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Review

Imaging of Vascular Graft/Endograft Infection with Radiolabeled White Blood Cell Scan and [^{18}F]FDG PET/CT

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Abstract: Diagnosis of vascular graft/endograft infection (VGEI) is a challenge for clinicians due to the heterogeneity of clinical presentation and the complexity of its management. Microbiological culture is the gold standard, but it often fails to isolate the causative microorganism. A non-invasive imaging approach is therefore needed to assess VGEI. CTA is currently the first-choice imaging modality. Nuclear medicine techniques are recommended in case of negative or doubtful CTA results with persisting clinical suspicion. This review aims to summarize data from original studies published in the last decades regarding the role of both white blood cell (WBC) scans and fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT), their respective diagnostic performances, and their integration into the diagnostic approach for patients with a suspicion of VGEI.

Keywords: infection diagnosis; vascular graft/endograft infection (VGEI); imaging

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1. Introduction

Vascular graft/endograft implantation is a widely performed surgical procedure indicated for occlusive peripheral artery disease, life-threatening aortic aneurysms, and aortic dissection. Graft options include polyester (e.g., Dacron), polytetrafluoroethylene (PTFE), and autologous vein. Surgical bypass for peripheral (aortoiliac, femoropopliteal, or tibial) artery disease is preferably performed using autogenous vein or PTFE. Surgeries for aortic aneurysm and aortic dissection can be performed through an open or an endovascular procedure. Dacron is the most commonly used graft for aortic replacement, although PTFE grafts are occasionally used in infrarenal aortic repairs [1].

Vascular graft/endograft infection (VGEI) is a rare complication mainly caused by bacterial colonization of the wound site and the contamination of underlying prosthetic graft during surgery [2]. The incidence of VGEI varies depending on the specific location of the prosthesis (<1% in aortoiliac, 2% in aortofemoral, and up to 6% in infrarenal prostheses), the type of surgical procedure (less than 1% after endovascular aneurysm repair), and the type of graft material [3,4]. VGEI is often polymicrobial with involvement of anaerobes. The most common causative bacteria are Staphylococcus (mainly *S. aureus* and epidermidis), accounting for 80% of VGEI. Other microorganisms involved include Candida, other enterococci, streptococci, and Gram-negative species (such as *Escherichia coli* and *Pseudomonas aeruginosa*) [2].

The diagnosis of VGEI often constitutes a major challenge for clinicians. Clinical presentation varies upon the location of the vascular graft and upon the timing of the infection after surgery. In early infections (less than 4 months after implantation), the clinical presentation is often more evident, including fever, bacteremia, pain, erythema, swelling, warmth, local bleeding, and ulcer formation. On the other hand, the clinical

presentation in patients with late infections (developed more than 4 months after surgery) is more subtle, showing faint and nonspecific symptoms [2].

The gold standard for the definitive diagnosis of VGEI is bacterial culture from the explanted grafts or from tissue surrounding the graft, ideally obtained with surgery [2]. However, cultures often fail to isolate the bacteria from the peri-graft, particularly in cases of previous antimicrobial therapy or in cases where biofilm-forming bacteria such as staphylococci are involved [2,5].

VGEI treatment requires the removal of the infected segment of the graft in conjunction with revascularization, which should be carried out whenever possible, as antibiotic therapy without surgery is associated with a worse response and a higher mortality [6]. Achieving an early and effective diagnosis is therefore mandatory to accurately detect and evaluate the extent of the infection, thus providing crucial information for ensuring the success of surgical or medical treatment.

Although several definitions of VGEI have been proposed, the diagnosis derives from the combination of clinical, imaging, and laboratory findings (including histology and microbiology). The most recent classification was provided in 2016 by the Management of Aortic Graft Infection Collaboration (MAGIC) group, who identified a set of major and minor criteria to diagnose the infection [7] (Table 1). Of note, the MAGIC criteria include the results of white blood cell (WBC) scans and fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) as a minor radiological criterion. Aortic graft infection (AGI) is diagnosed if there is one major plus any criterion (major or minor) from another category. AGI is suspected if a single major criterion or two or more minor criteria from different categories are present. These criteria have been approved by the European Society for Vascular Surgery (ESVS) and are nowadays largely used in clinical practice [8]. In 2021, the MAGIC criteria were validated for VGEI diagnosis in the prospective Vascular Graft Infection Cohort study (VASGRA), in which patients with thoracic, abdominal, and peripheral grafts were included. The results showed that the use of the MAGIC criteria for a definite diagnosis of VGEI was associated with a high specificity and sensitivity. However, a lower specificity was found in the case of a suspected diagnosis of VGEI [9].

Table 1. The MAGIC Classification [7].

	Clinical	**Radiological**	**Laboratory**
Major criteria	Pus (confirmed by microscopy) around graft of aneurysm sac at surgery Open wound with exposed graft or communicating sinus Fistula development Graft insertion in an infected site	Peri-graft fluid on CT > 3 months after insertion Peri-graft gas on CT scan > 7 weeks after insertion Increase in peri-graft volume demonstrated on serial imaging	Organism recovered from an explanted graft Organism recovered from an intra-operative specimen Organism recovered from a radiologically guided aspirate of peri-graft fluid
Minor criteria	Localized clinical features of graft infection at site (e.g., erythema, warmth, swelling, purulent discharge, pain) Febrile > 38 °C with AGI as the most likely cause	Other signs (e.g., suspicious peri-graft gas/fluid/soft tissue inflammation, aneurysm expansion, pseudoaneurysm formation, focal bowel wall thickening, discitis/osteomyelitis); suspicious metabolic activity on [^{18}F]FDG PET/CT; radiolabeled leukocyte uptake	Blood culture(s) positive and no apparent source except graft infection Abnormally elevated inflammatory markers with graft infection as most likely cause (e.g., ESR, CRP, white cell count)

Aortic graft infection (AGI) is *suspected* in a patient with any isolated major criterion or minor criteria from two of the three categories: clinical/surgical, radiological, or laboratory. AGI is *diagnosed* in the presence of a single major criterion plus any other criterion (major or minor) from another category. Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Imaging modalities for the diagnosis of VGEI include ultrasonography (US), computed tomography angiography (CTA), magnetic resonance angiography (MRA), radiolabeled WBC scans, and [^{18}F]FDG PET/CT.

Ultrasonography is an available, cost-effective, non-invasive, and radiation-free technique. Its utility in the diagnosis of VGEI is limited due to a low sensitivity and a high inter-operator variability [10]. The guidelines thus recommend not relying solely on US for the diagnosis of VGEI [8].

CTA is currently considered as the imaging modality of choice for the diagnosis of VGEI [8]. It provides information regarding the vascular anatomy and allows identification of features of infection such as fat stranding, fluid collection, contrast enhancement, and gas formation along the graft or pseudoaneurysm. CTA thus provides anatomical information for the surgical planning and may guide an aspiration biopsy. However, moderate sensitivity and specificity of 67% and 63%, respectively, were reported for the detection of VGEI in a recent meta-analysis by Reinders Folmer et al. [11]. Moreover, a declining sensitivity is observed in chronic low-grade VGEI, often associated with a non-specific clinical presentation that could therefore refrain prompt diagnosis. Other notable drawbacks include a significant radiation burden and the injection of iodinated contrast agents, which is not always feasible in this patient population with a higher prevalence of renal insufficiency [10].

MRA demonstrates peri-graft fluid collections with a higher resolution than CTA. However, it cannot accurately discriminate an infected from a post-operative collection, especially in chronic or late VGEI. Other disadvantages include a longer acquisition time, low availability, and higher costs. Due to its lack of ionizing radiation and the use of non-iodinated contrast material, the ESVS guidelines suggest considering MRA if CTA is contra-indicated [8].

The two main nuclear medicine modalities for the diagnosis of VGEI are radiolabeled WBC scans and [^{18}F]FDG PET/CT. To date, the use of a nuclear medicine modality is recommended in case of negative or doubtful CTA results with persisting clinical suspicion, according to the ESVS 2020 clinical practice guidelines and European Association of Nuclear Medicine (EANM) 2022 evidence-based guidelines [8,10].

In this review, we will discuss data from original papers and meta-analyses published in the last decades regarding the role of [^{18}F]FDG PET/CT and WBC scans, their respective diagnostic performances, and their integration into the diagnostic approach for patients with a suspicion of VGEI.

2. Radiolabeled White Blood Cell Scan

The radiolabeled WBC scan using in vitro labeling with [^{111}In]In-oxine or [^{99m}Tc]Tc-hexamethylpropyleneamine (HMPAO) is the cornerstone nuclear medicine technique for the diagnosis of infection, especially neutrophil-mediated infectious processes such as bacterial infection. Labeling with [^{99m}Tc]Tc-HMPAO is generally preferred over labeling with [^{111}In]In-oxine because of the former's more favorable radiation characteristics for imaging.

2.1. Image Analysis

Radiolabeled WBCs migrate via diapedesis into the infection site, where they accumulate over time. Guidelines have been published by the EANM to standardize labeling procedures, acquisition protocols, and interpretation criteria in all centers [12]. Image acquisition is usually conducted at 2–3 h and 20 h post-injection (p.i.). The WBC scan is considered positive for infection when at least one focal increased accumulation in terms of extent and/or intensity is observed along the graft from early to delayed images, whereas in a sterile post-surgical inflammatory reaction, the uptake decreases or remains stable over time [12]. The use of single-photon emission tomography co-registered with CT (SPECT/CT) allows the visualization of anatomical landmarks, therefore precisely assessing the location and the extent of the infection. As has emerged from other clinical indications and was further underlined in the EANM guidelines on VGEI, SPECT/CT ac-

quisitions are strongly recommended in addition to planar images [10], and nowadays, the term "WBC scan" should always be intended as the combination of planar and SPECT/CT acquisitions. Crucial information is hence provided to the surgeon for deciding between complete exeresis of the prosthesis and partial removal and replacement of the prosthesis, as demonstrated in a study by Erba et al. [13]. WBC scans hence contribute to the management of patients, which could be particularly interesting in high-risk patients for which an alternative surgical procedure could be chosen.

Normal distribution of radiolabeled WBCs includes physiological uptake by the bone marrow, the spleen, and the liver. Additionally, bowel activity secondary to hepato-biliary secretion is observed when using [^{99m}Tc]Tc-HMPAO. This may hamper the detection of infectious processes in the abdominal and pelvic region. For that reason, adapted protocols are recommended by the EANM procedural guidelines [10,12]. Notably, images should be obtained within 2 h after injection of [^{99m}Tc]Tc-HMPAO when evaluating patients with suspicion of abdominal VGEI in order to reduce the bowel activity (Figure 1).

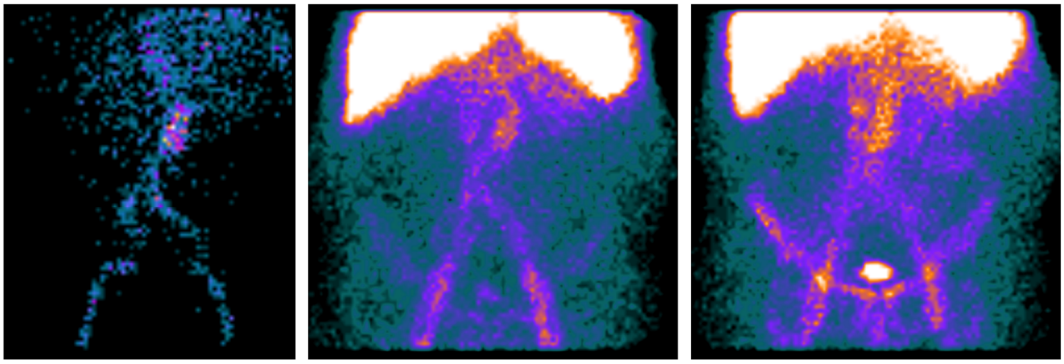

Figure 1. Radiolabeled WBC scintigraphy with [^{99m}Tc]Tc-HMPAO. Dynamic acquisition and planar images obtained at 30 min and 2 h p.i. show an increased uptake over time, consistent with an infection of the abdominal aortic graft.

2.2. Literature Review

In the past decades, several papers on the utility of WBC scans in VGEI have been published [13–20] (Table 2).

In a study by Vasquez et al., the sensitivity and specificity were 85.7% and 75%, respectively, for aortic graft infections versus 84.6% and 100%, respectively, for other vascular graft infections [17]. However, these values should be interpreted with caution, as this study included a limited number of patients. The ESVS guidelines recommend a WBC scan as a second imaging modality for the diagnosis of peripheral VGEI but not for aortic graft infections [8]. However, data regarding WBC scan accuracy with respect to graft locations are lacking.

Table 2. Summary of WBC scan studies on vascular graft/endograft infections.

	Patients	Methodology	Reference Standard	Imaging Protocol	Grafts	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Erba et al. [13], 2013	55 (47 confirmed)	Retrospective	Microbiological, clinical, and paraclinical criteria	[^{99m}Tc]Tc-HMPAO Images obtained 30 min, 2 h or 4–6 h (delayed), and 20–24 h (late) p.i.	Peripheral and aortic grafts	100	100	100	100	100
Khaja et al. [14], 2013	20	Retrospective	Results of tissue cultures from open surgical or percutaneous procedures and/or blood cultures	[^{111}In]In-oxine Images obtained 20 h p.i.	Peripheral and aortic grafts	75	100	100	50	80

Table 2. *Cont.*

	Patients	Methodology	Reference Standard	Imaging Protocol	Grafts	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Puges et al. [15], 2019	39 (15 confirmed)	Retrospective	Microbiological, clinical, and paraclinical criteria	[^{99m}Tc]Tc-HMPAO Images obtained after 4–6 h (early) and 20–24 h (delayed) p.i.	Peripheral and aortic grafts	89.5	90.9	70.8	97.2	90.6
De la Rubia-Marcos et al. [16], 2020	30 (10 confirmed)	Retrospective	Microbiological, clinical, and paraclinical criteria	[^{99m}Tc]Tc-HMPAO Images obtained 30 min and 2 h p.i.	Peripheral and aortic grafts	100	95	91	100	
Vasquez et al. [17], 2022	43 (32 confirmed)	Retrospective	MAGIC criteria	[^{99m}Tc]Tc-HMPAO Images obtained after a minimum of 3 h p.i.	Aortic grafts and peripheral grafts	85.7 84.6	75 100			
Lauri et al. [18], 2023	26 (11 confirmed)	Prospective	Microbiological/ histological findings	[^{99m}Tc]Tc-HMPAO Images obtained 30 min, 2 h, and 20 h p.i.	Aortic (abdominal)	81.8	100	88.2	100	92.3

PPV, positive predictive value; NPV, negative predictive value; p.i., post-injection.

De la Rubia-Marcos et al. reported a sensitivity, specificity, PPV, and NPV of 100%, 95%, 91%, and 100%, respectively [16]. For the use of WBC scans specifically in late low-grade VGEI, a high sensitivity (82–100%) and specificity (85–100%) were also reported, with a clear superiority compared with US and CTA [13]. This is particularly interesting, as the sensitivity of CTA declines in late VGEI due to its weakness to discriminate infection from non-infectious peri-graft inflammatory changes. A retrospective study by Khaja et al. comparing WBC-SPECT/CTA provided a higher sensitivity, accuracy, and NPV compared to stand-alone CTA and WBC scans, as software-based co-registration allowed negation of the weaknesses of both techniques [14].

In a retrospective study by Puges et al. conducted on 39 patients with suspected VGEI who underwent both a WBC scan and [^{18}F]FDG PET/CT, the specificity and accuracy were higher for the WBC scan [15]. The reason for this higher specificity is that radiolabeled WBCs identify neutrophil-mediated processes, whereas [^{18}F]FDG accumulates in infectious processes but also in neutrophils and macrophages located in a sterile post-surgical inflammation site.

There is a wide variability in diagnostic performance values amongst studies due to numerous factors: the absence of a clear definition of a proven graft infection (some studies considered a graft infection proven based on microbiological or histopathological results only, while others additionally included clinical parameters on follow-up), variable patient and graft characteristics, variable antimicrobial therapy before scanning, selection bias (as scans were often performed in patients with suspected VGEI that remained unconfirmed after standard workup), a limited number of enrolled subjects due to the rarity of the disease, and variability in the acquisition protocols and the interpretation criteria. Overall, WBC scans were demonstrated to be extremely reliable and accurate in differentiating VGEI from a sterile post-surgical inflammation. If standardized acquisition and interpretation protocols are used, this ability also is preserved in early post-surgical phases (1–4 months from surgery) [10,18,20] and even in low-grade infections [13,14], in which CTA and [^{18}F]FDG PET/CT exhibit their own limits.

Despite the high positive predictive values reported in all studies, the few false-positive results comprised non-infectious inflammatory changes persisting after surgery, hematoma, lymphoceles, sterile pseudoaneurysms, graft incorporation, graft thrombosis, and infection near the graft [15–17]. Table 3 summarizes the advantages and drawbacks of the WBC scan.

Table 3. Advantages and drawbacks of the WBC scan and [^{18}F]FDG PET/CT for the diagnosis of VGEI.

	Advantages	Drawbacks
WBC scan	Established acquisition protocols and interpretation criteria High accuracy both in early and late post-operative periods Accurately differentiates a VGEI from a sterile post-surgical inflammatory reaction Detection of alternative sites of infection Better inter-observer agreement than [^{18}F]FDG PET/CT, as shown by Puges et al. [15]	Expected lower accuracy in aortic grafts due to hepato-biliary secretion of [^{99m}Tc]Tc-HMPAO and physiological bone marrow uptake Limited image resolution Long acquisition and labeling time Manipulation of potentially infected blood Requires highly trained personnel for in vitro labeling Limited availability High radiation dose High cost
[^{18}F]FDG PET/CT	High sensitivity and ability to rule out infection High image resolution Accurately diagnoses a VGEI in the late post-operative period Detection of alternative sites of infections Short acquisition time Available in most centers	No established interpretation criteria Moderate specificity Lower accuracy inflammatory reaction in the early post-operative period than in the late post-operative period

To date, no study has directly compared patients with and without antimicrobial treatment for VGEI. However, in the abovementioned studies, antimicrobial therapy at the time of the study did not seem to affect the diagnostic accuracy of the WBC scans [13,15,18,19]. Consequently, the EANM evidence-based guidelines stated that antimicrobial therapy has no influence on the diagnostic accuracy of WBC scans in detecting VGEI [10].

As far as the role of radiolabeled WBC scans in detecting the healing of graft infection and therapy monitoring is concerned, in a study published by Erba and colleagues, patients with persistent infection demonstrated persistent pathological accumulation of radiolabeled WBCs on the follow-up scans. Conversely, normalization of the follow-up scan in some patients led to a shortening of the antimicrobial therapy [13]. Unfortunately, further studies on the use of serial imaging techniques during the follow-up to document the long-term evolution of a graft infection or the normalization of a physiologic post-surgical inflammation over time are lacking. Nevertheless, these data support the use of WBC scans to monitor the response to treatment and to promptly assess the healing process even in early phases after surgery, in which other modalities may still detect non-specific signs of inflammation [10,18,20]. To date, no guidelines have been published on the timing of imaging during the follow-up of patients with VGEI; therefore, at the moment, the decision to perform or not perform a CTA, a WBC scan, or [^{18}F]FDG PET/CT during the follow-up is based on clinical aspects, local availability, and waiting times.

3. [^{18}F]FDG PET/CT

3.1. Image Analysis

[^{18}F]FDG PET/CT is a well-established imaging modality in oncology for the staging and evaluation of the treatment response in various neoplasms. [^{18}F]FDG, a glucose analogue labeled with fluorine-18, accumulates in cells with increased glucose transporter expression and hexokinase activity, such as neoplastic cells (but also activated inflammatory cells). Increasing data published in the last decades demonstrate the usefulness of [^{18}F]FDG PET/CT in the diagnosis of various infectious and inflammatory diseases, including VGEI [21–25]. Indeed, considering the successful initial experiences in the use of [^{18}F]FDG PET/CT in VGEI imaging and with the wide availability of PET/CT tomographs, this modality quickly emerged as a reliable and non-invasive tool in this field. This is mainly due to the high sensitivity of [^{18}F]FDG and the possibility to accurately localize

foci with increased metabolic activity in anatomic structures. The use of hybrid imaging indeed allows the evaluation of graft and peri-graft tissue involvement and assessment of the extent of the infective process, thus being extremely helpful in therapy planning [21–25]. The CT component should always be considered when reporting a [^{18}F]FDG PET/CT scan, since the evaluation of a graft's borders, peri-graft lymph nodes, fluid collections, abscesses, or fistulae may be extremely helpful in determining if the infection is present or not. Collaboration with an experienced radiologist and evaluation with a diagnostic CTA are strongly suggested to improve the accuracy of the diagnosis [26]. In particular, irregular graft borders showing intense [^{18}F]FDG uptake are highly predictive of a VGEI [21,25,26]. Nevertheless, the main drawback of the use of [^{18}F]FDG PET/CT in this field is the limited specificity in low-grade processes, in which the metabolic activity may be reduced due to the presence of a chronic process, and in differentiating infection from post-surgical sterile inflammation, mainly due to the lack of well-standardized interpretation criteria. Table 3 summarizes the advantages and drawbacks of [^{18}F]FDG PET/CT.

Image analysis relies on visual assessment of the intensity and the biodistribution patterns of the [^{18}F]FDG uptake along the graft. A focal [^{18}F]FDG uptake is typically associated with VGEI (Figure 2), whereas a faint and homogeneous uptake is generally the expression of non-septic inflammatory process due to a physiological foreign-body reaction [19,21]. Indeed, vascular graft implantation provokes a chronic, low-grade, sterile inflammatory reaction that is part of the post-surgical healing, especially in the first 6 to 8 weeks after surgery [19,27–31]. This dichotomous classification is very easily applied when reporting a FDG scan. However, in clinical practice, the majority of patients studied with [^{18}F]FDG do not fit into any of these two patterns; instead, they show diffuse and heterogeneous [^{18}F]FDG uptake. This pattern is particularly challenging since it is common to both infected and non-infected patients [18,21], and despite many efforts being devoted to better defining solid and reproducible interpretation criteria, at the moment, none of these has been widely validated and universally adopted.

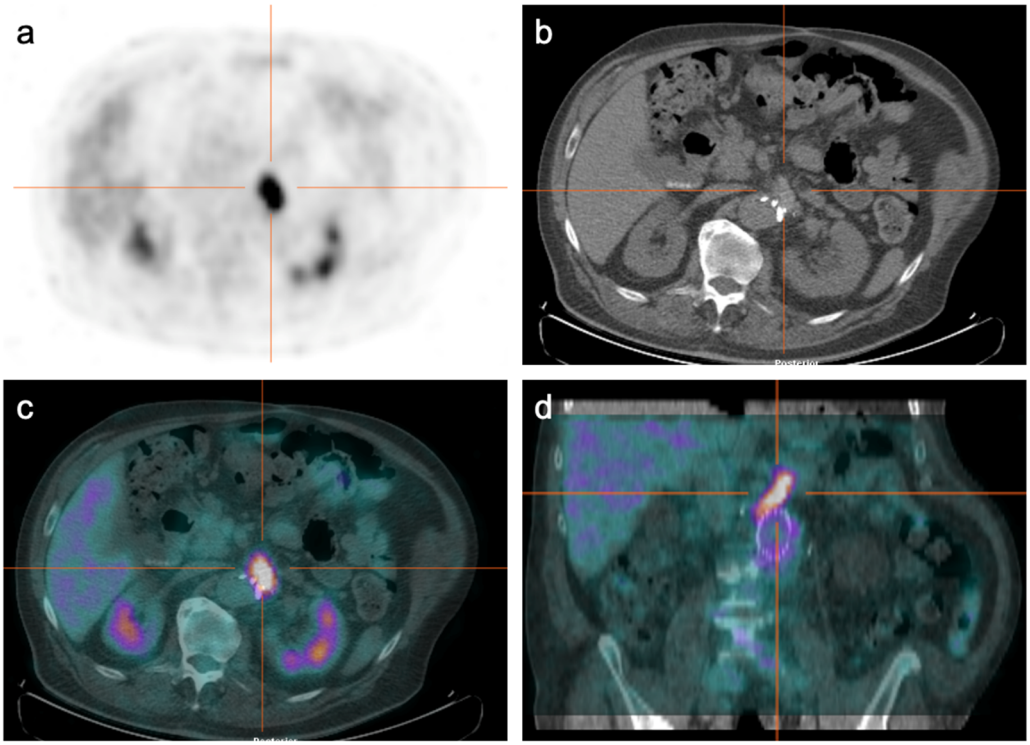

Figure 2. [^{18}F]FDG PET/CT performed in the same patient shown in Figure 1. The axial (**a**) PET, (**b**) CT, and (**c**) fused PET/CT images and (**d**) the coronal fused PET/CT image show a focal and intense [^{18}F]FDG uptake along the abdominal aortic graft. Peri-graft soft tissue enhancement is seen in the CT images.

3.2. Literature Review

Keidar et al. [31] assessed the pattern of [^{18}F]FDG uptake in a large series of uninfected prosthetic vascular grafts on PET/CT, showing that diffuse [^{18}F]FDG uptake was found in 92% of non-infected vascular prostheses. Similarly, Lauri et al. retrospectively assessed the uptake pattern in uninfected grafts after endovascular aortic repair (EVAR) on [^{18}F]FDG PET/CT performed at different time points after the procedure ranging from 1 to 36 months. All grafts showed mild and diffuse [^{18}F]FDG uptake, thus confirming that the absence of a focal pattern can rule out the infection. Moreover, no correlation was found between the time elapsed from the procedure and semi-quantitative parameters such as the maximum standardized uptake value (SUVmax) and the target-to-background ratio (TBR) [30]. It is important to note that the [^{18}F]FDG uptake patterns of a non-infected vascular prosthesis may vary depending on the material type. In Keidar et al., a homogeneous pattern with a low mean standardized uptake value (SUVmean) was often found in PTFE grafts and native vein grafts, whereas a heterogeneous and more intense uptake was more prevalent in Dacron grafts. Over time, [^{18}F]FDG uptake was stable for Dacron and Gore-Tex vascular grafts and significantly decreased for native vein grafts only [31].

In a prospective study by Groot Jebbink et al. comparing [^{18}F]FDG PET/CT before and 6 weeks after uncomplicated endovascular aneurysm sealing (EVAS), the homogenous uptake pattern, SUVmax, and TBR were stable before and after the procedure [32]. Marie et al. reported no increased [^{18}F]FDG uptake 1 month after EVAR compared with the [^{18}F]FDG uptake before the procedure [33]. The SUVmax values for non-infected endovascular grafts were all below the various cut-off values for the diagnosis of VGEI found in other studies [15,27,29,34,35]. Despite the lack of specificity of [^{18}F]FDG PET/CT, a mild and diffuse FDG uptake along the graft could reasonably exclude an infection, even in patients studied within the first 4 months of surgery [30,31].

As previously mentioned, well-standardized PET interpretation criteria for diagnosing an infection are still lacking, and many conditions such as hematoma, lymphocele, atherosclerotic inflammation (especially in large arteries), and graft thrombosis may mimic an infection and cause false-positive findings [22,29,36]. Additionally, abdominal aortic aneurysm shrinkage could present an increased [^{18}F]FDG uptake up to 6 months after procedure in patients who underwent EVAR, as reported by Marie et al. [33].

Visual analysis of [^{18}F]FDG distribution is always the first step. A focal uptake clearly located in the graft is considered a reliable criterion of positivity for VGEI [10,36–38] (Figure 3). Spacek et al., by using histopathology and clinical follow-up, reported a 93.5% PPV for predicting VGEI when an intense focal FDG uptake was observed. Conversely, they reported an NPV of 96.9% for excluding VGEI when no uptake was observed [21]. In a prospective follow-up study by Husmann et al., all patients with VGEI presented a focal FDG uptake at the baseline examination [37]. Although variable, diagnostic performances reported in various studies are generally high. For instance, Sah et al., using microbiology as the gold standard, reported a sensitivity, specificity, PPV, NPV, and accuracy of 96%, 86%, 96%, 86%, and 94%, respectively [36]. However, overlap between infected and non-infected vascular grafts has been observed [38]. Therefore, the interpretation of [^{18}F]FDG PET/CT could not solely rely on this parameter. Indeed, recent studies show a rising interest in the use of semi-quantitative parameters such as visual grading scales (VGSs), SUVmax, and TBR (Table 4).

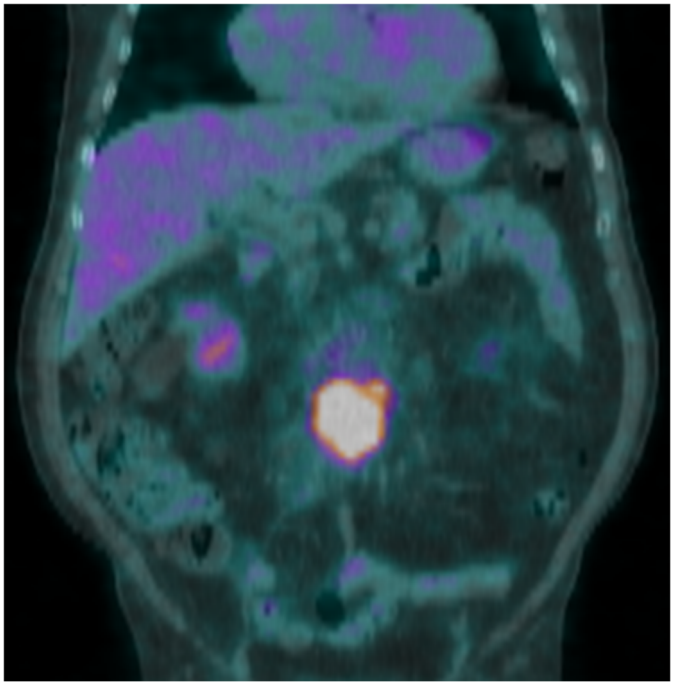

Figure 3. Coronal image of [^{18}F]FDG PET/CT showing focal and intense [^{18}F]FDG uptake on the abdominal vascular graft, consistent with an infection.

Table 4. Summary of [^{18}F]FDG PET/CT studies on vascular graft/endograft infections.

	Patients	Methodology	Reference Standard	Grafts	Interpretation Tool	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Keidar et al. [22], 2007	39, with a total of 69 implanted grafts (15 confirmed)	Prospective	Histopathological/ microbiological findings and clinical/imaging follow-up	Peripheral and aortic grafts	Intense focal pattern	93	91	88	96	
Spacek et al. [21], 2009	76, with a total of 96 implanted grafts (55 confirmed)	Prospective	Histopathology findings and clinical follow-up	Peripheral and aortic grafts	Intense focal pattern	78.2	92.7	93.5	76.0	84.4
					Focal or inhomogenous pattern	98.2	75.6	84.4	96.9	88.5
					Inhomogenous pattern + suspicious CT findings	72.7	85.77	88.9	66.7	77.8
Bruggink et al. [25]	25 (15 confirmed)	Retrospective	Microbiological findings	Peripheral and aortic grafts	Overall (based on VGS I–IV $\geq$ III (establshed by Fukuchi et al. [39]), SUVmax, and TBR)	93	70	82	88	
Tokuda et al. [29], 2013	9 (4 confirmed)	Retrospective	Microbiological findings and clinical follow-up	Thoracic aortic grafts	SUVmax $\geq$ 8	100	80			
Saleem et al. [34], 2015	37 (21 confirmed)	Prospective	Microbiological findings	Peripheral and aortic grafts (35 patients with aortoiliac grafts; 2 patients with axillobifemoral grafts)	VGS 0-IV $\geq$ III (established by Fukuchi et al. [39])	86	63	75	77	
					Focal pattern	90	25	61	67	
					SUVmax $\geq$ 8	40	88	80	54	
					TBR $\geq$ 6	40	81	73	52	

Table 4. *Cont.*

	Patients	Methodology	Reference Standard	Grafts	Interpretation Tool	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Sah et al. [36], 2015	34 (27 confirmed)	Prospective	Microbiological findings	Peripheral and aortic grafts	VGS I-V $\geq$ III Focal pattern SUVmax $\geq$ 3.8	100 96 100	86 86 86	96 96	100 86	97 94
Mitra et al. [27], 2018	21 (13 confirmed)	Retrospective	Microbiological findings	Peripheral and aortic grafts	Overall (based on VGS I-IV modified from Sah et al. [36]) SUVmax $\geq$ 6.3	92 92	63 88	80 92	83 88	
Puges et al. [15], 2018	39 (15 confirmed)	Retrospective	Microbiological, clinical, and paraclinical criteria	Peripheral and aortic grafts	VGS I-V $\geq$ III (Sah et al. [36])	85	68.4	41.5	94.5	71.9
Husmann et al. [37], 2019	23 (13 confirmed)	Prospective	Microbiological/ hisopathological findings and clinical follow-up	Aortic grafts	SUVmax $\geq$ 4.9	100	50	100	72.2	78.3
Einspieler et al. [40], 2019	50 (28 confirmed)	Retrospective	MAGIC criteria irrespective of the results of the PET/CT	Aortic grafts	VGS I-V $\geq$ III (Sah et al. [36]) SUVmax $\geq$ 4.96 $GBR_{BP} \geq 2.99$ $GBR_{NIAW} \geq 6.21$ $GBR_{T} \geq 3.24$	100 89.3 89.3 82.1 85.7	85.3 100 94.1 97.1 100	84.8 100 92.6 95.8 100	100 91.2 91.4 86.8 89.7	91.9 95.2 90.3 93.5 91.9
Zogala et al. [41], 2019	17 (9 confirmed)	Retrospective	Operative microbiological and clinical findings	EVAR	SUVmax $\geq$ 5.6 $TBR_{hep} \geq 2.2$ $TBR_{BP} \geq 3.5$ Overall (based on focal pattern and VGS 0-IV $\geq$ III modified from Saleem et al. [34])	90 89	100 100	 100	 89	
Dong et al. [42], 2020	35 (25 confirmed)	Prospective	MAGIC criteria irrespective of the results of the PET/CT	Aortic grafts	VGS I–V $\geq$ III (Sah et al. [36]) Focal pattern SUVmax $\geq$ 7.3 TBRmax $\geq$ 4.2 Overall (VGS $\geq$ III plus $\geq$ 1 other parameter)	96 84 88 92 96	70 90 80 80 80			88.6 85.7 85.7 88.6 91.4
Rahimi et al. [35], 2022	28 (15 confirmed)	Prospective	Clinical, laboratory, and radiologic findings	Peripheral and aortic grafts	SUVmax $\geq$ 4.5 SUVmean $\geq$ 3.7 TBR $\geq$ 1.6	93 100 93	92 92 92			
Lauri et al. [18], 2023	26 (11 confirmed)	Prospective	Microbiological findings	Aortic (abdominal)	VGS I–V $\geq$ III (Sah et al. [36]) VGS I–V $\geq$ IV (Lauri's scale [18]) SUVmax $\geq$ 4.52 SUVmean TBR	100 100 90.3 100 90.9	40 73.3 53.3 73.3 66.7	55 73.3	100 100	65.4 84.6

PPV, positive predictive value; NPV, negative predictive value; SUVmax, maximal standardized uptake value; VGS, visual grading scale; TBR, tissue-to-background ratio; GBR_{BP}, graft-to-background ratio with blood pool uptake as the reference; GBR_{NIAW}, graft-to-background ratio with non-inflammatory aortic wall uptake as the reference; GBR_{T}, graft-to-background ratio with tissue uptake as the reference; EVAR, endovascular aneurysm repair; TBR_{BP}, target-to-background ratio with blood pool uptake as the reference; TBR_{hep}, target-to-background ratio with liver uptake as the reference.

Sah et al. [36] introduced a semi-quantitative five-point visual grading scale (VGS) for the detection of VGEI that takes into account the intensity and the pattern of [^{18}F]FDG uptake as well as the CT information as follows:

- Grade I: normal background activity;
- Grade II: mildly increased but diffuse FDG uptake along the graft (mild uptake: less than twice the blood pool activity in the ascending aorta; strong uptake: more than twice the blood pool activity in the ascending aorta);
- Grade III: focal but only mild FDG uptake or strong diffuse FDG uptake along the graft;
- Grade IV: focal and intense FDG uptake ($\pm$diffuse FDG uptake along the graft);
- Grade V: focal and intense FDG uptake plus fluid collections/abscess formation.

A score value equal or superior to III is considered as positive for VGEI, whereas a score value of I and II is considered as negative. Using this five-point VGS, the authors

reported a sensitivity, specificity, PPV, NPV, and accuracy of 100%, 86%, 96%, 100%, and 97%, respectively, for the detection of both aortic and peripheral VGEI. Using the same VGS, high sensitivities were also reported by Einspieler et al. [40] and Dong et al. [42] for the detection of aortic graft infection only. Notably, a lower specificity of 70% was reported by Dong et al., mainly attributed to variability in the definition of the infection amongst studies. Other grading systems have been proposed by other groups with variable performances values [27,34,39,41]. In a prospective study from 2023, Lauri et al. proposed a new six-point VGS prioritizing the pattern of distribution over the intensity of uptake [18]. This new scale yielded a higher (although not significant) specificity than Sah's scale [36] due to a lower number of false-positive results.

The real challenge is how to interpret non-homogeneous [^{18}F]FDG uptake patterns that can be observed in both infected and non-infected grafts, and in these complex cases, the evaluation of CT findings may be helpful. Indeed, hybrid imaging allows the detection of abnormal CT findings in the vascular graft location, such as gas bubbles, peri-graft fluid retention, thickening of the graft wall, adjacent blurred fat, soft tissue swelling, abscesses, fistula, and pseudoaneurysms [28] (Figure 4). The incorporation of both morphological and metabolic information allows the assessment of the extent of the infection, thus helping the surgeon to decide on a more appropriate operative strategy [29]. Moreover, [^{18}F]FDG PET/CT is able to detect other pathological sites. In a prospective study by Husmann et al., [^{18}F]FDG PET/CT of patients with suspected VGEI revealed a high rate of relevant unknown incidental findings, which had implications on further therapeutic decisions in a significant percentage of patients [43].

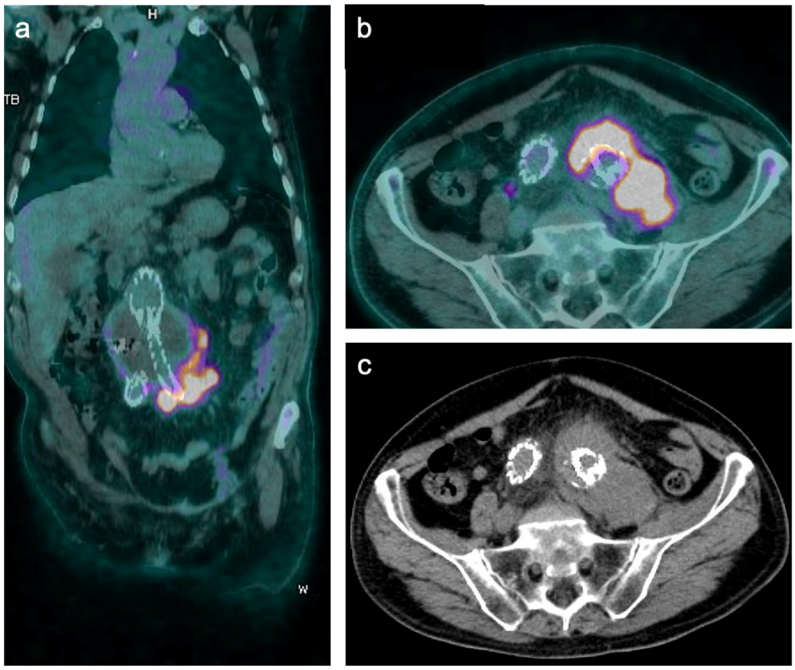

Figure 4. [^{18}F]FDG PET/CT. (**a**) Coronal and (**b**) axial fused PET/CT, and (**c**) CT images showing a focal and intense [^{18}F]FDG uptake along the left iliac branch of the graft extended to the left psoas muscle, consistent with vascular graft infection complicated by a psoas abscess.

SUVmax is the most widely used semi-quantitative parameter [27,29,37]. Various cutoff values have been suggested in the literature to differentiate infected from sterile post-surgical inflammatory reactions: SUVmax $\geq$ 3.8 [36], SUVmax $\geq$ 6.3 [27], and SUVmax $\geq$ 4.9 [37] (for studies on both peripheral and aortic graft infections); SUVmax $\geq$ 8 [34]; SUVmax $\geq$ 4.96 [40]; and SUVmax $\geq$ 8 [29]. However, currently, no cut-off value able to reliably distinguish an infected from a non-infected graft has been established.

Similarly, a broad range of thresholds for TBR have been published in the past years, and these achieved very different results due to the various methods of measurements (SUVmax graft/SUVmax background, SUVmax graft/SUVmean background, and others such as SUVmean graft/SUVmean background) and the different selected reference tissues to be used as the background (i.e., the caval vein, liver, and descending or abdominal aorta). Graft-to-background ratios compared with blood pool activity and non-inflammatory aortic walls were also evaluated as predictors by Einspieler et al. but did not provide any benefit in addition to VGS and SUVmax [40]. Using clinical and microbiological findings as the gold standard, Berger et al. independently assessed the VGS, uptake pattern, SUVmax, and TBR in infected and non-infected aortic grafts, showing that all parameters largely overlapped in the two groups [38]. However, at the moment, no definitive cut-offs able to differentiate infection from sterile inflammation or a low- from a high-grade infection have been identified.

Overall, data on the diagnostic performances of each parameter in the detection of VGEI are sparse due to the wide variability in patient characteristics, graft characteristics, time points of imaging after surgery, the gold standard used for the diagnosis of infection, and—most importantly—the interpretation criteria adopted by the different studies. Reinders Folmer et al. evaluated the pooled diagnostic performance of these interpretation methods in a recent meta-analysis [19]. The pooled sensitivities for the [^{18}F]FDG uptake intensity, uptake pattern, and SUVmax were 90%, 94%, and 95%, respectively. The pooled specificities for the [^{18}F]FDG uptake intensity, uptake pattern, and SUVmax were 59%, 81%, and 77%, respectively. Regardless of the parameters used (which mainly account for the specificity), [^{18}F]FDG PET/CT harbors a high sensitivity and excellent NPV; therefore, a negative [^{18}F]FDG PET/CT is able to rule out the diagnosis of VGEI [8,10,30].

The possible interference of antibiotic treatment on [^{18}F]FDG PET/CT performance is also a matter of debate. Sah et al. demonstrated that the diagnostic performance of [^{18}F]FDG PET/CT was higher in patients without previous antimicrobial treatment compared to patients with ongoing therapy [36]. However, other studies did not show a significant impact of previous antimicrobial treatment on [^{18}F]FDG PET/CT diagnostic accuracy for the detection of VGEI [37,40], consistent with the results of a large retrospective study by Kagna et al. that assessed the effect of antibiotic treatment for various infections on [^{18}F]FDG PET/CT diagnostic performances [44]. Currently, there is no recommendation regarding delaying antimicrobial treatment before scanning. This decision should therefore be considered on a case-by-case basis with a multidisciplinary team.

There are rapidly growing data on the use of [^{18}F]FDG PET/CT for assessing healing and the response to treatment in various infectious and inflammatory diseases. The use of [^{18}F]FDG PET/CT in the follow-up of patients with VGEI could offer individualized treatment approaches given the lack of a well-established duration of antimicrobial therapy [42,45,46]. A large prospective follow-up study by Husmann et al. [46] involving the treatment monitoring of 68 patients with confirmed aortic graft infections showed an overall decline in the SUVmax over time between the baseline and follow-up imaging. The authors suggested stopping the antimicrobial treatment in the case of complete response in follow-up PET/CT scans, the absence of clinical signs of infection, and normal inflammatory markers. In cases of a non-response or partial response, the authors suggested continuing antimicrobial therapy in the presence of elevated inflammatory markers and/or clinical signs of infections. However, there is currently a lack of approved guidelines for monitoring the response to treatment and for the timing of imaging modalities during the follow-up.

4. Conclusions

VGEI is a complex and heterogenous disease requiring a multidisciplinary management. CTA remains to date the first-choice imaging modality for the diagnosis of VGEI, mainly due to its high availability, morphological precision, and fast acquisition time. A nuclear medicine modality is recommended in the case of negative or doubtful CTA results

with persisting clinical suspicion. Variable diagnostic performances of both [^{18}F]FDG PET/CT and WBC scans have been reported amongst studies due to the absence of a clear definition of the infection, small-sized populations, different patient and graft characteristics, and a wide variability in the gold standard and follow-up used in the different studies. Moreover, there is a lack of data regarding the accuracy of both [^{18}F]FDG PET/CT and WBC scans with respect to the graft location (central or peripheral) and material type and in monitoring the long-term evolution of an infection and healing process. These limitations make a direct comparison amongst different studies difficult to perform and warrant more comparative studies to better define which modality is more appropriate in specific clinical scenarios.

Based on the available literature, both techniques are useful in assessing the extent of the infection, thus being extremely useful in selecting the best therapeutic strategy, but a clear superiority of one of these imaging modalities has not emerged due to the lack of large prospective comparative studies.

A negative [^{18}F]FDG PET/CT, due its high sensitivity and NPV, can be used to rule out the infection even in early post-surgical phases. A positive [^{18}F]FDG PET/CT, due to the lack of well-standardized interpretation criteria, should be interpreted with caution and possibly confirmed with a radiolabeled WBC scan, which is more specific and accurate in differentiating infection from sterile inflammation.

For [^{18}F]FDG PET/CT, a combination of different parameters such as the VGS, focal pattern, SUVmax, and TBR along with morphological information from the co-registered CT may improve the accuracy, but further efforts should be directed toward the standardization of interpretation criteria. In the near future, characterization of [^{18}F]FDG uptake heterogeneity using textural features could increase the accuracy of PET/CT in distinguishing non-infected from infected patterns of uptake [47].

In conclusion, imaging modalities play a complementary role in the diagnosis and monitoring of a VGEI, and a multidisciplinary and a multimodal approach is mandatory to ensure a successful management of these patients. After an initial CTA, the choice between a WBC scan and [^{18}F]FDG PET/CT should be based on local availability, waiting times, and personal expertise, and the decision should be shared within a multidisciplinary team in order to better meet the clinical need and to plan a personalized treatment.

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Abbreviations

PTFE	Polytetrafluoroethylene
VGEI	Vascular graft/endograft infection
MAGIC	Management of Aortic Graft Infection Collaboration
WBCs	White blood cells
[^{18}F]FDG PET/CT	Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography
AGI	Aortic graft infection

ESVS	European Society for Vascular Surgery
VASGRA	Vascular Graft Infection Cohort study
US	Ultrasonography
CTA	Computed tomography angiography
MRA	Magnetic resonance angiography
EANM	European Association of Nuclear Medicine
HMPAO	Hexamethylpropyleneamine
p.i.	Post-injection
EVAR	Endovascular aneurysm repair
SUVmax	Maximum standardized uptake value
SUVmean	Mean standardized uptake value
TBR	Target-to-background ratio
EVA	Endovascular aneurysm sealing
VGS	Visual grading scale

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