in patients with LVV/PMR.

Improvements of FDG-PET/CT(A) procedures will be beneficial to optimize the diagnostic and monitoring value of this technique in LVV/PMR.

Visual qualitative methods are most commonly used, but semi-quantitative methods such as the vascular/blood ratio and vascular/liver ratio using of SUVs are increasingly being used.

The addition of CTA to FDG-PET provides high-resolution imaging of vascular morphology that can potentially improve diagnostic accuracy, but more importantly provides information on the presence and possible complications such as stenosis, organ ischemia, aneurysm formation, and dissection.

Further prospective studies involving large cohorts of GCA/PMR patients are required to investigate and validate the role of the semi-quantitative methods for the assessment of LVV.

Several other open issues as stated before need to be studied for optimal performance of FDG-PET/CT(A) in the diagnosis, (treatment) monitoring and future theranostics in LVV/PMR, further improving the levels of evidence and grades of recommendations.

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This Joint Procedural Recommendation summarizes the views of Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine (EANM) and reflects recommendations for which the EANM cannot be held responsible. The Recommendations should be taken into context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

The Joint Procedural Recommendation was brought to the attention of all other EANM Committees and to the EANM National Societies of Nuclear Medicine. The comments and suggestions from the EANM Committees and the EANM National Societies are highly appreciated and have been considered for this Joint Procedural Recommendation.

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Tables:

Table 1. Recommendations for patient preparation and image acquisition for FDG-PET/CT for LVV and PMR.

Parameter	Recommendation
Dietary preparation	Fast for at least 6 hours prior to FDG administration In case of fever of unknown origin (FUO) or suspected cardiac involvement: Consider a fat-enriched diet lacking carbohydrates for 12-24 hours prior to the scan, a 12-18 hour fast, and/or the use of intravenous unfractionated heparin approximately 15 min prior to FDG injection
Blood glucose levels	< 11 mmol/L (200 mg/dL)
Glucocorticoids	Withdraw or delay therapy until after PET, unless there is risk of ischemic complications, as in the case of GCA with temporal artery involvement. FDG/PET within three days after start of GC is optional as an possible alternative [37,39]
Patient positioning	Supine, arms next to the body
Scan range	Head down to the feet
Scan duration	3D: 2-3 min/bed position*
Dose of FDG injection	3D: 2-3 MBq/kg (0.054-0.081 mCi/kg) body weight*
Incubation time after FDG injection	Standard 60 min
PET/CT	Low-dose non-contrast CT for attenuation correction and anatomical reference.

*Depending on the vendor suggestion of camera system.

Table 2. Literature review of the FDG-PET interpretation criteria used in LVV.

	PET evaluation criteria	References
	Visual analysis	
Giant Cell Arteritis / PMR	Uptake pattern	[7,57]
	Grading	[19,21,53,58-67]
	Total Vascular Score	[68,69]
	Semi-quantitative	
	SUV	[38,53,62]
	Target to liver ratio	[54]
	Target to lung ratio	[12]
	Target to blood pool	[52]
Takayasu Arteritis	Visual analysis	
	Grading	[53,60,61,66,67,70-76]
	Semi-quantitative	
	SUV	[55,77,78]
	Target to blood pool	[55]

Table 3. Proposal standardized FDG-PET/CT(A) interpretation criteria in LVV.

	Recommended PET interpretation criteria
For clinical use	**LVV Visual grading (GCA and TA)** Grade 0: No vascular uptake (≤ mediastinum) Grade 1: Vascular uptake < liver uptake Grade 2: Vascular uptake = liver uptake, considered as maybe PET positive Grade 3: Vascular uptake > liver uptake, considered as PET positive
	PMR Associated visual assessment (only GCA) Grade 0: No uptake Grade 1: Uptake < liver uptake Grade 2: Uptake = liver uptake Grade 3: Uptake > liver uptake Increased metabolic activity of the scapular and pelvic girdles Increased metabolic activity of the knee bursae and capsule Increased metabolic activity at the site of the cervical and lumbar interspinous bursae Increased metabolic activity of the trochantheric and ischiatic bursae
In general for research only	**PET Semi-quantitative analysis*** Target: Average SUV_{max} artery of the vascular ROIs Blood pool: Average SUV_{mean} of several vein ROIs TBR = average SUV_{max} artery / average SUV_{mean} vein Liver: SUV_{max} of a liver region, preferable the right lobe. TBR = average SUV_{max} artery / SUV_{max} of a liver region Vascular targets: - Carotid arteries - Subclavia arteries - Axillary arteries - Vertebral arteries - Ascending aorta - Aortic arch - Pulmonary arteries - Descending aorta - Abdominal aorta Joints: scapulae and pelvic girdles, knees, cervical and lumbar interspinous bursae, trochantheric and ischiatic bursae.
For clinical use	**Contrast-enhanced (PET/)CTA** Regular Vascular wall thickness in mm Contrast enhancement Presence of stenosis / aneurysm

Abbreviations: TBR = target to background ratio; SUV = standardized uptake value; ROI = region of interest; TA = Takayasu arteritis; PMR = polymyalgia rheumatica; GCA = giant cell arteritis. *SUV using EARL criteria [26].

Table 4. Systematic review of main findings of individual studies assessing the diagnostic accuracy of FDG-PET or FDG-PET/CT (A) at baseline in patients with large vessel vasculitis and/or PMR.

LVV type (indication)	Study type	Cases	Controls	IS therapy before baseline PET	Diagnostic criteria used for LVV	FDG injected activity	Time between FDG injection and PET acquisition (min)	Glucose serum levels before PET (mg/dL (mmol/L))	PET analysis	Threshold used for diagnosis of LVV at PET	Sensitivity	Specificity	Authors	Year
GCA and PMR (diagnosis)	P	15	9	33%	ACR, clinical criteria or TAB	4 MBq/kg (0.11 mCi/kg)	90	NR	QA (visual) and SQA (vessel wall SUVmax/blood pool SUVmean)	QA: high vascular uptake	66.7% (QA)	100% (QA)	Lariviere et al. [87]	2016
GCA (diagnosis)	R	18	53	33%	ACR, clinical criteria or TAB	3 MBq/kg (0.081 mCi/kg)	60±5	NR	QA (visual) and SQA (aortic SUVmax and aortic/liver, aortic/superior cava, aortic/inferior cava SUVmax ratios)	QA1: first impression QA2: diffuse vascular uptake = liver uptake QA3: diffuse vascular uptake > liver uptake	56% (QA1) 100% (QA2) 83% (QA3))	98% (QA1) 51% (QA2) 91% (QA3)	Stellingwerff et al. [40]	2015
GCA + PMR (diagnosis)	R	25	6	12%	ACR (GCA), Healey (PMR), clinical, biochemical criteriaor TAB	3 MBq/kg (0.081 mCi/kg)	60±5	NR	QA (visual)	QA1: first impression QA2: diffuse vascular uptake = liver QA3: diffuse vascular uptake > liver QA4: diffuse vascular uptake > femoral artery	92% (QA1) 100% (QA2) 100% (QA3) 80% (QA4)	90% (QA1) 60% (QA2) 98% (QA3) 96% (QA4)	Lensen et al. [25]	2015

GCA (diagnosis)	P	32	20	53%	TAB	370 MBq (10 mCi)	60	NR	SQA (vessel SUVmax)	SQA: vessel SUVmax cutoff 1.89	80% (SQA)	79% (SQA)	Prieto-Gonzalez et al. [38]	2014
GCA (diagnosis)	R	11	11	73%	TAB	4 MBq/kg (0.11 mCi/kg)	60	< 180 (10)	SQA (aortic/liver, lung or venous blood pool SUVmax ratio)	SQA: aortic/venous blood pool SUVmax ratio cutoff 1.53	81.8%(SQA)	91%(SQA)	Besson et al. [52]	2014
PMR	R	14	17	0	Chuang and Healey	370 MBq (10 mCi)	60	NR	QA (visual) and SQA (vessel SUVmax)	QA: mild vascular uptake (< liver uptake)	64.3% (QA)	76.5% (QA)	Yamashita et al. [88]	2012
GCA (diagnosis)	P	23	36	0	ACR, TAB or duplex sonography	361 ± 54 MBq (9.76 ± 1.5 mCi)	60	NR	SQA (vessel/liver SUVmax)	SQA: vessel/liver SUV ratio cutoff 1	88.9% (SQA)	95.1% (SQA)	Hautzel et al. [54]	2008
PMR (diagnosis)	P	13	6	0	Chuang and Healey	450 MBq (12.2 mCi)	90	NR	QA (visual) and SQA (vessel/lung uptake ratio)	NR	92.3% (QA)	100% (QA)	Moosig et al. [12]	2004
GCA + PMR (diagnosis)	P	25	44	0	TAB and ACR (GCA) or Hunder and Healey (PMR)	6.5 MBq/kg (0.18 mCi/kg)	60	NR	QA (visual)	QA: moderate uptake (= liver uptake)	76% (QA)	77% (QA)	Blockmans et al. [7]	2000
TA (diagnosis and disease activity)	R	51	50	75%	ACR and NIH	370 MBq (10 mCi)	60	< 150 (8.5)	QA (visual) and SQA (vessel SUVmax and vessel SUVmax/liver SUVmean)	QA: intense uptake (> liver uptake) in the ascending aorta, moderate uptake (= liver uptake) in the aortic arch and large aortic branch, and mild uptake (< liver uptake) in the descending or abdominal aorta	83.3% (QA)	90% (QA)	Santhosh et al. [75]	2014
TA (disease activity)	CS	22	NR	77%	ACR, NIH, DEI-Tak, clinical and biochemical criteria	480 MBq (13 mCi)	60	NR	QA (visual) and SQA (vessel SUVmax and vessel SUVmax/liver SUVmean)	QA: moderate uptake (= liver uptake) for aorta and mild uptake for other vessels	100% (QA)	88.9% (QA)	Karapolat et al. [72]	2013
TA (disease activity)	R	39	40	74%	ACR, JCS, and NIH	3.7 MBq/kg (0.1 mCi/kg)	69		QA (visual) and SQA (vessel SUVmax and vessel	SQA: vessel SUVmax cutoff 2.1	92.6% (SQA)	91.7% (SQA)	Tezuka et al. [55]	2012

								< 120 (7)	SUVmax/inferior cava SUVmean)					
TA (disease activity)	R	38	NR	37%	ACR and NIH	370 MBq (10 mCi)	40-60	74-122 (4-7)	QA (visual) and SQA (vessel/liver SUVmax)	QA: moderate vascular uptake (= liver uptake)	75% (QA)	64.3% (QA)	Lee et al. [73]	2012
TA (disease activity)	R	28	NR	70%	ACR and NIH	5 MBq/kg (0.135 mCi/kg)	60	NR	QA (visual) and SQA (vessel SUVmax and vessel SUVmax/liver SUVmean)	QA: moderate vascular uptake (= liver uptake)	69.2% (QA)	33.3% (QA)	Arnaud et al. [71]	2009
TA (disease activity)	R	32	NR	31%	ACR and NIH	551 ± 55 MBq (15 ±1.5 mCi)	60	97 ± 16 (5.5 ± 1)	QA (visual)	QA: moderate uptake (= liver uptake) for aorta and mild uptake for other vessels	78% (QA)	87% (QA)	Lee et al. [74]	2009
TA (disease activity)	P	14	6	79%	ACR	6 MBq/kg (0.16 mCi/kg)	45	NR	SQA (vessel SUVmax)	SQA: SUVmax cutoff 1.3	90.9% (SQA)	88.8% (SQA)	Kobayashi et al. [78]	2005
TA (disease activity)	R	18	NR	61%	ACR and angiography	185-259 MBq (5- mCi)	90	NR	QA (visual)	QA: mild vascular uptake (< liver uptake)	92% (QA)	100% (QA)	Webb et al. [76]	2004
GCA, PMR and TA (diagnosis and disease activity)	R	25	15	0 (at baseline)	NR	199-478 MBq (5.4-12.9 mCi)	50-60	NR	QA (visual) and SQA (vascular SUVmean)	QA: summed vascular visual score cutoff 8 SQA: average vascular SUVmean cutoff 0.697	84% (QA) 96% (SQA)	86.7% (QA) 86.7% (SQA)	Castellani et al. [89]	2016
GCA + TA (diagnosis)	P	43	15	NR	Clinical, biochemical criteriaor TAB	7 MBq/kg (0.19 mCi/kg)	180	102.2 ± 24(5.6 ± 1)	SQA1 (aortic SUVmax) SQA2 (aortic wall SUVmax/lumen SUVmax)	SQA1: aortic SUVmax cutoff 1.74 SQA2: aortic wall SUVmax/lumen SUVmax cutoff 1.34	80% (SQA1) 100% (SQA2)	83.3% (SQA1) 94% (SQA2)	Martínez-Rodríguez et al. [43]	2014
GCA + TA + other vasculitis (diagnosis)	R	31	33	50%	ACR, clinical and biochemical criteria	3.7 MBq/kg (0.1 mCi/kg)	60±10	< 140 (7.8)	QA (visual) and SQA (vessel SUVmax) or JA (QA and radiological/clinical elements)	QA1: mild vascular uptake (< liver uptake) QA2: moderate vascular uptake (= liver uptake) SQA: vessel SUVmax cutoff 2.4	93.5% (QA1) 64.5% (QA2) 74.2% (SQA) 93.5% (JA)	75.7% (QA1) 84.8% (QA2) 78.8% (SQA) 93.9% (JA)	Rozzanigo et al. [90]	2013
GCA + TA (diagnosis)	P	30	31	51%	ACR, clinical and biochemical criteria	5 Mbq/kg (0.29 mCi/kg)	45	< 180 (10)	QA (visual)	QA: moderate uptake (= liver uptake) for aorta and mild uptake for other vessels	73.3% (QA)	83.9% (QA)	Fuchs et al. [61]	2012

GCA + TA (diagnosis)	R	24	18	79%	Clinical and biochemical criteria or TAB	5 MBq/kg (0.135 mCi/kg	60	104 ± 25 (5.8 ± 1.6	QA (visual)	QA: moderate vascular uptake (= liver uptake)	92% (QA)	91% (QA)	Förster et al. [21]	2011
GCA + TA (diagnosis)	R	20	20	40%	ACR or TAB	350-400 MBq (9.5-10.8 mCi)	60	NR	QA (visual) and SQA (vessel SUVmax)	QA: intense vascular uptake (> liver uptake) SQA: SUVmax cutoff 2.24	65% (QA) 90% (SQA)	80% (QA) 45% (SQA)	Lehmann et al. [53]	2011
GCA and TA (diagnosis and disease activity)	P	13	8	62%	ACR and BVAS, duplex sonography, MRI or TAB	390-488 MBq (10.5-13.2 mCi)	60	< 120 (6.7)	QA (visual) and SQA (vessel SUVmax)	NR	92.3% (QA)	100% (QA)	Henes et al. [62]	2008

Abbreviations:

Abbreviations: GCA = giant cell arteritis; TA = Takayasu arteritis; LVV = large vessel vasculitis; DOR = diagnostic odd ratio; AUC = area under the curve; N.A. = not available. IS = immunosuppressive; NR = not reported. Study type: P = prospective; R = retrospective; CS = cross sectional. Type of vasculitis: LVV = large vessel vasculitis; PMR = polymyalgia rheumatica; RF = retroperitoneal fibrosis. Diagnostic criteria: ACR = American College of Rheumatology; NIH = National Institute of Health; TAB = temporal artery biopsy; MRI = magnetic resonance imaging; JCS = Japanese circulation society; BVAS = Birmingham vasculitis activity score; DEI-Tak = Disease Extent Index – Takayasu. PET analysis: QA = qualitative analysis; SQA = semi-quantitative analysis; JA = joint analysis; SUV_{max} = maximum standardised uptake value; SUV_{mean} = mean standardised uptake value.

Table 5. Main findings of available meta-analyses on the diagnostic accuracy of FDG-PET or FDG-PET/CT(A) in patients with large vessel vasculitis.

LVV	Studies included	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio	DOR	AUC	Authors	Year
GCA	3	66	83.3% (72-91)	89.6% (80-96)	7.10 (2.91-17.36)	0.2 (0.11-0.34)	37.93 (11.55-124.5)	0.88	Lee et al. [82]	2016
	4	57	90% (79-96)	98% (94-99)	28.7 (11.5-71.6)	0.15 (0.07-0.29)	256.3 (70.8-927)	0.98	Soussan et al. [47]	2015
	6	101	80% (63-91)	89% (78-94)	6.73 (3.55-12.77)	0.25 (0.13-0.46)	N.A.	0.84	Besson et al. [83]	2011
TA	7	191	87% (78-93)	73% (63-81)	4.2 (1.5-12))	0.2 (0.1-0.5)	19.8 (4.5-87.6)	0.91	Soussan et al. [47]	2015
	6	76	70.1% (58.6-80)	77.2% (64.2-87.3)	2.31 (1.11-4.83)	0.34 (0.14-0.82)	7.5 (1.65-34.07)	0.805	Cheng et al. [84]	2013
LVV (GCA and TA)	8	170	75.9% (68.7-82.1)	93% (88.9-96)	7.27 (3.71-14.24)	0.3 (0.23-0.4)	32.04 (13.08-78.45)	0.86	Lee et al. [82]	2016

Abbreviations, see table 4.

Table 6. Recommendations for patient preparation and image acquisition for the CTA scan.

Patient positioning	Supine, arms next to the body for hybrid PET/CTA, otherwise arms should be elevated.
Scan volume	Entire aorta including the cervical, upper extremity, visceral and renal, pelvic, and proximal lower extremity arterial branches
Contrast material administration	80 to 150 mL iodinated low-osmolar or iso-osmolar contrast material with concentrations of 300 to 400 mg iodine per mL is injected at flow rates of 3.0 – 5.0 mL/s via antecubital vein.
Specific CTA settings	Optimal arterial contrast phase: Bolus-tracking or test bolus technique, scanning in cranio-caudal direction Avoidance of aortic motion artefacts: ECG-triggering
Specific CT machine settings	Refer to individual CT scanner recommendations as parameters and protocols may differ among vendors and machines.

Table 7. Literature review of FDG-PET/CT(A) studies in monitoring patients with LVV/PMR

LVV type (indication)	Study type	Cases	Controls	Therapy	Diagnostic criteria used for LVV	PET analysis	Threshold used for diagnosis of LVV at PET	Follow up interval PET (months)	Diagnostic criteria	Authors	Year
GCA	P	35	NA	GC	TAB, baseline, PET, clinical data, lab	QA: visual uptake intensity, TVS	Decrease in vessel uptake, TVS,	3 and 6	clinical data, lab	Blockmans et al.[68]	2006
GCA	R	9	NA	GC	Clinical data, lab	QA: visual SQA:vessel SUVmax, vessell/liver SUVmax ratio	Decrease in: Vessel vessel/liver SUV ratio cutoff 1	3	Clinical data, lab	Bertagna et al.[97]	2010
LVV	R	13	13	GC	Clinical data, lab	QA: visual uptake intensity, TVS SQA: vessel SUVmax CT: W, W/R	Decrease in TVS, W and W/R	NR	Clinical data, lab	Muto et al.[103]	2014
GCA and PMR	R	5	NA	MTX	NR	QA: visual uptake intensity, vessel to liver uptake, TVS, TJS	Decrease in: TVS and TJS	Median 10.7	clinical data, lab	Camellino et al.[98]	2010
GCA, TA	R	10	NA	CYC	NR	QA: visual vessel to liver uptake	Decrease in vessel uptake	3-4	Clinical data, BVAS, lab	Henes et al.[104]	2011
GCA, TA	R	5	NA	GC	Clinical, lab, other imaging*	QA: vessel uptake intensity	Decrease in vessel uptake	Median 10	Clinical data, lab, other imaging	De Leeuw et al.[60]	2004
GCA and PMR	P	35	NA		TAB, baseline, PET, clinical data, lab	QA: visual uptake intensity, TVS, TJS	Decrease in: vessel uptake, TVS and TJS	3 and 6	clinical data, lab	Blockmans et al.[69]	2007

Abbreviations:

NA = not available; GC = glucocorticoids; CYC = cyclophosphamide; MTX = methotrexate; TVS = total vascular score; TJS = total joint score; BVAS = Birmingham vasculitis activity index; W = wall thickness; W/R = wall thickness ratio to the radius; * = CT angiography, MRA, duplex ultrasound; TAB = temporal artery biopsy.

Legends to the figures:

Figure 1. FDG-PET

Low (grade 1), intermediate (grade 2) and high (grade 3) LVV FDG uptake patterns including SUVmax values of the thoracic aorta in patients with GCA. Ratio is defined as average SUV_{max} of the thoracic aorta divided by the liver region. The total vascular score (TVS) is the highest for the right-positioned patient.

Figure 2. FDG-PET

Low (grade 1), intermediate (grade 2) and high (grade 3) FDG uptake patterns of the large joint regions in PMR patients, including SUV_{max} of the shoulders. Ratio is defined as average SUV_{max} in the shoulders divided by the liver region. The total number and intensity of affected joints is the highest for the right-positioned patient.

Figure 3. FDG-PET/CTA

On the left a transaxial view of a contrast chest CT in a 67-year old male with GCA, with an enlarged diameter of the ascending aorta of 41 x 41 mm with a moderate increased wall thickness of 3.1 mm, and a severely increased wall thickness of 4.7 mm of the descending aorta (diameter of 30 x 31 mm). On the right the fused transaxial images of the contrast chest CT and FDG-PET showing highly elevated FDG uptake (average SUV_{max} 5.5) in the ascending and descending aorta.

Figure 4. CT angiography chest in two patients with GCA

Upper row

CTA of the aorta and the supra-aortic arteries in a 64-year old male patient with giant cell arteritis. Mural thickening and contrast enhancement of the aortic wall (arrows in B). Please note hypodense inner ring delineating luminal contrast enhanced blood from contrast enhancing thickened aortic wall. Mural inflammatory changes are present in both subclavian arteries as visualized in cross section (bold arrow in A) and in a longitudinal section (light arrows in A). Asterix in A indicates the left subclavian vein.

Lower row

Axial view of a CT angiography of a 76-year old woman with GCA showing a severe increased wall thickness of 5.2 mm and contrast enhancement of the descending aorta (bold arrow) (A). Contrast CT of the same patient performed four years before, with no significant aortic wall thickening (B).

Supplementary appendix

Supplement 1: Levels of evidence and grades of recommendations [107].

Rating Level	**Description**
I	Evidence obtained from meta-analysis of multiple well-designed, controlled studies; randomized studies with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized studies with high false-positive and/or false negative errors (low power)
III	Evidence obtained from well-designed quasi experimental studies (e.g. nonrandomized controlled single-group, pre-post, cohort, time, or matched case-control studies)
IV	Evidence from well-designed non experimental studies (e.g. comparative and correlational descriptive and case studies)
V	Evidence from case reports and clinical examples

Grade	
A	Evidence of type I or consistent findings from multiple studies of types II, III or IV
B	Evidence of II, III or IV; findings are generally consistent
C	Evidence of II, III or IV; findings are inconsistent
D	Little or no systematic empiric evidence

Supplement 2: Search strategy and selection criteria**.**

We describe the different methods used to perform FDG-PET/CT in LVV, including PMR and the role of FDG-PET/CT in the diagnosis of LVV/PMR, assessment of response to therapy, as well as introducing a proposal to standardize image interpretation criteria. Literature search has been performed through PubMed database (search date: from inception to 01.03.2017) using the following key words combination: ((PET) OR (positron emission tomography) OR (computed tomography) OR (imaging) OR (FDG) OR (fluorodeoxyglucose)) AND ((sensitivity) OR (specificity) OR (accuracy) OR (diagnosis) OR (response) OR (monitoring)) AND ((Takayasu) OR (giant cell) OR (polymyalgia) OR (vasculitis) OR (aortitis) OR (arteritis)). Only articles in English language were selected. Small case series were excluded.

To inform our Review, we asked expert in the field to identify articles using the authors' own file system, on the topics addressed in this paper. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review. This Review and the recommendations on the use of FDG-PET/CT(A) were developed by an interdisciplinary panel of experts on FDG-PET/CT in LVV/PMR. Expert consensus was used to propose recommendations in the absence of sufficiently robust data. Levels of evidence and grades of recommendations were attributed to the different indications according to published criteria (Supplement 1). The paper was drafted and circulated among all panel members followed by subsequent rounds of revisions until consensus was achieved.