



A role of FDG PET/CT for Response Assessment in Large Vessel Disease?

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Currently, a large amount of evidence-based data clearly demonstrates the usefulness of [¹⁸F] FDG PET/CT in the diagnosis of several infectious and inflammatory diseases, including those related to the large vessels. The aim of this article is to clarify whether, beyond initial diagnosis, [¹⁸F]FDG PET/CT may have a role in treatment response assessment in inflammatory or infectious diseases of the large vessels, including large vessel vasculitis, vascular graft infection, retroperitoneal fibrosis/chronic periaortitis and infective native aortic aneurysms. Rapidly accumulating data suggest that [¹⁸F]FDG PET/CT could be a valuable imaging method for therapy monitoring in some infectious and inflammatory diseases of large vessels. The available data, albeit preliminary, indicate that [¹⁸F]FDG PET/CT could even play a pivotal role in the management of these diseases, leading to better drug dosage, confirmation of the usefulness of the treatment, and early modification of the therapeutic strategy. However, to date, the role of [¹⁸F]FDG PET/CT for treatment assessment in large vessel diseases, in particular large vessel vasculitis, is not clearly defined and well-designed prospective studies are needed to confirm its possible role in treatment monitoring and treatment guidance.

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Introduction

Nuclear medicine imaging techniques are non-invasive methods that can early detect pathophysiological changes in affected tissues not only in oncological diseases but also in patients with infectious or inflammatory diseases.^{1,2} These changes usually precede the development of morphological changes detected by conventional imaging techniques explaining the advantage of molecular imaging for early diagnosis of infectious and inflammatory diseases.^{1,2}

Currently, hybrid imaging modalities (eg, positron emission tomography/computed tomography - PET/CT) may

provide both functional and morphological information in the same imaging session allowing a clear advantage compared to stand-alone molecular imaging or conventional imaging methods.^{1,2}

Fluorine-18 fluorodeoxyglucose ([¹⁸F]FDG) is the most used radiopharmaceutical for PET/CT imaging. It is a radiolabeled glucose analog transported intracellularly via cell membrane glucose transporters and subsequently phosphorylated by hexokinase inside most cells.³ The ability of [¹⁸F]FDG PET/CT to identify sites of inflammation and infection is mainly related to the increased glycolytic activity of the cells

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involved in the inflammatory response.³ The immune cells involved in infectious and inflammatory diseases, especially neutrophils and the monocyte/macrophage family, are able to express high levels of glucose transporters and they usually show increased hexokinase activity.³⁻⁵ This represents the rationale for using [^{18}F]FDG PET/CT for imaging infectious or inflammatory diseases.³⁻⁵

Currently, a large amount of evidence-based data clearly demonstrates the usefulness of [^{18}F]FDG PET/CT in the diagnosis of several infectious and inflammatory diseases, including those related to the large vessels, and this method is currently widely used in daily clinical practice for diagnostic purposes.^{6,7}

The aim of this article is to clarify whether, beyond initial diagnosis, [^{18}F]FDG PET/CT may have a role in treatment response assessment in inflammatory or infectious diseases of the large vessels, including large vessel vasculitis, vascular graft infection, retroperitoneal fibrosis/chronic periaortitis and infective native aortic aneurysms.

[^{18}F]FDG PET Biomarkers for Treatment Response Assessment in Infectious and Inflammatory Diseases

A biomarker can be used as an indicator of a normal or pathologic process or for treatment response assessment. An ideal biomarker for infectious and inflammatory diseases should possess diagnostic, prognostic, and treatment follow-up characteristics.⁸ Currently, there is an ongoing unmet need for biomarkers that can reliably distinguish between treatment responders and non-responders in infectious and inflammatory diseases. These biomarkers could help to optimize treatment decisions hence patient management. However, a combination of biomarkers is usually needed to monitor infectious and inflammatory diseases.⁸

Conventional imaging techniques can be used to assess treatment responses in infectious and inflammatory diseases. However, these techniques are not adequate to provide an early assessment of therapeutic efficacy, because morphological changes in relation to treatment are detected only in a delayed/late phase.⁸ Conversely, molecular imaging using [^{18}F]FDG PET/CT, detecting functional abnormalities which precede morphological changes, is better suited to assess treatment response in several diseases including oncological diseases and inflammatory/infectious diseases.⁸

Treatment response assessment at sites of infectious/inflammatory diseases with [^{18}F]FDG PET/CT may be performed by using visual (qualitative) and/or semi-quantitative analysis, for example using the maximum standardized uptake value (SUV_{max}). However, determining an accurate and repeatable method for evaluating treatment response by [^{18}F]FDG PET/CT remains a challenge and several issues may hamper accurate quantification of treatment response in infectious/inflammatory diseases.⁸ First of all, a correct assessment of treatment response

should be performed using a follow-up or post-treatment [^{18}F]FDG PET/CT compared to a baseline scan. Second, there is currently limited data about the correlation between serum biomarkers and imaging biomarkers in infectious/inflammatory diseases. Third, even if most studies have focused on changes in SUV_{max} (delta SUV_{max}) considering treatment response as decrease in SUV_{max} between the baseline and the follow-up studies, there are several factors influencing this parameter, and specific thresholds of SUV_{max} value or delta SUV_{max} between two studies are not established. Lastly, in contrast to oncological diseases, the optimal time point during the course of treatment when the follow-up [^{18}F]FDG PET/CT scan should be performed has yet to be determined.⁸

[^{18}F]FDG PET/CT for Treatment Response Assessment in Large Vessel Vasculitis

Large vessel vasculitis (LVV) is defined as an inflammatory disease mainly affecting the large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA). GCA often coexists with polymyalgia rheumatica (PMR) in the same patient, since both belong to the same disease spectrum.^{9,10} [^{18}F]FDG PET/CT may demonstrate increased [^{18}F]FDG uptake in the vascular wall of large vessels in patients with LVV; therefore, this method may be suitable for diagnosis, monitoring of disease activity, and evaluating disease progression in LVV (Figs. 1-2).⁹

Visual analysis of [^{18}F]FDG PET/CT should remain the mainstay for diagnosing LVV in routine clinical practice by looking at the vascular distribution pattern of the radiotracer and the intensity of uptake as compared with general vascular or, as a surrogate, liver activity.^{9,11} Currently, there is no evidence that semi-quantitative PET indices are superior compared to visual analysis for diagnosing LVV. Semi-quantitative indices, based on ratios, shall be implemented in clinical trials only with a well-defined calculation.¹¹

To date, the role of advanced imaging modalities, including [^{18}F]FDG PET/CT, for monitoring LVV is still uncertain.¹²⁻¹⁶ Described pros for [^{18}F]FDG PET/CT include: possible correlation with disease activity, possible prediction of relapse after cessation of treatment, possibility of detecting other causes of increased glucose metabolism (eg, infections, tumors, other inflammatory diseases). Described cons for [^{18}F]FDG PET/CT include: unclear significance of (weak) persistent vessel uptake despite absence of clinical symptoms, reduced sensitivity in patients with high glucose serum levels and/or glucocorticoid use, use of ionizing radiation, relative limited availability and higher cost compared to other imaging methods.¹²⁻¹⁶

A recent systematic review and meta-analysis assessed the diagnostic value of [^{18}F]FDG PET/CT for treatment monitoring in patients with LVV.¹⁷ Twenty-one studies were included in the systematic review and 8 studies were eligible for the meta-analysis on sensitivity and specificity reporting

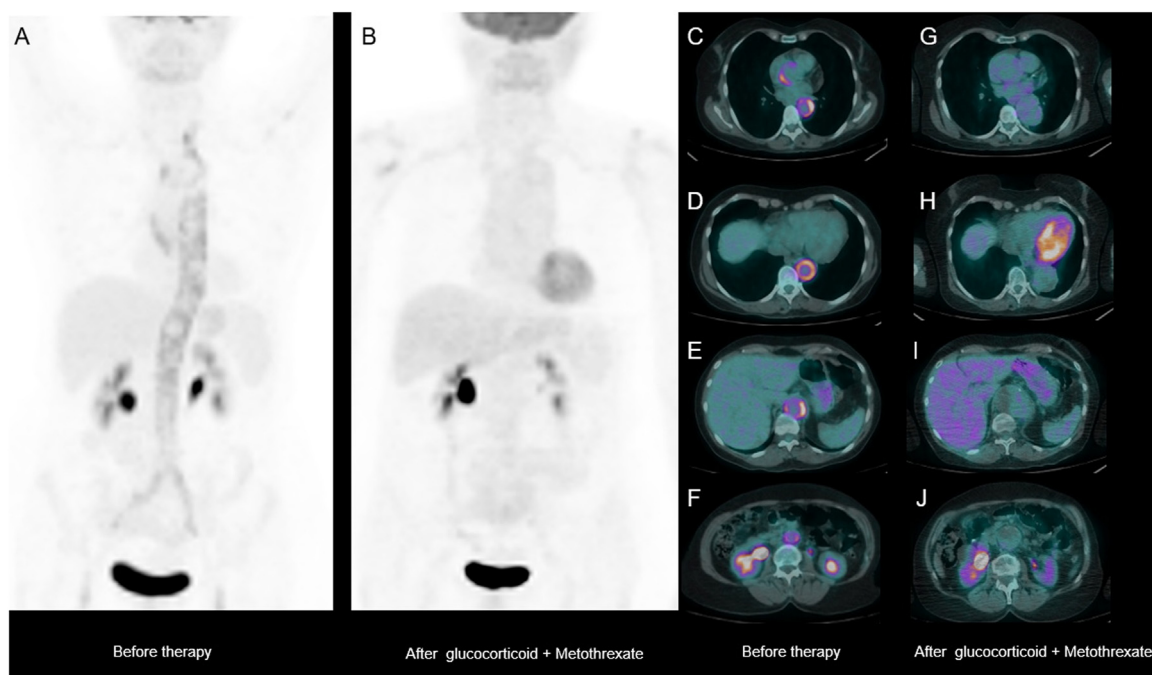


Figure 1 A 64-years-old woman with fever of unknown origin and increased CRP value from several weeks underwent [^{18}F] FDG PET/CT. At MIP (A), PET scan showed a diffuse increased tracer uptake along the descending aorta and iliofemoral arteries indicative of large vessel vasculitis. After therapy (high-dose glucocorticoid and methotrexate), MIP (B) demonstrated a complete metabolic response. Corresponding axial PET/CT fused images before (C-F) and after therapy (G-J) at different thoracic and abdominal aortic level showed with the disappearance of the previous radiopharmaceutical uptakes after treatment.

pooled values and 95% confidence interval (95% CI) values. Arterial wall [^{18}F]FDG uptake decreased upon clinical remission in longitudinal studies meaning that the extent and severity of vascular inflammation on [^{18}F]FDG PET/CT is responsive to therapy. Meta-analysis of cross-sectional studies indicated that [^{18}F]FDG PET/CT may detect relapsing/refractory disease with a sensitivity of 77% (95% CI: 57%-90%) and a specificity of 71% (95% CI: 47%-87%). Substantial heterogeneity was observed among the studies included in this systematic review, mainly due to variation in clinical aspects and imaging procedures among the studies.¹⁷ However, the findings provided by this evidence-based article suggested that [^{18}F]FDG PET/CT may aid in the assessment of disease activity in patients with LVV. In general, [^{18}F]FDG uptake decreases during clinical remission, but it remains unclear to what extent the arterial wall [^{18}F]FDG uptake normalizes. Although arterial [^{18}F]FDG uptake indicates vascular inflammation in LVV, it is possible that ongoing arterial [^{18}F]FDG uptake during treatment reflects vascular remodeling/healing in some patients.¹⁸ [^{18}F]FDG PET/CT has moderate accuracy to distinguish active disease from remission in LVV patients on treatment. Therefore, [^{18}F]FDG PET/CT findings should be interpreted in the context of clinical and biochemical findings.¹⁷ This evidence-based article also highlights the relevance of procedural recommendations for [^{18}F]FDG-PET/CT in LVV.⁹

Lack of a perfect reference standard for assessing disease activity in LVV remains a challenge. In addition, assessment of disease activity evaluated by the presence or absence of clinical

manifestations due to LVV is affected by the limitation that most symptoms in LVV are not specific and constitutional. This is exactly why imaging tools are increasingly applied for treatment response monitoring of LVV beyond clinical assessment. The poor relationship between [^{18}F]FDG PET/CT findings and the clinical evaluation should not be considered as evidence against the use of [^{18}F]FDG PET/CT in the monitoring of LVV or against the use of clinical evaluation. Conversely, the main role of [^{18}F]FDG PET/CT should be to complement, rather than replace, the clinical assessment for treatment response assessment in patients with LVV.¹⁸

The timing of baseline [^{18}F]FDG PET/CT scan is also crucial. It should be considered that arterial radiotracer uptake might be influenced by treatment, in particular, arterial [^{18}F]FDG uptake in LVV can be reduced after 3 days of glucocorticoid intake. Therefore, to adequately assess treatment response, the baseline [^{18}F]FDG PET/CT scan should not have been performed in patients under glucocorticoid therapy.¹⁸ On the other hand, the optimal timing for follow-up [^{18}F]FDG PET/CT scan in patients with LVV has yet to be determined.¹⁸

New developments in PET/CT camera systems, such as total body or digital systems, may further enhance the spatial resolution of PET/CT with a better target-to-background ratio. These new camera systems can also visualize abnormal [^{18}F]FDG uptake in medium-sized arteries and the smaller cranial vessels.¹⁸

Emerging PET radiotracers could potentially be more accurate than [^{18}F]FDG for the treatment monitoring of

patients with LVV. These specific tracers may provide lower background radioactivity and higher diagnostic accuracy, improving the ability to assess treatment effectiveness. Recent advances in specific tissue infiltrating leukocyte and stromal cell profiles in LVV may be exploited as a source of novel targets for PET imaging.¹⁹⁻²¹

Overall, despite the potential limitations described above, ^{18}F FDG PET/CT may be helpful to monitor treatment in LVV. Given the costs and radiation exposure, follow-up ^{18}F FDG PET/CT should not be performed routinely, but might be reserved for patients in which the disease activity remains uncertain despite thorough clinical evaluation.¹⁸ Further well-designed prospective research studies about the value of ^{18}F FDG PET/CT for treatment monitoring of LVV are warranted.

^{18}F FDG PET/CT for Treatment Response Assessment in Vascular Graft Infection

Vascular graft infection (VGI) is a serious complication characterized by a high morbidity and mortality rate. The diagnosis is challenging due to non-specific symptoms and the variable diagnostic accuracy of different imaging techniques.^{22,23}

Current guidelines indicate that for patients with a clinical suspicion of VGI and with non-convincing findings on CT-angiography, the use of ^{18}F FDG is recommended as an additional imaging modality to improve diagnostic accuracy, in particular in the late post-surgical phase, when the sterile

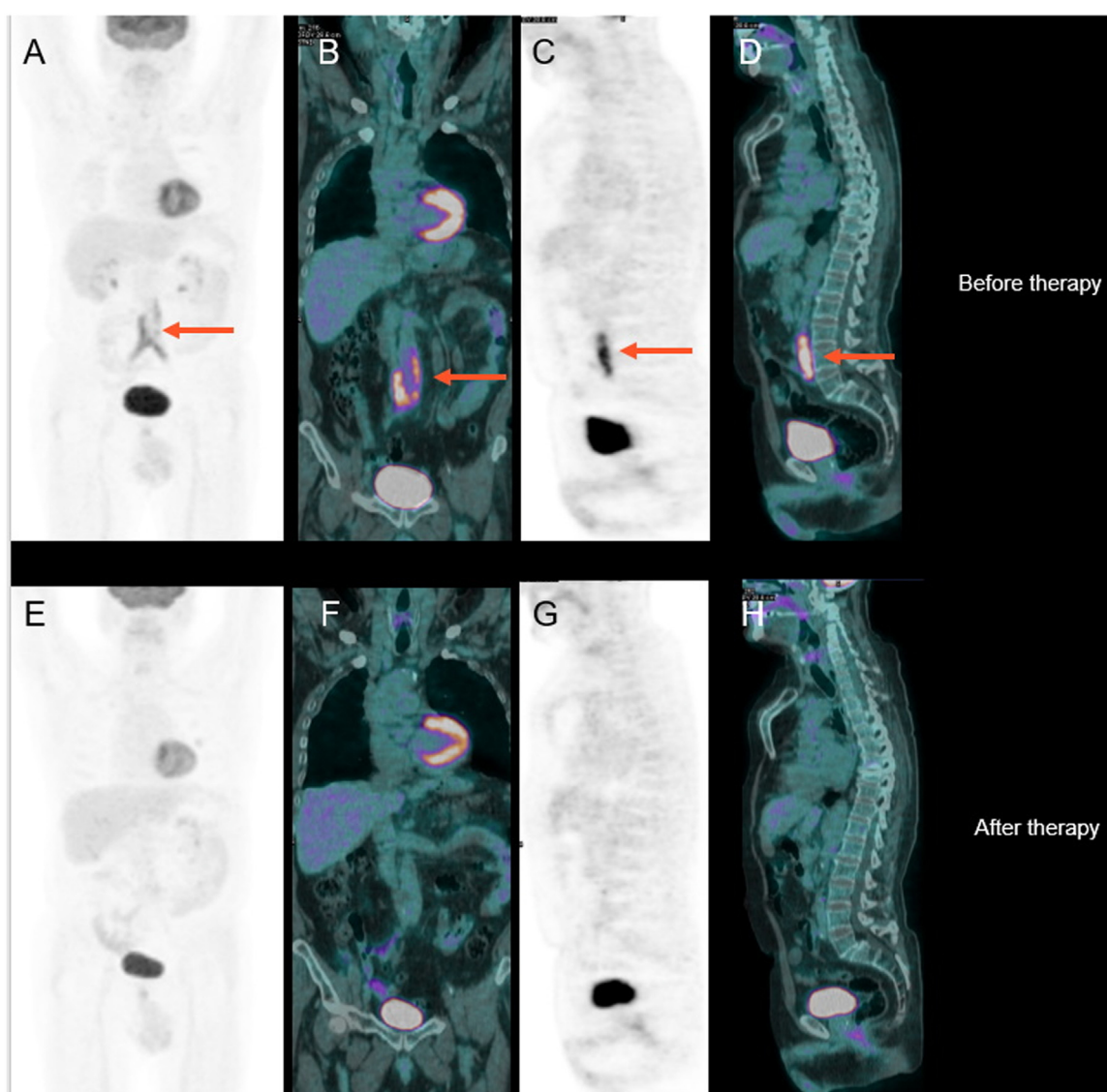


Figure 2 A case of a 71-years-old man with a localized vasculitis affecting sub-renal abdominal aorta and iliac arteries (red arrows) detected by ^{18}F FDG PET/CT before any treatment. Coronal PET (A), PET/CT fused images (B), sagittal PET (C) and PET/CT fused images (D) detected increased tracer uptake corresponding to the walls of sub-renal abdominal aorta and common iliac arteries. Four months after glucocorticoids, coronal PET (E), PET/CT fused images (F), sagittal PET (G) and PET/CT fused images (H) showed the disappearance of radiopharmaceutical uptake in the aorta and iliac arteries demonstrating excellent metabolic response to treatment.

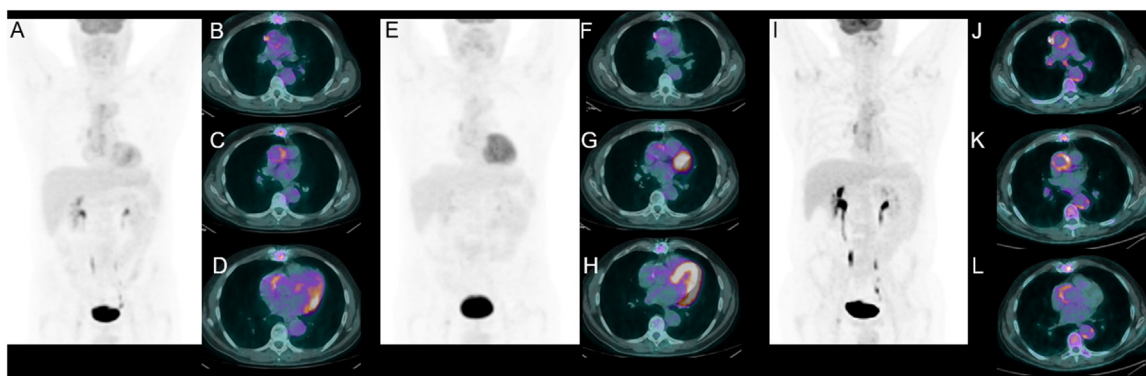


Figure 3 A 56-years-old man recently subjected to the replacement of ascending aorta with a vascular graft underwent a [^{18}F]FDG PET/CT for the suspicion of vascular graft infection. PET/CT showed the presence of increased [^{18}F]FDG uptake along the vascular graft (A-D) suggesting a vascular graft infection. The patient started antibiotic therapy with a combination of Meropenem, Daptomycin and Rifampicin. After 3 months, [^{18}F]FDG PET/CT demonstrated a significant metabolic response (E) with the reduction (F,G) or disappearance (H) of previous uptakes. Five months after baseline first PET/CT, the patient developed fever and CRP rise and a new [^{18}F]FDG PET/CT showed the relapse of vascular graft infection (I) involving all the course of ascending aorta (J-L).

inflammation (causing non-specific [^{18}F]FDG vascular uptake) decreases.^{22,23}

The main advantage of [^{18}F]FDG PET/CT in evaluating VGI is its high sensitivity as demonstrated by several meta-analyses; conversely, its moderate specificity, the high false positive rate in early phases after surgery (<4 months), the lack of standardized interpretation criteria and the moderate radiation exposure are its main drawbacks.²³

Due to its high negative predictive value in the setting of VGI, [^{18}F]FDG PET/CT can be used to rule out the presence of an infection regardless of the interpretation criteria used.²³ However, the interpretation criteria used may influence the diagnostic performance of [^{18}F]FDG PET/CT in patients with suspected VGI.^{24,25} Among the several qualitative and semi-quantitative interpretation criteria for [^{18}F]FDG PET/CT, focal [^{18}F]FDG uptake is considered a reliable tool for differentiating infection from a sterile post-surgical inflammation or foreign body reaction in patients with a suspected VGI.²³ According to a recent meta-analysis, the pattern of radio-tracer uptake in suspected VGI showed the highest pooled sensitivity and specificity compared to the [^{18}F]FDG uptake intensity and SUV_{max} methods.²⁵

Antibiotic therapy may affect the diagnostic accuracy of [^{18}F]FDG PET/CT in detecting VGI.²³ Once antibiotic treatment has started, a declining metabolic activity in VGI is expected. This might affect the sensitivity of [^{18}F]FDG PET/CT, and long-term antibiotic treatment could increase the number of false negative findings for VGI at both [^{18}F]FDG PET/CT and microbiology, thus resulting in inadequate treatment of infected patients. However, the influence of antibiotics and treatment duration on the number of false negative results for VGI at [^{18}F]FDG PET/CT remains under investigation.²³

Interestingly, some studies suggested a potential role of [^{18}F]FDG PET/CT in monitoring treatment response in patients with VGI (Fig. 3).^{23,26-28} In particular, a prospective study demonstrated a decrease in SUV_{max} values over time in patients with VGI undergoing antibiotic therapy and that the capability to detect residual infection by [^{18}F]FDG PET/CT

was not hampered by antimicrobial therapy. Higher C-reactive protein (CRP) was associated with higher SUV_{max} . CRP, metabolic and clinical findings informed the decision to either start, escalate, continue, or stop antibiotic treatment. Notably, decisions to escalate or continue antibiotic treatment were taken despite normal CRP values in a significant percentage of PET/CT scans.²⁷ Even if consecutive [^{18}F]FDG PET/CT could influence the clinical decision-making in patients with VGI, more high-quality studies are needed to further investigate this topic. Currently, the role of [^{18}F]FDG PET/CT in assessing treatment response in patients with VGI remains uncertain.

[^{18}F]FDG PET/CT for Treatment Response Assessment in Retroperitoneal Fibrosis/Chronic Periaortitis

Retroperitoneal fibrosis (RPF) is a rare disease characterized by the presence of inflammatory and fibrous retroperitoneal tissue that often encircles abdominal organs including the aorta and ureters. RPF may be idiopathic or secondary to infections, malignancies, drugs, or radiotherapy. The idiopathic form is an immune-mediated entity and a part of the broader spectrum of idiopathic diseases termed chronic periaortitis, characterized by fibro-inflammatory changes in the aorta and surrounding tissues.^{29,30}

Recently, the role of [^{18}F]FDG PET/CT, evaluating both morphological changes and inflammatory activity, is emphasized in the diagnosis and in the evaluation of disease activity as well as in the assessment of treatment response in patients with RPF (Fig. 4). Additionally, [^{18}F]FDG PET/CT may be a relevant and noninvasive tool to differentiate between idiopathic RPF and malignancy, as well as to guide biopsy sites.³⁰⁻³⁵

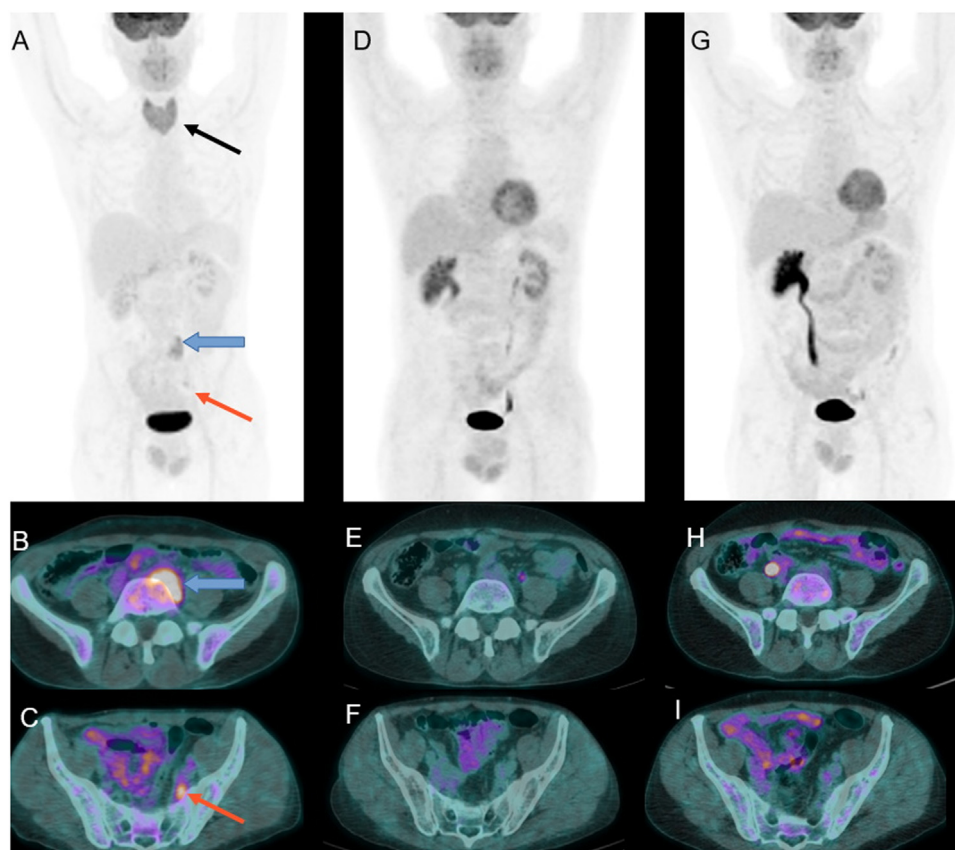


Figure 4 A 55-years-old man with a diagnosis of thyroiditis and concomitant fibrotic tissues in the retroperitoneum underwent [^{18}F]FDG PET/CT (A) that revealed a diffuse increased thyroid uptake (black arrow) and focal uptakes corresponding to retroperitoneal fibrotic tissue near to the left fourth and fifth lumbar vertebra (blue arrow) (B) and behind the left internal iliac artery (red arrow) (C). The final diagnosis was idiopathic retroperitoneal fibrosis. Subsequent [^{18}F]FDG PET/CT scan after 3 months of glucocorticoids showed a complete disappearance of [^{18}F]FDG uptakes (D-F). After 1 year, follow-up [^{18}F]FDG PET/CT (G-I) confirmed the absence of metabolically active disease.

Since [^{18}F]FDG PET/CT appears to be a better test for detecting inflammatory activity than conventional serum biomarkers, it is considered suitable for controlling treatment efficacy and risk of disease recurrence in RPF.³⁰⁻³⁶ [^{18}F]FDG PET/CT should be considered as an additional or primary imaging modality in RPF since hybrid imaging can evaluate both morphological changes and a decrease in inflammatory activity based on the reduced radiotracer uptake. Therefore, it is highly suited for the quantification and prediction of treatment response, allowing drug therapy adjustments.³⁰⁻³⁵

[^{18}F]FDG PET/CT for Treatment Response Assessment in Infective Native Aortic Aneurysms

Infectious aortitis is a rare and life-threatening cardiovascular disease. Early diagnosis and timely intervention are crucial for reducing mortality associated with infective native aortic aneurysms (INAA), also known as mycotic aortic aneurysms. However, early diagnosis is challenging due to the non-specific symptoms.³⁷ CT, MRI, and [^{18}F]FDG PET/CT are the

most commonly used imaging modalities for the detection and assessment of clinically suspected INAA. [^{18}F]FDG PET/CT is the most sensitive technique for detecting infection, which is depicted by increased [^{18}F]FDG uptake due to enhanced glucose metabolism in the INAA.³⁷⁻⁴⁰ Furthermore, [^{18}F]FDG PET/CT may detect other sites of infection that are usually associated with INAA (such as iliopsoas abscess or spondylitis), and inflammatory lesions in the para-aortic tissues (including hypermetabolic lymph nodes).³⁷⁻⁴⁰

[^{18}F]FDG PET/CT could also be used to monitor the response to antibiotic treatment in INAA (Fig. 5).³⁸ A recent study performing baseline and follow-up [^{18}F]FDG PET/CT scans in patients with INAA showed a decrease in metabolic activity of the infected aneurysms (as measured by SUV_{max}) between baseline and follow-up PET/CT scans performed prior to the end and after the end of treatment.³⁸ Compared to the course of CRP, [^{18}F]FDG PET/CT provided different information on the course of disease in a significant percentage of patients with INAA, occasionally altering the therapy control of INAA. Notably, metabolic activity in the aneurysms remains slightly elevated even after the end of antimicrobial therapy and should not be mistaken for persistent infection.³⁸

Overall, even if there might be a role for [^{18}F]FDG PET/CT in the management of INAA, in particular for patients with

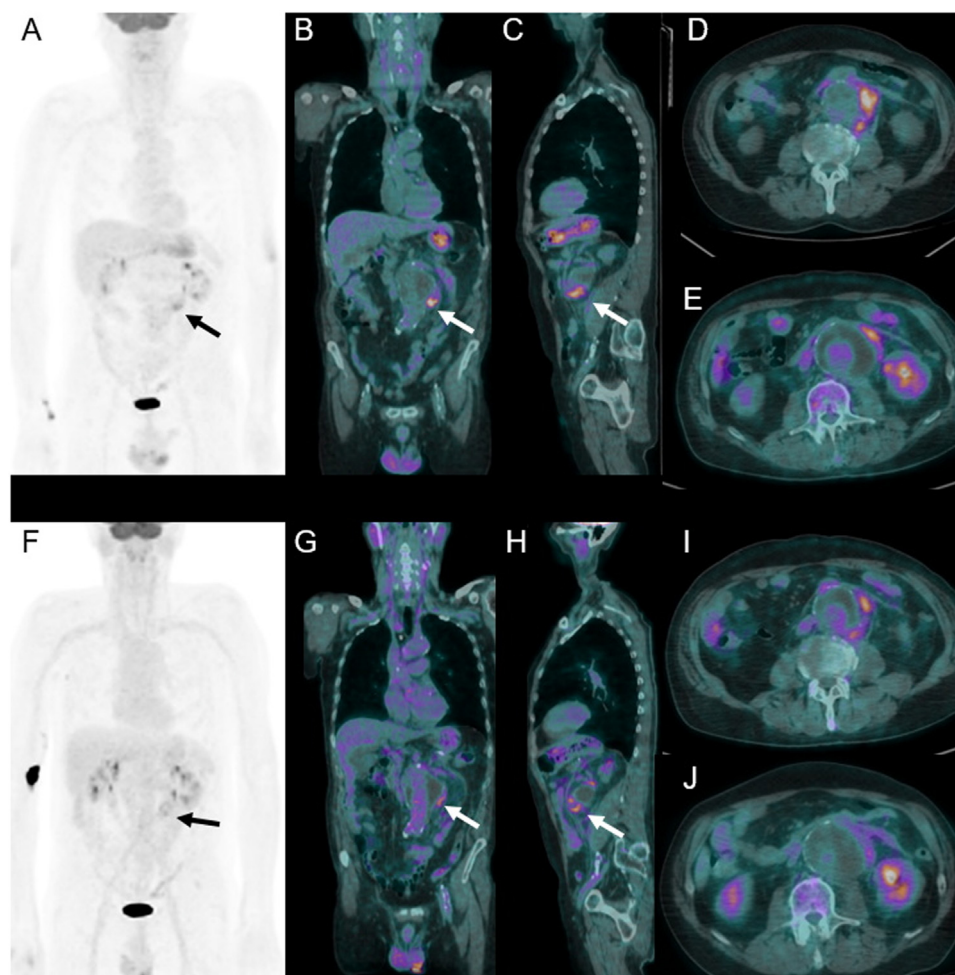


Figure 5 A 60-years-old man presented with fever of unknown origin and signs for infection (CRP: 111 mg/L). A baseline [^{18}F]FDG PET/CT (A) showed strongly increased [^{18}F]FDG uptake in the wall of abdominal aorta (black arrow). Coronal (B), sagittal (C) and axial PET/CT (D,E) fused images confirmed this increased uptake at sub-renal abdominal aortic aneurysm diagnosed as infective native aortic aneurysm (blood cultures positive for *Streptococcus agalactiae*). After 3 months of antimicrobial therapy, [^{18}F]FDG PET/CT (F) demonstrated a reduced but residual focal uptake at coronal (G), sagittal (H) and axial (I,J) views with persistence of fever and positive CRP level (23 mg/L). Then, the patient underwent abdominal endovascular repair.

clinical suspicion of INAA without convincing findings on CT or for assessing response to treatment, the literature on [^{18}F]FDG PET/CT in this setting is still very scarce and definitive conclusions on its usefulness are premature.³⁸

Conclusions

Currently, there is a lack of guidelines and established criteria for monitoring response to treatment with [^{18}F]FDG PET/CT in infectious/inflammatory diseases of large vessels; however, rapidly accumulating data provide preliminary evidence that [^{18}F]FDG PET/CT could be a promising valuable imaging method for therapy monitoring in some infectious and inflammatory diseases of large vessels.

The available data indicate that [^{18}F]FDG PET/CT could even play a pivotal role in the management of these diseases, leading to better drug dosage, confirmation of the usefulness of the treatment, and early modification of the therapeutic strategy.

Further well-designed prospective studies are needed to confirm the possible role of [^{18}F]FDG PET/CT for treatment response assessment and treatment guidance in large vessel diseases.

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