





BMJ Open Determining the usefulness of systematic ^{18}F -FDG PET/CT for the management of invasive fungal infection (PETIFI project): a prospective national multicentre cohort study protocol

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ABSTRACT

Introduction The evaluation of staging and activity of invasive fungal infection (IFI) is used to adjust the type and duration of antifungal therapy (AT). Typically anatomy-based imaging is used. Positron emission tomography/CT with ^{18}F -fluorodeoxyglucose (^{18}F -FDG PET/CT) not only evaluates more than one body area in one session, but adds functional information to the anatomic data provided by usual imaging techniques and can potentially improve staging of IFI and monitoring of the response to therapy. Our objective is to analyse the impact of the systematic use of ^{18}F -FDG PET/CT in IFI diagnostic and therapeutic management.

Methods and analysis Multicentre prospective cohort study of IFI with performance of systematic ^{18}F -FDG PET/CT at diagnosis and follow-up that will be carried out in 14 Spanish tertiary hospitals. It is planned to include 224 patients with IFI over a 2-year study period. Findings and changes in management before and after ^{18}F -FDG PET/CT will be compared. Additionally, the association of initial quantitative ^{18}F -FDG PET/CT parameters with response to therapy will be evaluated.

The primary endpoint is to compare the yield of ^{18}F -FDG PET/CT with standard management without ^{18}F -FDG PET/CT in IFI at initial assessment (staging) and in monitoring the response to treatment.

The impact of the results of ^{18}F -FDG PET/CT on the diagnostic-therapeutic management of patients with IFI (added value), as well as the prognostic ability of different quantification parameters of ^{18}F -FDG PET/CT will be secondary endpoints.

Ethics and dissemination The Clinical Research Ethics Committee of Puerta de Hierro-Majadahonda University Hospital approved the protocol of the study at the primary site. We plan to publish the results in high-impact journals.

Trial registration number NCT05688592.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a prospective study, so we will be able to evaluate the usefulness of systematic positron emission tomography/CT with ^{18}F -fluorodeoxyglucose (^{18}F -FDG PET/CT) for the management of invasive fungal infection (IFI).
- ⇒ We expect to enrol enough patients to detect significant results that will be generalisable to a wide population.
- ⇒ The study design does not allow us to evaluate the impact of the performance of ^{18}F -FDG PET/CT on survival.
- ⇒ Imaging tests will not be evaluated by the same team, however interpretation of conventional studies in IFI is well standardised in the guidelines.
- ⇒ If the period established for the follow-up ^{18}F -FDG PET/CT is too short, a prolongation of the study would be proposed.

INTRODUCTION

The diversity of clinical manifestations of invasive fungal infection (IFI) is greater than that caused by most micro-organisms and reflects a complex fungus/host interaction. In addition, the clinical and imaging manifestations in the initial stages are subtle. Multi-organ dissemination can occur, and it is frequently observed in immunocompromised patients.

Besides, the evaluation of the response in IFI is complicated due to the absence of reliable markers for follow-up. The duration of treatment is not standardised: in apparently cured cases, dissemination of the infection could occur during periods of immunosuppression, whereas in other cases the anatomical changes associated with IFI can persist, even with resolution of

the infection. Because of this, it is critical to determine the ideal moment to modify antifungal treatment (AT).

Assessment of IFI involvement and activity might impact the choice and duration of AT. These are usually set on techniques based on anatomical images. The positron emission tomography/CT with ^{18}F -fluorodeoxyglucose (^{18}F -FDG PET/CT) provides functional information that correlates with the anatomical data of IFI, in addition to having the ability to evaluate more than one body area in only one session. Therefore, ^{18}F -FDG PET/CT has the potential value of improving the assessment of the extent of the disease and its response to AT.^{1 2}

We aim to determine whether the systematic performance of ^{18}F -FDG PET/CT improves the diagnosis and management in IFI. To this end, ^{18}F -FDG PET/CT will be systematically performed at the onset and follow-up of IFI, and findings and changes in the management of IFI pre- ^{18}F -FDG PET/CT and post- ^{18}F -FDG PET/CT will be compared. Moreover, the association of the quantitative parameters of the initial ^{18}F -FDG PET/CT with the response to treatment will be analysed.

Hypothesis and objectives

Hypothesis

1. Does the use of ^{18}F -FDG PET/CT allow a better characterisation of IFI (performance) compared with the exclusive use of conventional radiological studies in terms of extension/staging and monitoring of response/follow-up?
2. Does the systematic and protocolised use of ^{18}F -FDG PET/CT in IFI allow a better management of these patients and increase the prognostic value of the initial evaluation?

Objectives

1. Primary objective: to compare the performance of ^{18}F -FDG PET/CT with standard management without ^{18}F -FDG PET/CT (including anatomy-based but non-functional imaging tests) in IFI.
 - a. At initial assessment (extension/staging) (discover hidden foci of infection).
 - b. In monitoring response to treatment (lesion activity: residual inactive lesions vs persistently active lesions).
2. Secondary objectives:
 - a. To evaluate the impact of the results of the ^{18}F -FDG PET/CT in the management of IFI (added value) in terms of:
 1. The performance of additional diagnostic tests.
 2. Treatment modifications (of the drugs used, or their duration).
 3. Outcome: resumption of chemotherapy or performance of stem cell transplantation (SCT), end of treatment of IFI, relapse.
 - b. Determine the value of the different parameters of quantification of ^{18}F -FDG PET/CT and the characteristics of the uptake in the IFI and the prognostic

capacity of the metabolic response/outcome of the patient with IFI.

METHODS AND ANALYSIS

Study design

National, multicentre, prospective cohort study involving patients with IFI diagnosed at any of the participating centres during the study period.

Setting

It will be conducted at 14 Spanish tertiary hospitals (Madrid five centres, Andalucía three, Barcelona two, Murcia two, Asturias and Salamanca one centre each).

Study period

It will take place during 24 months from January 2023.

Study population

Inclusion criteria

1. >18-year-old adult patients.
2. Admitted with a diagnosis of IFI.
3. Able to undergo a ^{18}F -FDG PET/CT.
4. That gives their informed consent.

Exclusion criteria

1. Concomitant active bacterial infection likely to produce uptake in organs and tissues
2. Recent surgery in the area of the IFI (previous 3 months).
3. Other medical conditions that interfere with the development of the study (eg, inability to tolerate the performance of the test, pregnancy).
4. Terminal situation.

Definition of IFI

Two types of IFIs will be considered:

1. Fungaemia: detection of fungal growth in blood cultures.
2. Focal IFI with tissue invasion: diagnosis of proven or probable IFI according to the corresponding criteria depending on the type of patient (haematology and other immunocompromised: European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium consensus definitions;³ solid organ transplantation: 2010 International Society for Heart and Lung Transplantation consensus statements for the definitions of infections in cardiothoracic transplant recipients;⁴ Intensive Care Unit (ICU)/Chronic obstructive pulmonary disease (COPD): Bulpa;⁵ COVID-19: European Confederation of Medical Mycology (ECMM)/International Society for Human and Animal Mycology (ISHAM).⁶

Patient recruitment

On suspicion of IFI, the attending physician will verify that the patient meets all the inclusion criteria and none of the exclusion criteria, and will contact the Nuclear

Medicine specialist to schedule the performance of ^{18}F -FDG PET/CT according to the study protocol.

Sample size

Based on the literature, we assume that ^{18}F -FDG PET/CT will detect lesions not previously visualised in approximately 50% of patients.¹ We anticipate that the findings in 50% of these patients will cause the management of IFI to change,⁷ which corresponds to 25% of the total number of patients. To achieve a 6% accuracy in estimating a proportion using a bilateral 95% normal asymptotic CI, assuming that the proportion is 25%, it will be necessary to include 201 patients in the study. Assuming 10% of abandonments, or loss of information, it would be necessary to enrol 224 patients.

Intervention

In addition to the usual management ('standard of care (SOC)', detailed in data collection section) ^{18}F -FDG PET/CT will be performed to patients included to evaluate:

1. Staging at diagnosis: in the first week after diagnosis (preferably in the first 48 hours of starting AT).
2. Response monitoring/follow-up: will be carried out on the same equipment as the initial ^{18}F -FDG PET/CT.
 - a. In the case of fungaemia, 2 weeks after the initial staging ^{18}F -FDG PET/CT.
 - b. In the case of focal IFIs, 2–4 and 12 weeks after the initial staging ^{18}F -FDG PET/CT.

Recent surgery is an exclusion criterion. As the protocol does not recommend any particular therapy, surgery in patients already included will be performed according to the treating physician criteria, registered in the study and subsequently repeat the imaging test.

^{18}F -FDG PET/CT technique

All ^{18}F -FDG PET/CT will be performed according to EANM (European Association of Nuclear Medicine) guidelines. The CT component of ^{18}F -FDG PET/CT will be non-contrast.¹

All patients must comply with a previous fasting period of at least 6 hours (16 hours in cases of suspected endocarditis; in that case a dietary modification protocol will also be applied).

Ideally, they will maintain blood glucose levels <180 mg/dL. If insulin is administered, the injection of ^{18}F -FDG should be spaced at least 4 hours apart.

For infectious and inflammatory diseases, the same acquisition, reconstruction and postprocessing described in the procedures of the EANM for tumours is recommended.^{8,9}

Administered ^{18}F -FDG activity will be approximately 2.5–5 MBq/kg depending on the available device. Full-body ^{18}F -FDG PET/CT imaging will begin approximately 50–60 min after injection, and will be performed from the cranial vertex to the feet by placing the patient in a supine position. The study will be completed with a late acquisition and focused on the field of interest.

If this is a long-term treatment response assessment study, it is important that the same interval from injection to imaging is applied as in the baseline study, so that maximum standardised uptake value (SUV_{max}) measurements are comparable.

The ^{18}F -FDG PET/CT will be analysed for increased uptake of ^{18}F -FDG outside the areas of physiological incorporation. A qualitative analysis will be carried out, taking into account the uptake pattern (focal, linear, diffuse) and the distribution of the radiotracer in the pathological area (homogeneous or heterogeneous), and semiquantitative considering the intensity of the uptake in terms of SUV_{max} , peak standardised uptake value (SUV_{peak}), mean standardised uptake value (SUV_{mean}), total lesion glycolysis (TLG) and mass tumour glycolysis. The ^{18}F -FDG PET/CT will be reported according to the specific criteria of interpretation of each clinical indication.

Analysis of ^{18}F -FDG PET/CT images

In order to standardise the interpretation of the images, a 1 day training session will be held before the start of the study.

The ^{18}F -FDG PET/CT will be reviewed by the specialist of the patient's centre who will be blind to the result of the tests performed according to SOC. Additionally, the images will be included in the database, for evaluation by a second specialist in Nuclear Medicine from the coordinating centre, blind for the initial interpretation of the ^{18}F -FDG PET/CT. This second evaluation will favour the standardisation of the interpretation, however, clinical decisions will be made based on the interpretation of the local Nuclear Medicine team.

Pre- ^{18}F -FDG PET/CT evaluation

1. Staging
 - a. In this phase, IFIs will be classified into localised or disseminated disease (involvement of more than one non-contiguous organ; in the case of fungaemia, detection of septic metastases), and the number of lesions and organs affected will be specified.
 - b. Prior to the completion of the initial ^{18}F -FDG PET/CT, the attending physician will establish a staging and management plan of the IFI based on the data known at that time, through a standardised questionnaire: need for diagnostic techniques, source control (including surgical treatment), selected drug (penetration into involved areas, need for combined treatment), expected duration of treatment.
2. Response monitoring (follow-up):
 - a. The relevant clinical, analytical, microbiological and imaging tests performed at the time of the ^{18}F -FDG PET/CT follow-up will be collected. Additional tests will be performed according to SOC.
 - b. An evaluation of the response to treatment and management plan of the IFI will be established prior to the performance of the ^{18}F -FDG PET/CT (pre-PET) (including prevision to discontinue or maintain antifungal).

Post-¹⁸F-FDG PET/CT evaluation

1. Staging

- Based on the findings of the ¹⁸F-FDG PET/CT, IFIs will be classified again in localised or disseminated disease, and the number of lesions involved will be specified.
- The contributions of the ¹⁸F-FDG PET/CT to the data that were known prior to its realisation will be specifically collected, as well as the specific data of the ¹⁸F-FDG PET/CT (SUV_{max} ...).

2. Response monitoring

- After the PET, a re-evaluation of the response will be established based on the PET findings and, in the first 48 hours after the performance and evaluation of the initial ¹⁸F-FDG PET/CT, the same responsible physician will reevaluate the management plan based on the findings of the ¹⁸F-FDG PET/CT establishing the modifications it deems necessary. Clinical decisions will be made based on the interpretation of the local Nuclear Medicine team.

Would the patient present any AT-related toxicity, it will be taken into consideration, however, unless the medical condition prevents the performance of the PET-CT, it will be done as planned.

The patient's outcome will be evaluated at 100 days and 6 months (completion of treatment, continuation of chemotherapy or performance of SCT, recurrence, survival).

The criteria for image interpretation and definitions of metabolic response are: normal, equivocal or with pathological uptake according to the standard uptake values (SUV) (visual score: 0: no pathological uptake; 1: uptake similar to the vascular pool in the mediastinum; 2: uptake higher than the vascular pool but lower than the liver pool; 3: uptake similar or slightly higher than the liver; 4: uptake clearly higher than the hepatic). Where 0 and 1 would be negative and 2, 3 and 4 positive (always assessing location and alternative causes that explain the uptake).

In each ¹⁸F-FDG PET/CT the IFI lesions will be identified, the number of lesions will be counted and the volumes of interest will be drawn around the lesions. IFI lesions will be defined as abnormal focal lesions with or without a hypometabolic centre not related to any pre-existing procedure or pathology. TLG, metabolic volume (MV), SUV_{max}, SUV_{peak} and SUV_{mean} will be recorded for each IFI lesion in each ¹⁸F-FDG PET/CT study. The TLG and MV of the individual lesions of each scanner will be added to calculate the global TLG and global MV of each patient.⁷

The IFI response to treatment will be classified into three groups based on the findings of the ¹⁸F-FDG PET/CT in the follow-up study:

- Complete metabolic response (CMR).
- Partial metabolic response.
- Progression of infection.

The CMR will be defined as full resolution of the ¹⁸F-FDG uptake due to IFI, compared with the background at the IFI site. The partial response, such as any reduction

in the uptake of ¹⁸F-FDG that does not reach full normalisation. Progression of infection shall be defined as the appearance of new lesions or the increase in the size or intensity of known IFI lesions.¹⁰

Data collection and analysis

The information shall be collected prospectively by means of a data collection notebook (eDCN) and stored in an anonymised form in a common database. The data will be obtained from the patient's medical history. From the database, they will be downloaded to the statistical programme for analysis, which will be carried out with the support of the Biostatistics Unit of Instituto de Investigación Sanitaria Puerta de Hierro - Segovia de Arana.

Demographic, clinical variables and results of conventional diagnostic tests including blood count, biochemistry, cultures, biomarkers such as galactomannan or β-D-glucan, and imaging tests performed according to SOC and following the guidelines^{8 9 11-13} will be collected. Specifically, anatomy-based imaging tests will be performed according to the protocols of each department, and will be interpreted by certified specialists (radiologists, echocardiographers, etc as appropriate) as part of routine care.¹

Patients lost to follow-up will be considered for the study only during the period with enough data, and excluded from the period without data. Their characteristics will be appropriately reported.

Study variables

- Performance variables: percentage of patients with IFI in whom ¹⁸F-FDG PET/CT has improved patient assessment compared with standard management in:
 - Initial staging of infection: change in staging (localised/disseminated); change in number of organs involved or number of fungal lesions detected (number of lesions discordant between pre-PET and post-PET).
 - Response to treatment: change in the assessment of the IFI response (clinical, anatomical and metabolic response).
- Clinical impact variables: added value (patients benefiting from PET).
 - ¹⁸F-FDG PET/CT will be considered to have added value over SOC when lesions are detected outside the region assessed by other imaging tests,¹ clinically hidden lesions, dissemination, PET 'reclassifies' a radiological finding² or leads to the performance of a new targeted diagnostic test.
 - When the metabolic information provided by the ¹⁸F-FDG PET/CT allows clinical decisions about the patient to be made, either to discontinue, prolong or change the AT (modification of the type of treatment, modification of the drug used, modification of the duration of treatment) or leads to surgical treatment, it will be considered to be a modification of the treatment and has added value.

- c. Added value shall be considered when baseline metabolic parameters allow predicting metabolic response to AT.
3. Outcome variables.
 - a. Baseline ^{18}F -FDG PET/CT parameters: TLG, MV, SUV_{max} , and SUV_{peak} and SUV_{mean} of each lesion. Global TLG and MT for every ^{18}F -FDG PET/CT.
 - b. Duration of AT, resumption of chemotherapy or performance of SCT, recurrence, survival.

Statistical analysis

Objective 1

1.a. The proportion of patients classified as pre-PET localised and disseminated IFI and patients reclassified as disseminated IFI will be established by adding the information of ^{18}F -FDG PET/CT. The net reclassification index¹⁴ between the two approximations will be estimated. The gold standard will be the classification made 6 months after the inclusion of the patient, with all the information added during that time (tests, treatments and response to treatments). Likewise, the % of patients in whom new lesions are detected with PET, or lesions in organs that were not previously affected, will be evaluated, even if it does not involve a change in staging.

1.b. The modifications in the assessment of the outcome after the ^{18}F -FDG PET/CT follow-up (complete response/partial response/non-response/worsening) compared with pre-PET will be analysed.

A study of the concordance between the pre-PET evaluation and the gold standard, and the post-PET versus gold standard evaluation (both in terms of staging and monitoring of the response), will be carried out using a weighted kappa index.

Objective 2.1

The impact (added value) of ^{18}F -FDG PET/CT on the management of IFI will be analysed, both at the time of initial staging and at the time of response monitoring through the follow-up ^{18}F -FDG PET/CT (proportion of patients in whom ^{18}F -FDG PET/CT involves a change in management).

In addition, the characteristics of patients who benefit from ^{18}F -FDG PET/CT (those who receive an added value from PET) will be compared with those who do not benefit.¹⁵ A multivariate predictive model will be constructed to identify patients who would potentially benefit from performing systematic ^{18}F -FDG PET/CT. The dependent variable will be: benefit, yes or no. To account for the effect on the variability of the benefit by the centre, mixed models will be made.

Objective 2.2

The prognostic value of the parameters of ^{18}F -FDG PET/CT in the IFI will be analysed, comparing the baseline characteristics of the parameters of ^{18}F -FDG PET/CT in patients who achieved CMR with those who did not, using binary logistic regression. An analysis will also be carried out using receiver operating characteristic

curves to determine if the metabolic parameters allow to discriminate which patients will have CMR in the final examination.¹⁰

Bilateral p values below 0.05 shall be considered significant. The statistical package SPSS V.25 and Stata V.17 will be used. The analysis will be carried out according to the Standards for Reporting of Diagnostic Accuracy initiative)¹⁶ guidelines.

The full protocol is attached as an online supplemental file 1.

Patient and public involvement

None

Ethics and dissemination

Ethical aspects

The study will be carried out in accordance with international ethical recommendations (Declaration of Helsinki and Oviedo Convention) and the recommendations of Good Clinical Practice (CPMP/ICH/135/95), and in accordance with the current legislation in force in relation to biomedical research projects (Law 14/2007, of July 3, on Biomedical Research). It has been approved by the Ethics Committee for Clinical Research with Medications of the primary centre (Hospital Puerta de Hierro-Majadahonda; PI 02/23). Four secondary centres have already obtained approval and seven secondary centres remain to obtain it (see online supplemental file 2).

Patients will be identified by a numerical code in order to respect the confidentiality of their personal data, as established by Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights.

The subjects will be informed of all those details concerning their participation in the study and will freely give their written consent.

The intervention of performing ^{18}F -FDG PET/CT involves the protocolisation of a technique that is used in usual practice, and therefore does not constitute an additional risk for patients. The clinical management of IFI will be done at the discretion of the responsible physician.

Dissemination

The results will be presented in national and international conferences of Infectious Diseases and Nuclear Medicine, and when final results will be available, we plan several publications in high impact journals.

DISCUSSION

Imaging techniques play a fundamental role in the management of IFI.¹⁷ The techniques based on anatomical images are typically used. In the case of ^{18}F -FDG PET/CT, PET provides functional information that correlates with anatomical data from CT. Using ^{18}F -FDG as a radio-tracer, information on glycidic metabolism is obtained in the different tissues. ^{18}F -FDG PET/CT is able to evaluate more than one body area in addition to providing

metabolic information. In contrast, conventional radiological techniques only study a part of the anatomy at a time, allowing ^{18}F -FDG PET/CT to more easily detect clinically silent lesions.¹

^{18}F -FDG PET/CT in the early diagnosis of IFI appears to have a greater sensitivity for the identification of lesions than conventional CT, and is especially valuable when it comes to identifying clinically hidden or disseminated infections.² ^{18}F -FDG PET/CT can provide information at the molecular level and detect the activity of the disease at the earliest manifestations.¹⁸ However, information on its usefulness in clinical practice is scarce, although retrospective studies suggest that it can detect lesions hidden from conventional studies in 48.6%, and add value in 74% of patients.¹ Current indications include identifying disseminated IFIs in immunocompromised patients and monitoring response to treatment, when CT suggests persistent lesions, as well as detecting IFIs in immunocompromised patients with persistent fever when conventional CT is inconclusive.

Clinical signs of invasive aspergillosis (IA) are usually non-specific. Due to the absence of reliable and objective markers for follow-up, the evaluation of the response is complicated. Follow-up is based primarily on monitoring the radiological response and decreased serum galactomannan.¹⁹

Consensus criteria have been published to assess the response to antifungals²⁰ and, more recently, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID)-ECMM-European Respiratory Society (ERS) guidelines of IA propose a combined evaluation of the response using clinical, radiological and mycological criteria.¹¹ These guidelines, however, are mostly based on haematological patients and were created to be used predominantly in clinical trials.¹²

Patients with IFI are usually treated for long periods, partly because the duration of treatment is not standardised,²¹ and a minimum of 6–12 weeks is recommended.¹² Inadequately short AT could promote the spread and complications of IFI, increasing morbidity and mortality.

In addition, the dissemination of the infection could also occur during periods of immunosuppression such as intensive chemotherapy or SCT. For this reason, it is of paramount importance to determine the ideal time to modify the treatment. Moreover, since the anatomical changes associated with IFI can persist, even with resolution of the infection, there is a risk of unnecessarily delaying the continuation of treatment of the underlying disease.

IFIs are hypermetabolic processes. These metabolic changes correlate with disease activity, and precede anatomical changes in tissues affected by IFI.²² Therefore, the ^{18}F -FDG PET/CT, may be able to distinguish between active infection and residual scar tissue.² This technique could be useful tool for monitoring the IFI response.²³

In one study, functional imaging with ^{18}F -FDG PET/CT, has been useful in the monitoring of IFIs, altering management in up to 50% of cases.⁷

The identification and monitoring of lesion response to AT would be of great value, especially in the categories of probable or possible IFI.¹ In addition, ^{18}F -FDG PET/CT may serve as a filter for patients considered for an SCT or other procedures that could cause IFI dissemination.¹ Both positive and negative findings of ^{18}F -FDG PET/CT could aid in clinical decision-making and add value to the management of IFI.

In addition, in fungaemia, particularly candidaemia, it is necessary to identify patients with complicated infection, since they will require longer treatment and in certain cases, source control. Techniques used to assess the dissemination of fungaemia include imaging tests such as echocardiogram.²⁴ In inconclusive cases, PET has been used to rule out or to confirm endocarditis. In this sense, several studies demonstrate the usefulness of PET in the diagnosis of endocarditis,¹⁵ as well as in the detection of septic metastases,⁷ though specific evaluation in candidaemia is lacking.

In a retrospective study,⁷ some ^{18}F -FDG PET/CT parameters such as TLG and MV showed the ability to predict whether a patient will achieve a CMR. This finding indirectly supports the idea that both TLG and MV may be better parameters than those derived from SUV to compare ^{18}F -FDG PET/CT of patients with IFI.⁷

Strengths and limitations

Contribution

To our knowledge, there are no prospective studies that evaluate the added value of ^{18}F -FDG PET/CT in IFI management. The present study will be prospective and thus will be able to evaluate systematic and protocolised use of ^{18}F -FDG PET/CT,²⁵ with an initial test that determines the extent of the infection, followed by another ^{18}F -FDG PET/CT to assess the response to treatment.

This study will be multicentric allowing to enrol sufficient patients to achieve significant results that will be generalisable to a wide population.

Limitations

The study design does not allow us to evaluate the impact of ^{18}F -FDG PET/CT on survival. However, the pre and post- ^{18}F -FDG PET/CT comparison will allow to evaluate its contribution to the diagnosis and management better than comparing a group of patients who undergo ^{18}F -FDG PET/CT to another group without ^{18}F -FDG PET/CT, as in the present study each patient is compared with himself. Given the heterogeneity of patients with IFI, this design eliminates a multitude of confounding factors.

A potential limitation is that the standardisation of SOC management in the participating centres may not be fully superimposable. In any case, the objective of this study is to compare the performance of protocolised ^{18}F -FDG PET/CT with the usual management, and we consider that when carrying out the study in this way the results will be of great value.

Another limitation is that imaging tests will not be all performed and evaluated by the same team. Interpretation

of conventional studies in IFI is well standardised in the guidelines. Besides, the images will be interpreted by a second Nuclear Medicine specialist from the coordination centre.

It could happen that the period established for the ^{18}F -FDG PET/CT follow-up is too short. In this case, a prolongation of the study would be proposed.

Finally, our design does not assess whether adding systematic ^{18}F -FDG PET/CT to IFI management is cost-effective or whether it leads to unnecessary procedures and increased costs.

Potential limitations of ^{18}F -FDG PET/CT

The value of the quantitative analysis of the SUV has not been validated in IFI, and the absence of a validated SUV_{max} cut-off point or other parameters prevents to differentiate malignant lesions from fungal lesions.²³ Furthermore, different species of fungi may have different SUV_{max} .² So, for now, in clinical practice it should be used merely as a descriptive means of the degree of activity of the process, but not to distinguish IFI of malignancy.

^{18}F -FDG PET/CT has limitations derived from the low specificity of ^{18}F -FDG to differentiate infection from acute or chronic sterile inflammation.^{23 26} The use of ^{18}F -FDG PET/CT for IFI monitoring in cases of predominantly cerebral or renal involvement, may not be optimal.^{7 10}

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