

# <sup>18</sup>F-FDG PET/CT for the Diagnosis of Malignant and Infectious Complications After Solid Organ Transplantation

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## Abstract

**Purpose** Infection and malignancy represent two common complications after solid organ transplantation, which are often characterized by poorly specific clinical symptomatology. Herein, we have evaluated the role of <sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) in this clinical setting.

**Methods** Fifty-eight consecutive patients who underwent FDG PET/CT after kidney, lung or heart transplantation were included in this retrospective analysis. Twelve patients underwent FDG PET/CT to strengthen or confirm a diagnostic suspicion of malignancies. The remaining 46 patients

presented with unexplained inflammatory syndrome, fever of unknown origin (FUO), CMV or EBV seroconversion during post-transplant follow-up without conclusive conventional imaging. FDG PET/CT results were compared to histology or to the finding obtained during a clinical/imaging follow-up period of at least 6 months after PET/CT study.

**Results** Positive FDG PET/CT results were obtained in 18 (31 %) patients. In the remaining 40 (69 %) cases, FDG PET/CT was negative, showing exclusively a physiological radiotracer distribution. On the basis of a patient-based analysis, FDG PET/CT's sensitivity, specificity, PPV and NPV were respectively 78 %, 90 %, 78 % and 90 %, with a global accuracy of 86 %. FDG PET/CT was true positive in 14 patients with bacterial pneumonias (n = 4), pulmonary fungal infection (n = 1), histoplasmosis (n = 1), cutaneous abscess (n = 1), inflammatory disorder (sacroiliitis) (n = 1), lymphoma (n = 3) and NSCLC (n = 3). On the other hand, FDG PET/CT failed to detect lung bronchoalveolar adenocarcinoma, septicemia, endocarditis and graft-versus-host disease (GVHD), respectively, in four patients. FDG PET/CT contributed to adjusting the patient therapeutic strategy in 40 % of cases.

**Conclusions** FDG PET/CT emerges as a valuable technique to manage complications in the post-transplantation period. FDG PET/CT should be considered in patients with severe unexplained inflammatory syndrome or FUO and inconclusive conventional imaging or to discriminate active from silent lesions previously detected by conventional imaging particularly when malignancy is suspected.

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**Keywords** FDG · PET · Organ transplantation · Post-transplant lymphoproliferative disorders · Post-transplant complication · Infection

## Introduction

Solid organ transplantation represents a valuable therapeutic option for patients with end-stage organ dysfunction related to chronic diseases such as chronic respiratory failure due to cystic fibrosis, chronic obstructive pulmonary disease, chronic kidney diseases or heart failure [1]. Both infectious diseases and malignancies represent two groups of common complications in the post-transplant period. These complications are often characterized by poorly specific clinical symptoms particularly in early stages [2, 3].

The long-term follow-up of patients with solid organ transplantation is challenging including standard clinical and biological examinations, the assessment of organ function, infectious status and monitoring of immunosuppressive drugs. Moreover, when a specific complication is suspected, more investigations are required including further biological analysis and diagnostic imaging examinations. Unfortunately, both biological tests and imaging techniques are often poorly sensitive and not specific in transplant patients. Finally, biopsy represents a diagnostic alternative, but it is not free of further complications [4–8].

<sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is a noninvasive imaging tool with high diagnostic accuracy and therapeutic impact in oncological clinical practice [9, 10]. FDG PET provides the *in vivo* estimation of pathologically increased glycolytic activity. Thereafter, the latest generation of high-resolution PET scanners is coupled with multidetector CT (PET/CT), allowing a simultaneous co-registration of morphological and functional data [11]. Activated inflammatory cells such as neutrophils, macrophages and lymphocytes present an increased FDG uptake, causing significant FDG accumulation during inflammation [12, 13]. Hence, the slight specificity of FDG PET/CT emerges as a potential advantage in the management of patients with inflammatory or infectious diseases [14]. Moreover, FDG PET/CT seems to be useful in the setting of unexplained inflammatory syndrome and fever of unknown origin (FUO) in both the overall population [15–18] and immunosuppressed patients [19, 20]. Finally, FDG PET/CT plays a role in assessing treatment efficacy in neoplastic [21] and selected non-neoplastic conditions [22, 23], leading to the detection of residual tumoral or inflammatory localizations. Accordingly, FDG PET/CT may represent an interesting technique in the post-transplantation follow-up in patients with inflammatory syndrome of unknown origin and unspecific clinical symptomatology [2, 24–27].

In real-life practice, FDG PET/CT often represents a second-line diagnostic investigation in patients with negative or inconclusive conventional radiologic examinations. This diagnostic condition may be explained by the necessity to obtain a definitive and prompt diagnosis in this particular high-risk patient population as well as by the more important

availability of conventional radiography and CT devices. Therefore, patients often undergo FDG PET/CT after other diagnostic procedures, without a structured protocol or diagnostic hypothesis and, at worst, after the beginning of an empiric treatment. Accordingly, the main objective of this retrospective single-center study was to evaluate the diagnostic role and therapeutic impact of FDG PET/CT in daily clinical practice in a cohort of patients with suspicion of malignant or infectious complications after renal, lung or heart transplantation.

## Materials and Methods

### Patient Population

Fifty-eight consecutive patients with suspicion of a complication after renal, lung or heart transplantation and presenting to our institution between August 2004 and September 2012 for FDG PET/CT were retrospectively included in this study. Patient mean age at the time of PET/CT was  $48 \pm 2$  years ranging from 21 to 80 years. Patients underwent a standard evaluation including: (1) history and physical examination, (2) standard biological tests comprising the measurement of C-reactive protein (CRP), fibrinogen, hepatic transaminases, lactate dehydrogenase (LDH) and leucocyte count, (3) Epstein-Barr virus (EBV) and cytomegalovirus (CMV) DNA PCR quantification and (4) radiological evaluation including standard radiography and/or high-resolution chest and/or abdominopelvic CT and/or magnetic resonance imaging (MRI) and/or ultrasonography (US). Suspicion of a post-transplant complication was based on a variable combination of clinical symptoms (32 patients), biological test results (27 patients) and radiological abnormalities (14 patients). Follow-up data were obtained until final diagnosis or when the diagnosis of a post-transplant complication was discarded after a spontaneous regression of clinical symptomatology and/or normalization of biological tests without specific medical treatment within 6-month follow-up. Besides neoplastic suspicion, carrying out FDG PET/CT was justified by a cross-disciplinary discussion between an organ transplant specialist and nuclear medicine physician.

### Patient Clinical Assessment

The selected patients had previously undergone lung (15 patients), kidney (30 patients) or heart transplantation (13 patients). Table 1 details the patient clinical situation requiring transplantation. A post-transplant complication was suspected about  $61 \pm 3$  months after organ transplantation, ranging from 11 days to 21 years. Eighteen patients (30 %) had a history of pre-transplant malignant tumors including three cases of Hodgkin lymphoma (HL), seven cases of non-Hodgkin

**Table 1** Pathological condition requiring solid organ transplantation in the studied cohort

Organ	Pathology	No. of patients
Kidney	Glomerular nephropathy	19
	Vascular nephropathy	2
	Tubulointerstitial nephropathy	6
	Calcineurin inhibitor toxicity	1
	Polycystic kidney disease	2
Lung	Cystic fibrosis	4
	Chronic obstructive pulmonary disease	6
	Emphysema	3
	Idiopathic pulmonary fibrosis	1
	Eisenmenger's syndrome	1
Heart	Ischemic cardiomyopathy	5
	Non-obstructive cardiomyopathy	2
	Valvular cardiomyopathy	2
	Restrictive cardiomyopathy	1
	Toxic cardiomyopathy	2
	Cardiac rhabdomyosarcoma	1

lymphoma (NHL), two cases of basal-cell carcinoma, one case of leukemia, one case of rhabdomyosarcoma, one case of Kaposi's sarcoma, one case of squamous cell carcinoma, one case of prostate carcinoma and one case of in situ uterine cervical adenocarcinoma. CRP, leucocyte count, LDH and gamma glutamyl transferase (GGT) were abnormally increased in 60 %, 3 %, 48 % and 28 %, respectively, and 7 % of patients had fever.

Twelve patients underwent FDG PET/CT to strengthen or confirm a diagnostic suspicion of malignancies (3 lymphomas, 1 adrenal mass of unknown etiology and 8 lung cancers) on conventional imaging. The remaining 46 patients presented with (1) unexplained inflammatory syndrome and FUI, defined as persistent fever up to 38.5 °C without any diagnosis reached from the usual investigations, or (2) CMV or EBV seroconversion during the post-transplant follow-up period. In these 46 patients, conventional imaging was not conclusive.

At the time of FDG PET/CT, all patients were treated in accordance with the international guidelines [28] with a variable combination of tacrolimus (20 patients), mycophenolate mofetil (34 patients) or mycophenolate sodium (3 patients), corticosteroids (40 patients), cyclosporine (16 patients), azathioprine (5 patients) and everolimus (17 patients).

### FDG PET-CT Technical Features and Interpretation Criteria

A combined FDG PET/CT scanner was employed for all patients (Discovery ST, GE Medical System, Milwaukee, WI, USA). In order to obtain a serum glucose level less than 6.6 mmol/l, patients fasted for 6 h before intravenous injection

of 5.5 MBq/kg FDG (Flucis, CIS Bio International, France). Five milligrams of diazepam and 80 mg of phloroglucinol (musculotropic antispasmodic) had been previously administered to patients. Whole-body (WB) PET/CT acquisitions started about 60 min after tracer injection, including a head to midhigh CT scan (140 kV, 80 mAs, 0.8 s/rotation) during current breathing, followed by a PET scan (7 fields of view, 15 cm/field, 4 min/field, 3.27 mm slice thickness). In selected patients, PET acquisitions (6–7 fields of view, 3 min/field) and low-dose CT were performed on the lower limbs. PET data were reconstructed with and without CT-based attenuation correction by iterative algorithm [ordered subset expectation maximization (OSEM), 2 iterations, 15 subsets, 128 × 128 matrix]. CT, PET (corrected) and combined PET/CT images were displayed on a Xeleris workstation (GE Medical System, Milwaukee, WI, USA) for visual interpretation. The maximum standardized uptake value (mSUV) per focus was employed for semiquantitative analysis of FDG uptake. FDG PET/CT data analysis of all patients was done by an experienced nuclear medicine physician, who was aware of the clinical situation and pathological background and had access to patients' biological results. Each focus of increased extra-physiologic uptake of FDG was recorded and interpreted according to each patient's situation. The original FDG PET/CT report was considered for the analysis of each examination result.

FDG was used following marketing authorization. Conforming to local institutional guidelines, all included patients gave free and informed consent for the use of anonymous personal medical data extracted from their file for scientific purposes. The Local Institutional Review Board approved this retrospective study.

### Data Analysis

In the present study, FDG PET/CT results were compared to histology after biopsy or more complex surgical procedures (when available) or to clinical follow-up (after FDG PET/CT study) within 6 months including a variable combination of physical examination, biological tests, conventional imaging (CT, MRI, US) and virologic, bacteriologic and mycologic investigations.

The FDG PET/CT was considered contributory to modifying the diagnostic workup and therapeutic strategy when it allowed any of the following: (1) identification of the presence and site of infection or malignancy (other conventional tests performed at the time of FDG PET/CT imaging were negative and/or noncontributory); (2) elimination of the radiological hypothesis of malignancy; (3) determination of the extent of the infection or malignancy in a specific organ or the involvement of other organs; (4) targeting the diagnostic procedure; (5) removing the infection site; (6) changing the duration of antibiotic therapy.

## Statistical Analysis

Results are expressed as mean  $\pm$  SD, range and percentage. Diagnostic performances of FDG PET/CT were evaluated according to a patient-based analysis. FDG PET/CT studies were interpreted as:

- True positive (TP) when positive FDG PET/CT findings were confirmed by histology or clinical/imaging follow-up;
- True negative (TN) when FDG PET/CT was interpreted as normal and the diagnosis of post-transplant complication was finally discarded;
- False positive (FP) when FDG PET/CT findings were not finally confirmed by complementary investigations;
- False negative (FN) when FDG PET/CT failed to detect the post-transplant complication diagnosed by complementary investigation.

From the TP, FP, TN and FN results, FDG PET/CT's sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were determined. Finally, the Youden Index, which is independent from the prevalence of the disease, was estimated as  $(Sp + Se) - 1$ . A  $p$  value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using SPSS 17.0 software.

## Results

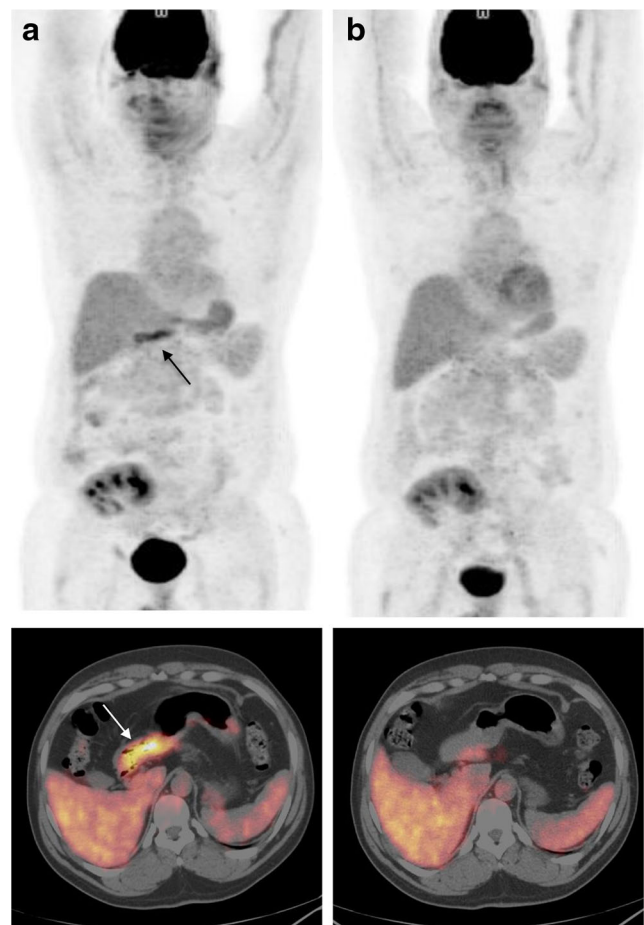
A post-transplant complication was finally diagnosed in 18 (31 %) patients, corresponding to 7 deep infections, 1 septicemia of unknown origin, 1 endocarditis, 1 inflammatory disorder, 1 GVHD, 3 aggressive lymphomas and 4 lung cancers.

### Overall FDG PET/CT Results

Analysis was performed to evaluate FDG PET/CT as a tool for the detection of both infectious and neoplastic post-transplant complications. Positive FDG PET/CT results were obtained in 18 patients. In the remaining 40 cases (69 %), FDG PET/CT was negative, showing exclusively a physiological radiotracer distribution.

Among the 18 patients (31 %) with positive FDG PET/CT:

- Fourteen patients were TP: seven deep infections [four bacterial pneumonias, one pulmonary fungal infection, one histoplasmosis (Fig. 1), one cutaneous abscess (Fig. 2)], 1 inflammatory disorder (sacroiliitis), 2 large B cell lymphomas (LBCLs) of stage II and IV, one Hodgkin lymphoma (stage I) and three NSCLCs presented with solitary, small and irregularly shaped nodules



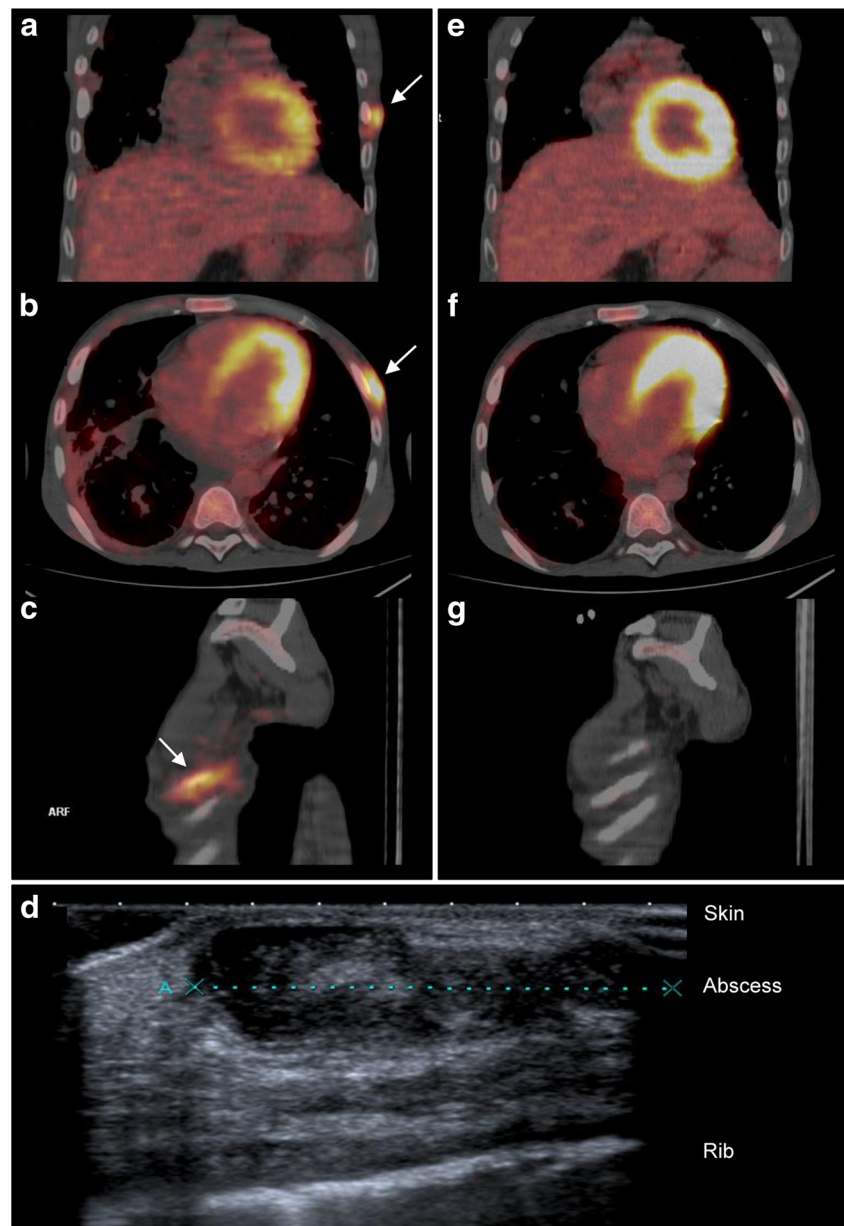
**Fig. 1** Anterior view of FDG PET whole-body maximum intensity projection (MIP) image (upper panel) and axial FDG PET/CT slice (lower panel) in a 56-year-old male with inflammatory syndrome and a history of kidney transplantation. FDG PET/CT showed pathological uptake in the pyloric region. **a** Further investigations following FDG PET/CT investigations allowed the diagnosis of gastric histoplasmosis. After 2 years of itraconazole treatment, FDG PET/CT showed the complete regression of FDG uptake abnormalities (**b**) allowing the withdrawal of the antifungal treatment

sometimes associated with emphysematous parenchymal dystrophy.

- Four patients were FP: (1) a kidney-transplanted patient with fever and inflammatory syndrome spontaneously improving during follow-up showed a mild increase of FDG uptake in the hepatic hilum lymph nodes; (2) a kidney-transplanted patient with previous EBV-induced bowel lymphoma and a high serum LDH value presented with increased FDG uptake in the cecum and terminal bowel suggesting tumoral relapse. Histological examination after surgical biopsy showed benign inflammatory granulomas (Fig. 3); (3) a kidney-transplanted patient with unexplained inflammatory syndrome showing a focally increased FDG uptake in the lower esophagus suggesting a primary tumor, with endoscopic biopsy evaluation showing grade C reflux esophagitis; (4) a heart-transplanted patient with radiological suspicion of primary lung cancer



**Fig. 2** **a** Coronal, **b** axial and **c** sagittal FDG PET/CT images in a 27-year-old lung-transplanted male with inflammatory syndrome showing intense focal uptake in the left thoracic wall. The following ultrasound examination revealed a 35 × 15-mm abscess in the subcutaneous tissue, around the fifth rib, at the periphery of the surgical scar (**d**). Note the complete regression of tracer uptake abnormalities after surgical treatment **e–g**



because of a mildly hypermetabolic nodule that remained stable in size during a 3-year follow-up.

The intensity of FDG uptake (as measured by mSUV) for the 18 patients with positive FDG PET/CT results was on average 8.2 (ranging from 3.2 to 22.5) (Table 2). There was no statistically significant difference between malignancies and infectious diseases in terms of mSUV.

Among the 40 patients (69 %) with negative FDG PET/CT:

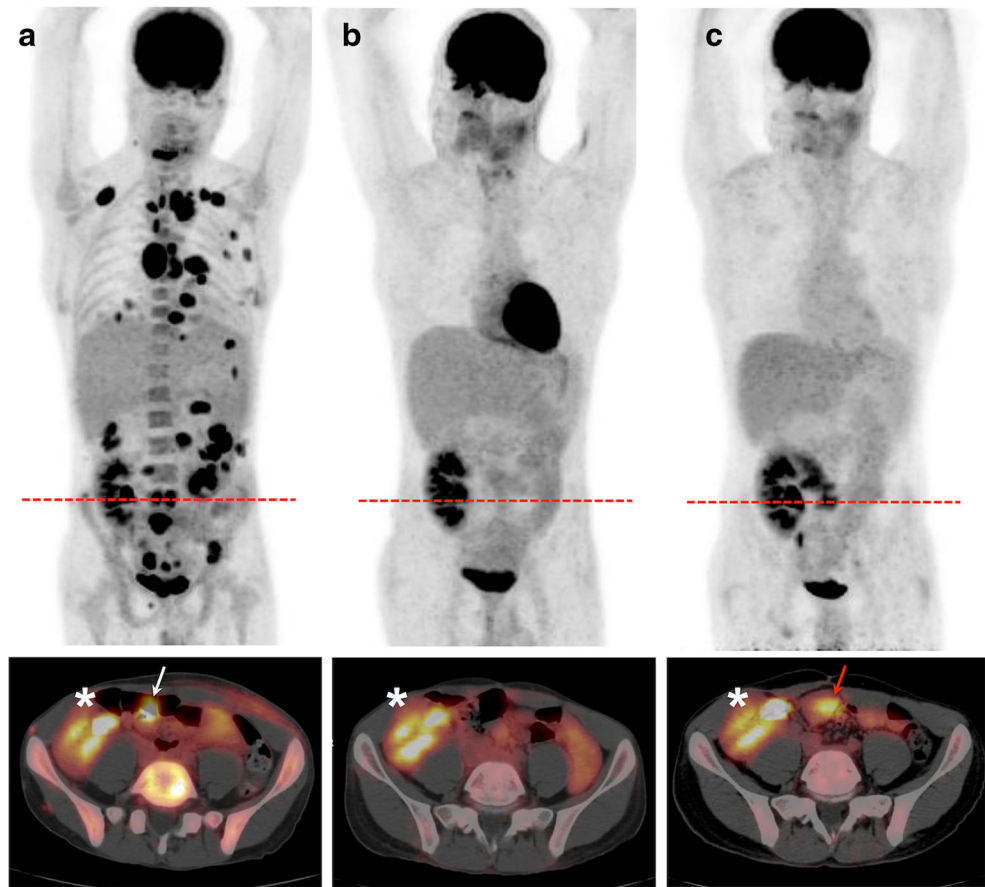
- Thirty-six patients were TN. A definitive negative diagnosis of post-transplantation complication was retained after a spontaneous regression of clinical symptomatology and/or normalization of biological tests without specific

medical treatment within the 6-month follow-up. Moreover, in three patients, FDG PET/CT showed functional thyroid nodules and post-traumatic hypermetabolic bone fractures. In one additional patient, stage II sarcoidosis was suggested and afterwards confirmed by pathological examination.

- Four patients were FN: one with histologically proven lung bronchoalveolar adenocarcinoma (mSUV: 1.4) and three with septicemia of unknown origin with proved endocarditis and GVHD, respectively, showing no FDG uptake abnormalities.

Based on our patient-based analysis, FDG PET/CT's sensitivity, specificity, PPV and NPV were respectively 78 %, 78 %, 78 %, and 78 %.

**Fig. 3** Anterior view of FDG PET whole-body maximum intensity projection (MIP) and axial FDG PET/CT image in a kidney-transplanted (\*) 27-year-old male with a history of digestive non-Hodgkin lymphoma (white arrow; **a**) considered in complete metabolic remission at the end of chemotherapy (**b**). Because an increased serum LDH value and general weakness appeared during follow-up, the patient underwent FDG PET/CT, which showed intense FDG uptake in the right colon and distal ileum (red arrow; **c**) suggesting disease relapse. The pathological examination after surgical biopsy revealed benign granuloma without tumoral relapse



90 %, 78 % and 90 %, with a global accuracy of 86 %. The Youden Index was estimated to be 0.68. Clinical presentation and the biological characteristics of 18 patients with true-positive and false-negative FDG PET/CT results are summarized in Table 3.

### Impact of FDG PET/CT on the Diagnostic Workup and Therapeutic Strategy

Among the 12 patients with radiological suspicion of malignancies, FDG PET/CT allowed eliminating the hypothesis of malignancy in seven patients and strengthening the diagnosis in three other patients (1 LH, 2 NSCLC) with previous history of lung (n = 2) and kidney (n = 1) transplantation. In the remaining two patients, FDG PET/CT was false negative [i.e., histologically proven lung bronchoalveolar adenocarcinoma (mSUV: 1.4)] and false positive [i.e., a lung hypermetabolic nodule suspected of neoplasia (mSUV: 9.1)], but stable in size during a 3-year follow-up) without inducing a modification of patient management.

Among the remaining 46 patients with clinical and/or biological abnormalities and inconclusive conventional imaging, the FDG PET/CT contributed to patient management in 13 cases (22 %) by:

- Guiding the diagnostic interventional radiologic procedure in three patients. FDG PET/CT allowed the diagnosis of two LBCLs and one NSCLCs in patients with a previous history of lung (n = 1), heart (n = 1) and kidney (n = 1) transplantation;
- Suggesting deep infectious disease in seven patients allowing the diagnosis of lung aspergillosis (n = 1), gastro-duodenal histoplasmosis (n = 1), bacterial pneumonia (n = 3), cutaneous abscess (n = 1) and sacroiliitis (n = 1).

The TN FDG PET/CT result enabled stopping antifungal treatment for dubious active aspergillosis and diagnosing immunosuppressive treatment intolerance in two patients with a history of cardiac transplantation.

Finally, in one kidney transplant patient with fever and biological inflammatory syndrome, FDG PET/CT exclusively showed some enlarged and hypermetabolic lymph nodes of the mediastinum and both lung hila, suggesting a stage II sarcoidosis, successively confirmed by pathological examination.

Accordingly, FDG PET/CT contributed to adjusting the patient therapeutic approach in 23 cases (40 %). The clinical presentation and therapeutic impact of 23 patients for whom

**Table 2** Clinical presentation of the 18 patients with suspicion of post-transplant complications and positive FDG PET/CT results

No.	Sex	Age	Graft	Patient presentation	Hypermetabolic lesion	Maximum SUV	Final diagnosis	PET results
1	M	27	Kidney	Inflammatory syndrome	Mediastinal lymphadenopathy	17.6	Deep infection	TP
2	F	42	Kidney	Mediastinal mass	Right paratracheal lymphadenopathy	3.2	Lymphoma	TP
3	M	44	Kidney	Esophagitis	Left laterocervical lymphadenopathy	5.4	Lymphoma	TP
4	M	22	Kidney	FUO	Hepatic hilum lymph nodes	4.2	No neoplasia	FP
5	M	24	Kidney	EBV increase	Cecum and terminal bowel	5.2	Benign inflammatory granulomas	FP
6	M	27	Kidney	EBV DNA increase	Left lung area	3.4	Deep infection	TP
7	M	31	Kidney	FUO	Esophagus	6.0	Esophagitis	FP
8	M	52	Kidney	Suspicion of digestive histoplasmosis	Gastroduodenal	6.6	Deep infection	TP
9	M	32	Lung	EBV DNA increase	Left lung nodule	22.5	Lymphoma	TP
10	F	63	Lung	Pulmonary lesion on CT	Right lung nodule	6.1	Lung cancer	TP
11	M	28	Lung	Inflammatory syndrome	Right lung nodule	5.4	Deep infection	TP
12	F	39	Lung	Inflammatory syndrome	Left sacroiliac joint	5.2	Sacroileitis	TP
13	M	53	Lung	Pulmonary lesion on CT	Right lung nodule	9.8	Lung cancer	TP
14	F	58	Lung	Pulmonary lesion on CT	Left lung area	9.5	Deep infection	TP
15	M	68	Heart	FUO	Left lung area	9.5	Deep infection	TP
16	M	65	Heart	Inflammatory syndrome, fever	Right lung nodule	9.8	Lung cancer	TP
17	F	36	Heart	Right arm edema	Right lung nodule	4.1	Deep infection	TP
18	F	65	Heart	Pulmonary lesion on CT	Right lung nodule	9.1	Benign lesion	FP

SUV Standardized uptake value, CT computed tomography, EBV Epstein-Barr virus, FUO fever of unknown origin, TP true positive, FP false positive

FDG PET/CT contributed to adjusting the therapeutic approach are summarized in Table 4.

## Discussion

The present study evaluates FDG PET/CT's accuracy in diagnosing post-transplant complications in solid organ transplant recipients in clinical practice. Fifty-eight patients with lung, heart and kidney transplantation were included in this retrospective monocentric study. Furthermore, we investigated the proportion of patients whose management strategy was modified according to FDG PET/CT results.

Post-transplant lymphoproliferative disorders (PTLDs) are the most frequent post-transplant malignancy in the pediatric population and the second in adult patients. PTLD represents a wide spectrum of monomorphic and polymorphic lymphoproliferative disorders, and large B cell lymphoma is the most frequent type [3, 29–32]. PTLDs are often extranodal, with graft, cerebral or digestive involvement [33, 34]. Clinical symptoms depend on tumoral localization and are often poorly specific [2, 34, 35]. Other types of malignancies, especially cutaneous tumors [36] and virus-related diseases, are also more frequent in immunocompromised patients compared to the general population [3]. Moreover, single-lung transplant

confers a significantly elevated risk of developing primary lung cancer in native lung [37]. Infectious diseases are also life-threatening complications in an immunosuppressive context, and they can potentially affect several organs [38]. Therefore, a diagnostic tool able to detect the appearance of post-transplant complications during follow-up with high sensibility is mandatory to optimize the therapeutic strategy. FDG PET/CT is recognized to have a great impact on diagnosing, staging and restaging cancer patients [39–41]. Recently, Kubota et al. [42] evaluated the impact of FDG PET findings on decisions regarding patient management strategies (i.e., the strategy modification rate) in a prospective multicenter trial in neoplastic patients. The authors reported a strategy modification rate of 71.6 % and 70.0 %, respectively, for patients with lung cancer and malignant lymphoma. Von Flack et al. [24] compared FDG PET/CT to conventional imaging such as MRI and CT in the primary staging and therapy monitoring in 17 pediatric patients with post-transplant lymphoma. The authors concluded that FDG PET/CT seemed more efficient than conventional imaging to evaluate early treatment efficacy with potential consequences for patient management. In our series, FDG PET/CT contributed to adjusting the patient's therapeutic strategy in 23 of 58 (40 %) patients. In particular, FDG PET/CT allowed confirming or excluding lymphoma and other malignancies in 10 of 12 patients with inconclusive

**Table 3** Summary of the clinical presentation, biological characteristics and FDG PET/CT result of patients with final diagnoses of post-transplant complications

No.	Sex	Age	Graft	Patient presentation	Fever	CRP (mg/l)	Leucocytes (Nb/mm <sup>3</sup> )	CMV DNA (IU/ml)	Final diagnosis	PET Results
1	M	27	Kidney	Inflammatory syndrome	No	21	5300	Undetectable	Deep infection	TP
2	F	42	Kidney	Mediastinal mass	No	<4	8740	NA	Lymphoma	TP
3	M	44	Kidney	Inflammatory syndrome, enlarged cervical lymph node	Yes	14	5100	NA	Lymphoma	TP
4	M	38	Kidney	LDH increase	Yes	55	8880	Undetectable	Endocarditis	FN
5	M	73	Kidney	Inflammatory syndrome, FUO	Yes	122	5320	Undetectable	Septicemia	FN
6	M	27	Kidney	EBV DNA increase	No	<4	NA	NA	Deep infection	TP
7	M	53	Kidney	Pulmonary lesion on CT	No	8	4700	Undetectable	Lung cancer	FN
8	M	52	Kidney	Suspicion of digestive histoplasmosis	No	7	5890	Undetectable	Deep infection	TP
9	M	32	Lung	EBV DNA increase	No	121	10210	Undetectable	Lymphoma	TP
10	F	63	Lung	Pulmonary lesion on CT	No	<4	6320	Undetectable	Lung cancer	TP
11	M	28	Lung	Inflammatory syndrome	No	16	4540	Undetectable	Deep infection	TP
12	F	39	Lung	Inflammatory syndrome	No	28	9770	Undetectable	Sacroileitis	TP
13	M	53	Lung	Pulmonary lesion on CT	No	13	6470	Undetectable	Lung cancer	TP
14	F	58	Lung	Pulmonary lesion on CT	No	70	8790	3,62 log	Deep infection	TP
15	M	68	Heart	FUO	Yes	144	9200	Undetectable	Deep infection	TP
16	M	65	Heart	Inflammatory syndrome, fever	No	5	8030	Undetectable	Lung cancer	TP
17	F	36	Heart	Right arm edema	No	14	7800	NA	Deep infection	TP
18	F	40	Heart	FUO	No	58	4400	Undetectable	GVHD	FN

GVHD graft-versus-host disease, LDH lactate dehydrogenase, EBV Epstein-Barr virus, CT computed tomography, FUO fever of unknown origin, NA not available, TP true positive, FN false negative

CT results. FDG PET/CT also suggested infectious complications in seven patients (12 %), guiding the following diagnostic procedures. Hence, independently from the cost and access to this type of medical imaging, FDG PET/CT could have a potential role in optimizing the treatment planning in both neoplastic and selected non-neoplastic conditions during the post-transplant period. FDG PET/CT allows morpho-functional cartography of residual disease after the end or during the course of treatment. Moreover, the evolution of radiotracer uptake intensity reflects the efficacy of treatment, permitting either a better modulation of the drug dosage or a radical modification of the therapeutic strategy.

Graute et al. [26] retrospectively evaluated the diagnostic role of FDG PET or FDG PET/CT in 17 patients with symptoms suspicious of malignancy after heart transplantation. They reported a global accuracy of 71 %, ranging from 43 % to 90 % in patients examined by FDG PET or FDG PET/CT, respectively. Our study population included not only heart transplant patients, but also patients who underwent kidney and lung transplantation. Moreover, the presence of both infectious diseases and malignancies was investigated obtaining an

overall diagnostic accuracy of 86 %. Compared to Graute's results, we obtained a higher specificity value, which is probably due to the systematic use of FDG PET/CT scanners but also to a possible bias related to the studied population. Panagiotidis et al. [43] investigated the role of FDG PET/CT in the diagnosis of PTLD in 40 patients who had previously undergone solid organ or hematopoietic cell transplantation. In this study, FDG PET/CT's sensitivity and specificity were 88 % and 91 %, respectively. Dierickx et al. [44] analyzed 170 FDG PET scans in 150 patients with suspicion of PTLD after solid organ and hematopoietic cell transplantation, reporting a sensitivity and specificity of 89 %.

Guy et al. [19] assessed the diagnostic performances of FDG PET/CT in 20 patients with febrile neutropenia, reporting a sensitivity of about 93 %. Dong et al. [16] published a meta-analysis on the value of FDG PET/CT in the evaluation of FUO, reporting a pooled sensitivity of 83 %. In our patient cohort, four patients were investigated because of FUO without neutropenia, and FDG PET/CT was false negative in only one patient showing septicemia at the time of examination.



**Table 4** Therapeutic impact of FDG PET/CT

No.	Sex	Age	Graft	Patient presentation before PET/CT	Final diagnosis	PET/CT results	Therapeutic impact
1	F	42	Kidney	Noncontributory conventional imaging	Lymphoma	TP	Identification of the presence and site of malignancy
2	F	63	Lung	Noncontributory conventional imaging	Lung cancer	TP	Identification of the presence and site of malignancy
3	M	53	Lung	Noncontributory conventional imaging	Lung cancer	TP	Identification of the presence and site of malignancy
4	M	39	Kidney	Noncontributory conventional imaging	Cyst	TN	Elimination the radiological hypothesis of malignancy
5	M	28	Lung	Noncontributory conventional imaging	Benign lesion	TN	Elimination the radiological hypothesis of malignancy
6	M	66	Heart	Pulmonary lesion on CT	Benign lesion	TN	Elimination the radiological hypothesis of malignancy
7	M	20	Kidney	LDH increase, Cervical lymphadenopathy	No neoplasia	TN	Elimination the radiological hypothesis of malignancy
8	F	38	Kidney	Pelvic lymphadenopathy	No neoplasia	TN	Elimination the radiological hypothesis of malignancy
9	M	38	Lung	Right inguinal lymphadenopathy	Benign lesion	TN	Elimination the radiological hypothesis of malignancy
10	M	73	Kidney	Mediastinal lymphadenopathy	Benign lesion	TN	Elimination the radiological hypothesis of malignancy
11	M	65	Heart	Inflammatory syndrome	Lung cancer	TP	Guiding interventional radiologic procedure
12	M	32	Lung	EBV DNA increase	Lymphoma	TP	Guiding interventional radiologic procedure
13	M	44	Kidney	Inflammatory syndrome, clinical enlarged cervical lymph node	Lymphoma	TP	Guiding interventional radiologic procedure
14	F	58	Lung	Noncontributory conventional imaging	Deep infection	TP	Identification of the site of infection and introduction of treatment
15	M	27	Kidney	EBV DNA increase	Deep infection	TP	Identification of the site of infection and introduction of treatment
16	M	52	Kidney	Inflammatory syndrome	Deep infection	TP	Identification of the site of infection and introduction of treatment
17	F	39	Lung	Noncontributory conventional imaging	Sacroileitis	TP	Identification of the site of infection and introduction of treatment
18	M	28	Lung	Inflammatory syndrome	Deep infection	TP	Identification of the site of infection and introduction of treatment
19	M	68	Heart	FUO	Deep infection	TP	Identification of the site of infection and introduction of treatment
20	F	36	Heart	Inflammatory syndrome and right arm edema	Deep infection	TP	Identification of the site of infection and introduction of treatment
21	M	64	Heart	Pejorative evolution of systemic aspergillosis during treatment	Inactive aspergillosis	TN	Changing of antifungal treatment duration (stop treatment)
22	F	65	Heart	Inflammatory syndrome and polyarthralgia	Immunosuppressive treatment intolerance	TN	Modification of immunosuppressive treatment
23	F	55	Kidney	Inflammatory syndrome and FUO	Sarcoidosis	TP	Introduction of treatment

CT computed tomography, EBV Epstein-Barr virus, FUO fever of unknown origin, TP true positive, TN true negative

In our series, false-negative FDG PET/CT results were obtained in a case of histologically proven lung adenocarcinoma, in two patients with pyelonephritis and GVH disease and in two patients with septicemia. It is known that FDG PET/CT's sensitivity is not optimal in certain tumoral types such as

MALT lymphoma or carcinoid tumor. Moreover, low uptake intensity has been previously described in pulmonary adenocarcinoma [45]. Urinary FDG excretion and the physiological and heterogeneous intestinal FDG uptake probably reduced the sensitivity of FDG PET/CT for detecting pyelonephritis

and GVH reactions. Concerning septicemia, other authors reported false-negative results in this clinical situation [26].

Although interesting results were obtained from an important cohort of kidney, lung and heart-transplanted patients, this study has several limitations such as its retrospective design and the lack of histopathologic confirmation for all lesions. Moreover, the high number of true-negative patients could represent a bias with an impact on the sensitivity and specificity.

## Conclusion

Our study supports the potential of FDG PET/CT in the diagnostic workup of complications in the post-transplant period. FDG PET/CT should be considered in transplanted patients with severe unexplained inflammatory syndrome/FUO and normal CT or to discriminate active from silent lesions previously detected by conventional imaging without definitive interpretation when malignancy is suspected.

Considering the recent development of interventional radiology procedures guided by FDG PET/CT [46–48], we can foresee an evolution toward multimodality imaging allowing the definition of a metabolic target for the diagnostic biopsy. However, prospective and larger multicentric studies are needed to completely define the place of FDG PET/CT in the post-transplantation period.

## Compliance with Ethical Standards

**Conflict of Interest** Nastassja Muller, Romain Kessler, Sophie Caillard, Eric Epailly, Fabrice Hubel , C line Heimburger, Izzie-Jacques Namer, Raoul Herbrecht, Cyrille Blondet and Alessio Imperiale declare that they have no conflict of interest.

**Ethical Statement** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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