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MINI - REVIEW

Diagnostic performance of FDG PET in large vessel vasculitis

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Abstract

Purpose This mini-review aims to qualitatively analyze the diagnostic performance of FDG PET in patients with diagnosis or suspected large vessel vasculitis (LVV). The future perspectives of PET in this field are also described.

Methods A comprehensive computer literature search of case–control studies published in PubMed/MEDLINE database in the last 10 years and regarding the diagnostic performance of FDG PET in LVV was carried out. Patient preparation, FDG PET image acquisition, and interpretation criteria were analyzed with respect to the recent joint procedural recommendations in LVV.

Results We have summarized the methodological aspects and the diagnostic performances of FDG PET in detecting LVV considering 15 articles published in the literature. The data confirm the good diagnostic performance of FDG PET in this setting, using both visual and semiquantitative analysis. However, some heterogeneity has been found in several methodological aspects, as well as in the results of the included studies.

Conclusions Overall, FDG PET has a good diagnostic performance for the detection of active disease in LVV. Future prospective studies, more consistent with the joint procedural recommendations in LVV, are needed to support the use of standardized procedures and reproducible criteria for defining the presence of LVV with FDG PET/CT. Hybrid imaging and novel radiopharmaceuticals, more specific than FDG, are the future of PET in this field.

Keywords Large vessel vasculitis · FDG · PET · Takayasu arteritis · Giant cell arteritis

Introduction

Large vessel vasculitis (LVV) is an inflammatory disease mainly involving the large arteries [1]. The two major variants are the giant cell arteritis (GCA) and the Takayasu's arteritis (TA). GCA is the most common primary systemic vasculitis in western countries. It is a segmental panarteritis with and without the cranial involvement or with or without large vessel involvement [2]. The main clinical features are headache, scalp tenderness, temporal artery abnormalities, and systemic manifestations such as polymyalgic symptoms, weight loss, fatigue, and fever [2, 3]. GCA often overlaps with polymyalgia rheumatica (PMR). About 20% of patients with PMR have GCA and more than 50% of biopsy proven GCA cases present with PMR symptoms [4]. TA is a panarteritis involving mainly aorta and its major branches. It affects predominantly young women with substantial morbidity and mortality [5]. Prompt diagnosis and treatment of LVV are very important to prevent potentially serious ischemic complications such as visual loss and stroke in GCA or vascular stenosis/occlusion and aneurysmatic dilatation in TA [6, 7]. The American College of Rheumatology (ACR) classification is widely used for the diagnosis of GCA and TA [8, 9] and the National Institutes of Health (NIH) criteria are applied for the disease activity of TA [10]. However, GCA diagnosis can be challenging, especially in patients with symptoms consistent with GCA, but negative temporal artery biopsy (TAB) [11]. In TA, biopsies of the large vessels are generally not feasible and the assessment of disease activity may be challenging due to the difficult differential diagnosis of fibrotic stenosis from active arterial

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lesions [12]. In the clinical practice, LVV diagnosis often relies on the combination of clinical symptoms, elevated serum inflammatory markers, and imaging finding [13].

Fluorine-18 fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) is a functional non-invasive established technique in oncology, but it also plays an important role in the field of inflammatory diseases. In active LVV, the increased FDG uptake of vessel wall, typically with a smooth linear pattern, is due to elevated FDG uptake in inflammatory cells such as macrophages, monocytes, and lymphocytes. In the last years, several studies have evaluated the utility of FDG PET in the diagnosis of arterial involvement in LVV [12, 14, 15]. Moreover, a joint procedural recommendation paper on FDG PET/CT in LVV and PMR has been recently published to assist imaging specialists and clinicians in recommending, performing, and interpreting the results of FDG PET/CT in LVV patients [16]. In this review, we will provide an overview of the diagnostic performance of FDG PET in LVV, emphasizing the main strengths and limitations, as well as the future perspectives of PET imaging in this field.

Materials and methods

A comprehensive computer literature search of PubMed/MEDLINE database was conducted to find published articles on the diagnostic performance of FDG PET for the diagnosis of LVV. Two researchers conducted literature search, study selection, and data extraction and discrepancies were resolved by consensus. A search algorithm based on the combination of the following terms was used: (A) "positron emission tomography" OR "PET" OR "PET/CT" OR "FDG" OR "fluorodeoxyglucose" and (B) "vasculitis" OR "giant cell arteritis" OR "Takayasu arteritis". Additional studies were identified in the reference lists of publications. An initial selection was based on the exclusion of review articles, editorials or letters, comments, conference abstracts, case reports, and small case series (articles including less than ten patients with LVV). Only articles written in English conducted in human subjects and published over the last ~ 10 years (January 2010–August 2019) were eligible for inclusion. To assess the diagnostic performance of FDG PET in LVV patients, all studies that fulfilled all of the following criteria were selected: FDG PET performed as diagnostic tool to determine active TA or GCA, ACR and/or NIH criteria or clinical consensus used as reference standard for the diagnosis of TA or GCA, TAB positivity for GCA diagnosis, and the use of a control group. For each selected study, information was collected about basic study characteristics (authors, year of publication, and study design), patient characteristics (number of patients and controls and type of LVV), applied reference standard (ACR and/or NIH criteria, TAB or clinical consensus), patient preparation (fasting duration and serum glucose levels before FDG administration), glucocorticoids and/or immunosuppressive (IS) treatment and duration of treatment before the scan, imaging delay after FDG administration and imaging interpretation criteria (qualitative and semiquantitative analysis). For each selected article, further features of imaging analysis were recorded, if available: visual grading scale score, total vascular score (TVS), standardized uptake value (SUV) and/or target to background ratio (TBR) and derived thresholds. For each included study, sensitivity and specificity measures, including 95% confidence interval (95% CI) values were reported.

Results

From the comprehensive computer literature search and analysis, 15 studies met the inclusion criteria with 464 cases of LVV and 410 controls (Table 1). Seven out of 15 (47%) studies were on GCA patients, two (13%) on TA patients, and six (40%) on mixed populations. Nine out of 15 (60%) studies were performed in a retrospective manner. Controls could be oncological, atherosclerotic, or inflammatory subjects. Regarding the ongoing treatment at the time of PET study, 208/472 (44%) of cases and controls were under glucocorticoids and 87/266 (33%) on IS treatment, for a very variable time between studies. The methodological aspects of PET technique of each study are shown in Table 2. Fasting for less than 6 h prior to FDG administration was allowed in six of 14 (43%) studies. No studies reported the use of intravenous unfractionated heparin prior to FDG injection. Blood glucose levels above 126 mg/dL were allowed in five of five (100%) studies. Head down to the feet scan range was performed in 5/7 (71%) studies. The imaging delay after FDG injection was ~ 60 min in ten of 14 (71%) studies. In two studies, the imaging delay was 120 and 180 min, respectively. Low-dose non-contrast CT was performed in 13/15 (87%) studies. One study used CT with intravenous contrast in the same PET session in 5/51 (9%) patients. The interpretation criteria used to detect active vascular inflammation with FDG PET were different among the studies (Table 3). Qualitative analysis was used in 10/15 (67%) studies. A vascular uptake equal or higher than the liver uptake (Grades 2 and 3) for the diagnosis of LVV in comparison to controls was used in 5/10 (50%) studies. A vascular uptake higher than liver uptake (Grade 3) was used in 3/10 (30%) studies. The TVS, a measure of artery inflammatory burden, was reported in 3/10 (30%) studies. According to the joint procedural recommendation in LVV, the TVS can be calculated at seven different vascular regions (carotid arteries, subclavian arteries, axillary arteries, thoracic aorta, abdominal aorta, iliac arteries, and femoral

Table 1 Characteristics of individual studies assessing the diagnostic performance of FDG PET in patients with suspected large vessel vasculitis

First author	Year	Study design	LVV type	Cases	Controls	Glucocorticoids		Duration of glucocorticoid treatment before PET	IS therapy		Duration of IS therapy before PET	Reference standard
						Cases (%)	Controls (%)		Cases (%)	Controls (%)		
Forster [32]	2011	R	GCA + TA	24	18	n.a	n.a	n.a	19 (79%)	n.a	n.a	Clinicaland biochemical criteria or TAB
Lehmann [33]	2011	R	GCA + TA	20	20	n.a	n.a	n.a	8 (40%)	n.a	n.a.	ACR, TAB
Fuchs [34]	2012	R	GCA + TA	30	31	16 (53%)	12 (40%)	n.a	7 (23%)	7 (21%)	n.a.	ACR and NIH
Tezuka [24]	2012	R	TA	39	40	29 (74%)	n.a	n.a	n.a.	n.a	n.a.	ACR and clinical criteria
Besson [20]	2014	R	GCA	11	11	n.a	n.a	n.a	8 (73%)	n.a	n.a.	TAB
Martínez-Rodríguez [25]	2014	P	GCA + TA	43	15	n.a	n.a	n.a	n.a.	n.a	n.a.	TAB
Prieto-González [27]	2014	P	GCA	32	20	32 (100%)	n.a	< 3 days	n.a.	n.a	n.a.	Clinical and biochemical criteria or TAB
Santhosh [21]	2014	R	TA	51	50	n.a	n.a	n.a	12 (23%)	n.a	35 ± 7 months (mean ± SD)	ACR and NIH
Lensen [35]	2015	R	GCA	25	6	3 (12%)	n.a	n.a	n.a.	n.a	n.a.	ACR
Stellingwerff [22]	2015	R	GCA	18	53	6 (33%)	n.a	n.a	n.a.	n.a.	n.a.	ACR and clinicalcriteria
Castellani [17]	2016	R	GCA + TA	25 (diagnosis)	15	n.a	n.a	n.a	n.a.	n.a	n.a.	ACR and TAB
Lariviere [26]	2016	P	GCA	15 (diagnosis)	9	5 (33%)	n.a	Median 4 days (range 1–7)	n.a.	n.a	n.a.	ACR or clinical criteria
Clifford [18]	2017	P	GCA	28	28	28 (100%)	28 (100%)	Mean 11.9 days	n.a.	n.a	n.a.	ACR and TAB
Grayson [19]	2018	P	GCA + TA	40	59	n.a	n.a	n.a	n.a.	n.a	n.a.	ACR and TAB
Imfeld [23]	2018	P	GCA	63 (diagnosis)	35	34 (54% diagnosis)	15 (43%)	Median 6 days (diagnosis) 13 days (controls)	n.a.	n.a	Median 6 days	ACR

GCA giant cell arteritis, *TA* Takayasu arteritis, *NIH* National Institutes of Health, *ACR* American College of Rheumatology, *R* Retrospective, *P* Prospective; *TAB* temporal artery biopsy, *SD* standard deviation, *n.a.* not available

Table 2 Main methodological aspects of PET in the included studies

First author	Hours of fasting before FDG injection	Use of i.v. unfractionated heparin	Blood glucose level before PET (mg/dl)	Scan range	Scan duration (min/bed position)	FDG injected activity	Imaging delay after FDG injection (min)	CT (a.c. and a.r.)
Forster [32]	–	n.r.	104 ± 25	Head to knees/head to feet	n.r.	5 MBq/kg	–	No
Lehmann [33]	≥ 6	n.r.	n.r.	Skull base to middle femur	3	350–400 MBq	60	Yes
Fuchs [34]	12	n.r.	< 180	n.r.	n.r.	5 MBq/kg	45	No
Tezuka [24]	≥ 4	n.r.	n.r.	n.r.	2	3.7 MBq/kg	60	Yes
Besson [20]	4–6	n.r.	< 180	n.r.	3	4 MBq/kg	60	Yes
Martínez-Rodríguez [25]	≥ 6	n.r.	< 160	n.r.	n.r.	7 MBq/kg	180	Yes
Prieto-González [27]	4	n.r.	n.r.	n.r.	5	370 MBq	60	Yes
Santhosh [21]	≥ 6	n.r.	< 150	Skull base to middle femur	2-3	370 MBq	60	Yes[a]
Lensen [35]	≥ 4	n.r.	n.r.	Head to knees/head to feet	n.r.	3 MBq/kg	60 ± 5	Yes
Stellingwerff [22]	≥ 4	n.r.	n.r.	Head to knees/head to feet	n.r.	3 MBq/kg	60 ± 5	Yes
Castellani [17]	8	n.r.	n.r.	Head to feet	2	199–478 MBq	50–60	Yes
Lariviere [26]	≥ 12	n.r.	n.r.	n.r.	n.r.	4 MBq/kg	90	Yes
Clifford [18]	4	n.r.	n.r.	Head to feet	n.r.	370 MBq	60	Yes
Grayson PC [19]	Carbohydrate-sparse meal 24 h before the scan and 12 h fast	n.r.	n.r.	n.r.	n.r.	370 MBq adults 3.7 MBq/kg pediatrics	120	Yes[b]
Imfeld S [23]	≥ 6	n.r.	< 180	n.r.	n.r.	5 MBq/kg	60	Yes

a.c. attenuation correction, *a.r.* anatomical reference, *n.r.* not reported

[a]CT with contrast in five patients at diagnosis

[b]PET/MRI in patients aged < 18 years

arteries) using a semiquantitative score from 0 (= no FDG uptake) to 3 (very marked FDG uptake) [16]. Therefore, TVS may range from 0 (= score 0 in all 7 vascular regions) to 21 (= score 3 in all 7 vascular regions). In the study by Castellani et al., the TVS was calculated by summing the scores from 0 to 3 of 11 arterial segments (carotids, subclavian arteries, innominate trunk, ascending and descending aorta, aortic arch, abdominal aorta, and iliofemoral arteries, maximum score = 33) [17]. The TVS was significantly higher in LVV patients at diagnosis ($n = 12$) or with active disease ($n = 9$) vs. patients with complete remission ($n = 20$) or controls ($n = 15$). At ROC analysis, a summed score > 8 resulted in the optimal threshold to distinguish LVV patients at diagnosis from controls. In the study by Clifford et al., the TVS was calculated by summing the scores from 0 to 3 of eight major vascular territories (carotid, subclavian/axillary, ascending and descending aorta, aortic arch, abdominal aorta, iliac, and femoral arteries; maximum score = 24) [18]. A TVS ≥ 9 resulted in the optimal cutoff for distinguishing GCA cases from controls. Grayson et al. scored from 0 to 3 nine arterial territories (ascending, aortic arch, descending thoracic aorta, abdominal aorta, innominate, carotids, and subclavians; maximum score = 27) [19]. The TVS was significantly higher in LVV patients with active disease than in comparator groups as well as in LVV patients during periods of active disease compared to periods of clinical remission.

Table 3 Main findings of the included studies on the diagnostic performance of FDG PET in large vessel vasculitis

First author	QA	Positivity for QA	TVS (n)[a]	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy 95% CI	SQA	Cutoff	Sensitivity	Specificity
Forster [32]	Visual grading	≥ Grade 2	No	92%	91%	–	No	–	–	–
Lehmann [33]	Visual grading	= Grade3	No	65% (41–85)	80% (56–94)	72% (56–85)	Vessel SUV_{max}	SUV_{max}: 1.78	90%	45%
Fuchs [34]	Visual grading	≥ Grade 2	No	73.3% (54–88)	83.9% (66–94)	78.7%	No	–	–	–
Tezuka [24]	No	–	No	–	–	–	Vessel SUV_{max}; TBR: vessel SUV_{max}/ICV SUV_{mean}	SUV_{max}: 2.1	92.6%	91.7%
Besson [20]	No	–	No	–	–	–	TBR: aorta/liver $SUV_{max}SUV_{max}$; target/lung SUV_{max}	TBR: 1.53	81.8%	91%
Martínez-Rodríguez [25]	No	–	No	–	–	–	Aortic wall SUV_{max}; TBR: aortic wall SUV_{max}/aortic lumen SUV_{max}	TBR: 1.34	100%	94.4%
Prieto-González [27]	No	–	No	–	–	–	Vessel SUV_{max}	SUV_{max}: 1.89	80%	79%
Santhosh [21]	Visual grading	≥ Grade 2	No	83.3%	90%	–	Vessel SUV_{max}; TBR: vessel SUV_{max}/liver SUV_{mean}	–	–	–
Lensen [35]	Visual grading	= Grade 3	No	100% (61–100)	98% (82–100)	–	No	–	–	–
Stellingwerff [22]	Visual grading	= Grade 3	No	83%	91%	–	Aorta SUV_{max}; TBR: aorta/liver SUV_{max}	TBR: 1.03	69%	92%
Castellani [17]	Visual grading	≥ Grade 2	Yes (11)	84%	86.7%	–	Vessel SUV_{mean}	–	96%	86.7%
Lariviere [26]	No	–	No	–	–	–	Vessel SUV_{max}; TBR: vessel SUV_{max} SUV_{max}/blood SUV_{mean}	–	66.7%	100%
Clifford [18]	Visual grading	–	Yes (8)	71.4%	64.3%	–	No	–	–	–
Grayson [19]	Visual grading	–	Yes (9)	85% (69–94)	83% (79–91)	–	No	–	–	–
Imfeld [23]	Visual grading	≥ Grade 2	No	77%	75%	–	Vessel SUV_{max}; TBR: vessel SUV_{max}/liver SUV_{mean}	TBR: 1	71%	91%

QA qualitative analysis, *SQA* semiquantitative analysis, *TVS* total vascular score, *CI*: confidence interval, *SUV* standardized uptake value, *TBR* target to background ratio, *ICV* inferior caval vein, *SCV* superior caval vein

[a]Number of vascular regions analyzed

A TVS ≥ 20 resulted in the optimal cutoff for identifying patients with clinical active compared to patients in clinical remission (area under the curve = 0.72, 68% sensitivity, 71% specificity). The semiquantitative analysis to detect vascular inflammation with FDG PET was performed in 10/15 (67%) studies and in five studies in addition to visual analysis. SUV_{max} and/or TBR thresholds were calculated in 7/10 (70%) studies. In detail, TBR methods using lung [20], liver [20–23], or blood pool [24–26] as a reference have been used. The joint procedural recommendation in LVV encourages the use of the arterial wall uptake-to-venous blood pool method instead of SUV for semiquantitative analysis, because this normalization limits the effects on signal quantification of errors in patient weight, injected dose, and imaging delay [16]. The sensitivity and specificity of FDG PET to detect vascular inflammation in LVV patients compared to controls by visual analysis ranged from 65 to 100% and from 64 to 98%, respectively (Table 3). The semiquantitative analysis of FDG PET to detect vascular inflammation in LVV patients compared to controls showed sensitivity and specificity from 66 to 100% and from 45 to 100%, respectively (Table 3). Different vessel SUV_{max} (from 1.78 to 2.1) or TBR cutoff values (from 1.03 to 1.53) were determined in each study by receiver operating characteristic (ROC) curves to optimize sensitivity and specificity.

Discussion

FDG PET has a good performance for the detection of active disease in LVV patients. However, the results are quite heterogeneous among the included case–controls studies. Several factors may explain this wide heterogeneity such as characteristics of studied populations, reference standard, methodological aspects, as well as interpretation criteria of PET imaging. First, since LVV is a rare disease, one limitation of some articles is the small number of cases and controls [20, 26]. Second, case and control groups were retrospectively analyzed in more than half of the included studies. Third, it is well known that the vascular FDG uptake may be affected by several factors such as glucocorticoid treatment and IS drugs. Patients with suspected LVV often immediately receive high-dose of glucocorticoids before PET scan and this may reduce the intensity of vascular FDG uptake by the inhibition of glucose transporters and the increase of liver uptake, producing a lower visual uptake ratio. For instance, in the study by Stellingwerff et al., GCA patients on glucocorticoids clearly showed an increased liver uptake compared to GCA patients not on steroid treatment, resulting in a lower diagnostic accuracy of the SUV_{max} aorta-to-liver ratio [22]. In addition, oncological and/or inflammatory controls could be also on glucocorticoids, affecting therefore the comparison between groups. Moreover, the sensitivity of FDG PET can vary in relation to the delay between the initiation of treatment and the scan. Regarding the analyzed studies, only one (6%) article included GCA patients treated with glucocorticoids for ≤ 3 days before FDG PET/CT with a sensitivity and specificity of semiquantitative analysis for GCA diagnosis of 80% and 79%, respectively (vessel SUV_{max} cutoff of 1.89) [27]. Clifford et al. reported a sensitivity and specificity of 71% and 64% in newly diagnosed GCA patients taking glucocorticoids, lower than those previously reported [18]. Recently, Nielsen et al. studied 24 patients with new onset GCA and demonstrated the existence of a diagnostic window of opportunity within the first 3 days of the glucocorticoid treatment [28]. GCA was accurately diagnosed in 10/10 patients after 3 days of treatment, but only in 5/14 (35%) patients after 10 days of treatment. FDG PET within 3 days after start glucocorticoids, withdraw or delay therapy until after PET, unless there is risk of ischemic complication, is recommended by the joint procedural recommendation in LVV [16]. Moreover, IS drugs may have hepatic toxicity and cause alterations in hepatic metabolism modifying liver FDG uptake and consequently the qualitative and semiquantitative analysis [18, 22, 29]. However, in the study of Santhosh et al., FDG PET was positive for active vasculitis in 14/43 (32%) scans in patients on IS [21]. Twelve PET scans were performed for suspected clinical features of active disease. This suggests that vascular inflammation may be detected by FDG PET/CT even under IS. According to the authors, this property may help in guiding the dosage of treatment. Furthermore, the accurate assessment of the diagnostic performance of FDG PET in LVV may be limited by the differences in reference standard and above all by the lack of a true reference standard for the diagnosis. The ACR criteria mainly identify patients with cranial GCA, but extracranial large arteries are involved in up to 80% of patients with GCA [30]. TAB is highly specific, but is invasive and has a lower sensitivity in patients with predominant large vessel GCA compared to cranial GCA. TAB has up to a 61% false negativity rate compared with a clinical diagnosis of GCA [31]. Therefore, the specificity of FDG PET may be underestimated since TAB is frequently falsely negative in extracranial GCA. In addition, extracranial arteries are not accessible for histological assessment. Consequently, in some cases FDG PET/CT is the only modality that allows a non-invasive diagnosis of LVV, providing the imaging of the entire vascular system, especially in patients without typical clinical manifestations and/or without temporal artery involvement or with a negative TAB. Indeed, FDG PET scores were similar between TAB + and TAB − patients with GCA in the study by Clifford et al. [18]. TA diagnosis is often based on NIH score, which integrates clinical, biological, and radiological criteria [10]. The NIH criteria have been reported to have low sensitivity or else biased. Discrepancies between TA activity

evaluated by NIH score and FDG PET/CT results raise the question of whether FDG PET/CT is more sensitive than NIH score and which reference should be used in future studies [16].

In several studies, FDG PET protocol was not optimized for vascular imaging. Much heterogeneity has been found in aspects such as fasting, blood sugar before FDG administration, and imaging delay after FDG administration. It is well known that blood glucose levels and especially imaging delay may affect qualitative and quantitative analysis of PET images. The cumulative effect of these factors together with acquisition and reconstruction parameters can significantly affect the qualitative and semiquantitative analysis, especially in longitudinal or multicenter studies. Fasting for at least 6 h prior to FDG administration, blood glucose levels preferably less than 126 mg/dl, and 60 min of imaging delay after FDG administration are recommended for FDG PET/CT in LVV patients [16]. Regarding the interpretation criteria, some authors used the visual grade score (0–3 Grade) [17, 21–23, 32–35], others a composite score, the TVS obtained by the sum of the visual scores of predefined vascular regions [17–19]. Moreover, a semiquantitative analysis based on the calculation of vessel SUV_{max} and/or TBR values was performed in some of the included articles [20–27, 33]. Many interpretation criteria of PET images have been proposed, nevertheless the joint procedural recommendation in LVV supports the use of a visual grading scale with vascular FDG uptake ≥ liver uptake (Grades 2 and 3) as LVV positivity criterion for the clinical use [16] (Fig. 1). In general, SUV of TBR measurements should be preferred for research purposes and for subsequent PET assessment during follow up. In these cases, TBR measurement could improve the diagnostic performance and homogenize the interobserver interpretation.

Several factors may significantly influence vascular FDG uptake and must be taken into consideration for the correct interpretation of FDG PET/CT in LVV. For instance, one of the main limitations of FDG is the non-specific nature of the tracer uptake. Vascular FDG uptake can be detected in different conditions, as atherosclerosis and graft infection [36, 37]. These conditions may be a source of false positivity for LVV evaluation, despite the typical patchy uptake pattern. However, Grayson et al. in a prospective study, including 56 LVV patients and 59 controls with hyperlipidemia and other diseases that mimic LVV, rather than healthy controls or patients with cancer, demonstrated that FDG PET/CT is able to distinguish patients with clinically active LVV from comparator subjects with a sensitivity and specificity of 85% (95% CI 69–94) and 83% (95% CI 71–91), respectively [19]. Stellingwerff et al. also compared vascular FDG uptake in GCA patients vs. three different control groups, including an atherosclerosis control group and reported a high diagnostic accuracy of visual score (Grade 3) for active disease with a sensitivity and specificity of 83% and 91%, respectively [22]. The sensitivity significantly increased, from 83% to 92%, when patients on glucocorticoids were excluded from the analysis.

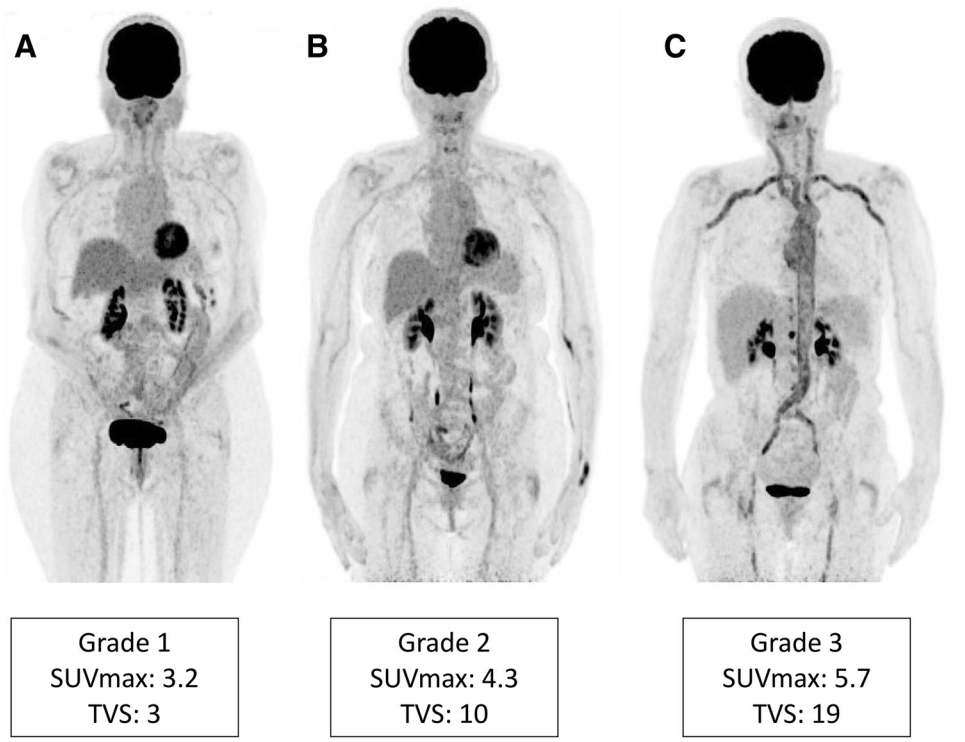

Fig. 1 The three maximum intensity projections (MIPs) represent different vascular FDG uptake patterns in comparison to liver uptake. In detail: **a** low uptake (< liver, Grade 1), **b** intermediate uptake (= liver, Grade 2), and **c** high uptake (> liver, Grade 3). A Grade 3 is considered positive for active large vessel vasculitis, while Grade 2 possibly indicative. SUV_{max} of the thoracic aorta is reported. A total vascular score (TVS) at seven different vascular regions was also determined, ranging from 0 (no vascular FDG uptake in any of the seven vascular regions) to 21 (vascular FDG uptake scored 3 in all territories)

Only one of the 15 included studies used CT with intravenous contrast in five patients at diagnosis [21]. Intravenous contrast provides data on luminal anatomy (i.e., dilation, stenosis, aneurysm), vessel alterations such as atherosclerotic plaques and detailed wall characterization, including extent of mural thickening [21]. In addition, CT with intravenous contrast may help in the delineation of vessels by distinguishing, for example, FDG uptake between the common carotid artery and neck nodes, since these structures are closely located. In the study by Lariviere et al. comparing PET to CT with contrast in GCA patients, FDG PET showed higher specificity and positive predictive value as compared to CT (100% vs. 84%) [26]. Future larger studies assessing the complementary role of FDG PET and CT with iv contrast in a single session, rather than comparing the techniques, could be useful for clinical decision making.

One of the 15 (6%) studies included assessed the clinical impact of FDG PET/CT in LVV patients and demonstrated that FDG PET/CT increased the number of indicated biopsies from 36 to 41% and changed the treatment in 27% of patients not receiving IS drugs and in the 22% of patients receiving IS treatment [34]. Future larger studies evaluating the clinical effectiveness and the outcome of LVV patients studied with FDG PET/CT could be useful to gain more reliable and comprehensive data.

Disadvantages of FDG PET include high costs, radiation exposure, no rapid access to PET in routine practice considering the significant reduction of sensibility after 7–10 days of glucocorticoids and misinterpretation of atherosclerosis as LVV, mostly with inexperienced readers. From nuclear physician's point of view, a standardized approach to FDG PET/CT seems to be the major limitation in LVV. In addition to differences in image interpretation, the variability is in patient preparation and image acquisition. Imaging examinations should be done by trained specialists using appropriate and standardized operational procedures. This recommendation is central for providing sensitive, specific, and reliable imaging results. In this context, a greater adherence to the joint procedural recommendation in LVV [16] in larger prospective future studies is desirable. A better way to test the diagnostic accuracy of FDG PET/CT would be to perform larger prospective studies, including patients suspected of having LVV compared to controls, possibly not oncological. Control patients in whom LVV diagnosis was suspected but ultimately ruled out should be preferred to preserve blinding, as in the study by Lariviere et al. [26].

A recent meta-analysis of nine studies including 298 patients with GCA or TA and 65 controls showed a pooled sensitivity of 88% (95% CI 79–93) and a pooled specificity of 81% (95% CI 64–91) for the identification of active disease in LVV patients by FDG PET/CT [38]. Moreover, the findings of meta-analyses published in the last 10 years on the diagnostic performance of FDG PET/CT in infectious and inflammatory disease have been recently summarized and a good diagnostic performance has been reported in LVV [39]. However, larger multicentre prospective studies are needed to test the more reproducible criteria for active LVV diagnosis, as well as to evaluate the clinical impact of FDG PET/CT on the management of patients with suspected or diagnosed LVV.

Future perspectives

The future perspectives for LVV imaging are mainly represented by the use of digital PET detectors, integrated PET/MRI analysis, and new radiopharmaceuticals. Digital PET detectors may increase the quantitative accuracy for the detection of LVV [40, 41]. This aspect could be of great value not only in the initial assessment of disease activity, but especially during or after treatment. To date, the literature data mainly concern the combined use of PET and MRI as separate procedures in the evaluation of LVV patients. Very few studies have focused on FDG with hybrid PET/MRI in LVV. Regarding soft tissue contrast, MRI appears to be superior to CT, as it is more sensitive in detecting vessel wall changes in LVV patients [42]. Fully integrated PET/MRI might be useful in the diagnosis and management of LVV, given its high sensitivity based on PET, the multimodal analysis of vascular wall inflammation and vascular lumen by MRI and the reduced radiation exposure compared to the well-established PET/CT. In detail, increased wall thickening, vessel wall edema, and mural contrast enhancement are MRI signs of vascular inflammation, while MRI angiography provides vascular lumen information such as arterial stenosis, occlusion, and dilatation. In addition, MRI may be useful for the differential diagnosis with other inflammatory aortic diseases as inflammatory abdominal aortic aneurysm, retroperitoneal fibrosis, and atherosclerotic plaques. Patient radiation dose may be further reduced with PET/MRI compared to PET/CT, because the longer time needed for MRI acquisition allows to reduce the injected radiopharmaceuticals activity by increasing the duration of PET acquisition [43]. The reduction of exposure to ionizing radiation is a non-negligible factor in a population like this, usually non-oncological and includes young people and women of child-bearing age. A pilot study on the feasibility of fully integrated PET/MRI scanner in LVV was recently published [44]. No significant differences were found between PET/CT and PET/MRI in relation to semiquantitative measurements and visual scores. In addition, the authors showed that adding the anatomical information provided by MRI, the number of vascular segments classified as vasculitic by PET increased from 86 to 95. Recently, in a retrospective study using hybrid PET/MRI in 13 patients with LVV, three different PET/MRI patterns

were well related to the clinical setting [45]. The inflammatory pattern, defined as both abnormal PET and MRI, was highly associated with disease activity, particularly in TA. This technique seems to offer promising perspectives for the diagnosis and monitoring of LVV, but prospective studies on large series of LVV patients are needed to establish its role in this field. Radiopharmaceuticals other than FDG are potentially applicable in LVV imaging. Radiopharmaceuticals targeting a specific marker, rather than metabolic activity are theoretically preferable due to the high specificity [46]. Macrophages play a key role in the pathogenesis of vasculitis and they can be used as a diagnostic imaging target [47]. Pugliese et al. first used ^{11}C-PK11195, a radiopharmaceutical targeted to a translocator protein (TSPO) for LVV imaging [48]. TSPO is a 18 kDa protein expressed on the outer membrane of macrophage mitochondria. Fifteen patients with a systemic inflammation and a high suspicion of LVV were studied. Visual analysis revealed focal arterial uptake in all six symptomatic patients and the absence of uptake in the asymptomatic patients. All symptomatic patients had individual TBR of > 1.20, while all asymptomatic patients had TBR of < 1.20. In one symptomatic patient, a PET/CT scan was repeated after 20 weeks of glucocorticoid treatment and showed a reduction of vascular ^{11}C-PK11195 uptake. At the same time, the patient presented a reduction of serum inflammatory markers and clinical improvement. Lamare et al. also used ^{11}C-(R)-PK11195 in seven patients with systemic inflammatory disease suspected for LVV demonstrating a major increase of vascular ^{11}C-(R)-PK11195 uptake in symptomatic patients compared to asymptomatic patients [49]. However, TSPO tracers have some limitations: in some patients they were less efficient to bind the target receptor [50, 51]. Moreover, older TSPO targeted radiopharmaceuticals may have high background blood-pool accumulation, which reduces their accuracy. New TSPO targeted radiopharmaceuticals with improved binding characteristics compared to classic TSPO radiopharmaceuticals have been developed and are being evaluated in pre-clinical and clinical studies. Newly developed ^{18}F-PBR06, ^{18}F-FEDAC, ^{18}F-FEDAA1106, and ^{18}F-GE-180 may have a great potential for LVV imaging [47]. In addition to glucose metabolism and TSPO, macrophage targeted radiopharmaceuticals labeling other biological pathways and receptors are already available and could potentially be used for LVV imaging. For instance, surface receptor imaging as somatostatin receptors or biological pathways using radiolabeled choline and methionine could be used for activated macrophages imaging. However, it is important to compare these radiopharmaceuticals in vasculitis and other diseases that mimic vasculitis such as atherosclerosis to discover radiopharmaceuticals ability of distinguishing vasculitis from others. An interesting future approach could be to radiolabel specific therapeutic antibodies or drugs with radionuclides, thus providing both imaging capability and identification of potential therapeutic target, followed by higher unlabeled therapeutic dose. The development of a possible theranostic approach in LVV patients would be highly desirable in the era of precision and personalized medicine.

Conclusions

FDG PET has a good diagnostic performance in detecting active disease in LVV patients, based on the available evidence. Larger future prospective studies are needed to support the recent joint procedural recommendation of FDG PET/CT in LVV, from patient preparation and image acquisition to interpretation criteria of PET images. More uniform and reproducible results are expected, as well as a further improvement of performance diagnostic of FDG PET in LVV patients. New radiopharmaceuticals targeting macrophage surface receptors or different biological pathway, in association to hybrid imaging as PET/CT with contrast or PET/MRI, will probably improve visualization and quantification of vessel inflammation.

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Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest regarding the publication of this article.

Ethical approval This article does not contain any studies with human or animal subjects performed by the any of the authors.

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