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ORIGINAL ARTICLE

What do we know About the Usefulness of ^{18}F-FDG PET-CT for the Management of Invasive Fungal Infection? An International Survey

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Abstract

Background Recent data support ^{18}F-FDG PET-CT for the management of infections in immunocompromised patients, including invasive fungal infection (IFI). However, its role is not well established in clinical practice. We performed an international survey to evaluate the knowledge of physicians about the usefulness of ^{18}F-FDG PET-CT in IFI, in order to define areas of uncertainty.

Methods An online survey was distributed to infectious diseases working groups in December 2023-January 2024. It included questions regarding access to ^{18}F-FDG PET-CT, knowledge on its usefulness for IFI and experience of the respondents. A descriptive analysis was performed.

Results 180 respondents answered; 60.5% were Infectious Diseases specialists mainly from Spain (52.8%) and Italy (23.3%). 84.4% had access to ^{18}F-FDG PET-CT at their own center. 85.6% considered that ^{18}F-FDG PET-CT could be better than conventional tests for IFI. In the context of IFI risk, 81.1% would consider performing ^{18}F-FDG PET-CT to study fever without a source and around 50% to evaluate silent lesions and 50% to assess response, including distinguishing residual from active lesions. Based on the results of the follow-up ^{18}F-FDG PET-CT, 56.7% would adjust antifungal therapy duration. 60% would consider a change in the diagnostic or therapeutic strategy in case of increased uptake or new lesions. Uncovering occult lesions (52%) and diagnosing/excluding endocarditis (52.7%) were the situations in which ^{18}F-FDG PET-CT was considered to have the most added value. There was a great variability in responses about timing, duration of uptake, the threshold for discontinuing treatment or the influence of immune status.

Conclusion Although the majority considered that ^{18}F-FDG PET-CT may be useful for IFI, many areas of uncertainty remain. There is a need for protocolized research to improve IFI management.

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Keywords ^{18}F-FDG PET-CT · Survey · Febrile neutropenia · Immunocompromised · Invasive fungal infection · Invasive fungal disease

Abbreviations

^{18}F-FDG PET-CT	Positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose
FN	Febrile neutropenia
IFI	Invasive fungal infection
HSCT	Hematopoietic stem cell transplantation
GEMICOMED	Grupo de Estudio de Micología Médica dentro de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
GESITRA-IC	Grupo de Estudio de Infección en el Trasplante y el Huésped Inmunocomprometido de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica
GIM	Grupo de Infectólogos de Madrid
ESGICH	European Society of Clinical Microbiology and Infectious Diseases. Study Group for Infections in Compromised Hosts
EFISG	European Society of Clinical Microbiology and Infectious Diseases. Fungal Infection Study Group
EANM	European Association of Nuclear Medicine
SITA	Società Italiana di Terapia Antinfettiva
ICU	Intensive Care Unit
FUO	Fever of unknown origin
HRCT	High-resolution computed tomography
FN	Febrile neutropenia

Introduction

Positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET-CT) is an imaging Nuclear Medicine technique that provides functional information as well as anatomical data, in addition to having the ability to evaluate more than one body area in a single session [1–3]. Those are potential advantages over conventional imaging techniques that are the current standard for invasive fungal infection evaluation.

In recent years, the contribution of ^{18}F-FDG PET-CT to the management of infectious complications in hematological patients has been studied [4–6]. Several studies suggest that ^{18}F-FDG PET-CT has the potential of improving the evaluation of patients with febrile neutropenia (FN) and invasive fungal infection (IFI) and also the assessment of the response to treatment [4, 7–10]. On the other hand, it is known that the use of excessively broad-spectrum empirical therapies in febrile immunocompromised patients may lead to adverse effects, increasing antimicrobial resistance and unnecessary expenses; therefore, several authors have analyzed the usefulness of ^{18}F-FDG PET-CT for optimizing empirical antimicrobial therapy and allowing early de-escalation and withdrawal of antimicrobials, and specifically antifungals [5, 7, 11–13]. Despite the results of these publications supporting the use of ^{18}F-FDG PET-CT, in hematological patients its role has not been clearly defined and its use is not yet protocolized. This is even more true for other populations at risk for IFI, such as solid organ transplant recipients [14].

Along the same lines, even if ^{18}F-FDG PET-CT for the diagnosis of infectious endocarditis is recommended in the guidelines [15], especially in prosthetic endocarditis (IB), experience in fungal endocarditis so far is scarce [14].

We performed an international online survey to evaluate the knowledge of clinicians who care for patients at risk for IFI about the usefulness of ^{18}F-FDG PET-CT for the management of IFI, and to clarify areas of uncertainty to guide further research.

Methods and Analysis

Survey Development

A team of Infectious Diseases and Nuclear Medicine physicians developed an online survey through Google Forms that was initially tested on a small group of clinicians to ensure understanding,

interpretability, and relevance to clinical practice, both in Spanish and English.

The online survey (supplementary material 1) included questions related to the characteristics of the hospital facility, the physician's overall experience caring for immunocompromised patients, and access to ^{18}F-FDG PET-CT, and then focused on specific questions regarding ^{18}F-FDG PET-CT indications in IFI, and its added value in different clinical scenarios (diagnosis, staging and therapy of IFI). The physician's experience in using ^{18}F-FDG PET-CT specifically for the management of fungal infection was also queried.

Once the correct functioning of the tool was verified, it was distributed via email during December 2023 and January 2024. The survey was administered to clinicians through an online link, allowing 28 days to respond. No financial incentives were provided for completing the survey.

Study Population

The survey was distributed to clinicians from different countries who care for patients at risk for IFI, including infectious diseases specialists, hematologists, solid organ transplant clinicians and others, or who interpret ^{18}F-FDG PET-CT scans (Nuclear Medicine physicians). Members of Infectious Diseases and Nuclear Medicine work groups such as GEMICOMED, GESITRA-IC, GIM, ESGICH, EFISG, EANM and SITA were invited to participate, and, additionally, calls for participation were disseminated across various online platforms.

Data Analysis

Before the analysis, the Spanish and English datasets were combined into a unified unit, ensuring meticulous consistency. Once the results were compiled, descriptive statistics were used to analyze the responses to the questions proposed in the survey. All questions were included and analyzed, specifying the denominator of responses whenever it did not reach 100%. The presentation of data involved organizing frequencies, percentages, and proportions into contingency tables.

Ethics

The Institutional Review Board (CEIm) at Hospital Universitario Puerta de Hierro (Majadahonda) approved the study as an opinion survey (EXE-01/24).

Results

Out of 1863 physicians subscribing to the target email groups, 180 answered the survey (10.4% response rate). There were 31.1% complete responses and 68.9% partially complete.

The results organized by questions can be checked in supplementary material 2.

Characteristics of the Practitioners who Responded to the Survey

Table 1 summarizes the characteristics of the clinicians who responded to the survey.

The majority of the respondents (109; 60.5%) were Infectious Diseases specialists, notwithstanding there was a wide array of other specialties caring of different types of immunocompromised patients from different perspectives.

Most of the respondents (51.7%) were consultants, 66 (36.7%) were attending and 20 (11.1%), fellows.

The distribution by country of practice is shown in Fig. 1. The majority of responses came from European countries such as Spain (52.8%), Italy (23.3%) or Greece (3.9%), though there is a sample of respondents from all over the world. Of those who responded, 89.4% worked in a public center, generally a large hospital (> 500 beds), (72.8%). As such, most hospitals had Oncology (87.2%) and Hematology units (92.8%), which included leukemia unit in 66.7%, and performed autologous HSCT (hematopoietic stem cell transplantation) in 140 (77.8%), allogenic HSCT in 66.1% and CAR-T cell therapy in 57.2%. Among the solid organ transplantation units, more than 50% had a kidney transplantation program (68.3%), while the remaining types of solid organ transplantation programs were less common: lung, 32.2%; heart, 43.9%; liver, 51.7%; pancreas, 18.9%, and intestine 12.2%.

Almost every center had an ICU (96.1%) but only 55% had specialized ICUs.

Table 1 Characteristics of surveyed clinicians

Characteristic	N	%
Specialties		
Internal medicine	28	15.5
Infectious diseases	109	60.5
Nuclear medicine	12	6.6
Microbiology	5	2.6
Intensive care	4	2.1
Pediatrics	4	2.1
Hematology	12	6.6
Geriatrics	1	0.5
Surgery	1	0.5
Nephrology	1	0.5
Pneumology	2	2.1
Liver transplant specialist	1	0.5
Category of the respondent		
Attending	66	36.7
Consultant	93	51.7
Fellow	20	11.1
Hospital characteristics: number of beds		
> 500	131	72.8
200–500	36	20
< 200	13	7.2
Hospital characteristics		
Public	161	89.4
Private	15	8.3
Departments		
Hematology unit	167	92.8
Leukemia unit	120	66.7
Autologous SCT	140	77.8
Allogenic SCT	119	66.1
CAR-T cell therapy	103	57.2
Oncology unit	157	87.2
Lung transplantation	58	32.2
Heart transplantation	79	43.9
Liver transplantation	93	51.7
Kidney transplantation	123	68.3
Pancreas transplantation	34	18.9
Intestinal transplantation	22	12.2
Intensive care unit (ICU)	173	96.1
Specialized ICU (hemato-oncologic, cardio-thoracic surgery, other)	99	55

Access to ^{18}F-FDG PET/CT

Although a vast majority of the respondents had onsite access to ^{18}F-FDG PET-CT (84.4%), as much as 7.9% were not authorized to use ^{18}F-FDG PET-CT for infection management.

^{18}F-FDG PET-CT was generally performed within a week since it was requested (30.8%), and even in less than 3 days in another 31.4%, but still in almost in half of the cases the clinicians considered that the delay between requesting and performing ^{18}F-FDG PET-CT was too long to be clinically useful.

Other barriers to the use of ^{18}F-FDG PET-CT for the management of IFI were the disagreement regarding the indication in 49 (41.2%) or the lack of reimbursement in 22 (18.5%).

Usefulness of PET in Invasive Fungal Infection

Respondents considered that ^{18}F-FDG PET-CT could be better than conventional techniques in IFI diagnosis in 53.9% of the cases and for staging in 65%, and, above all, 85.6% for monitoring response to treatment.

Figure 2 summarizes the multiple indications where the respondents would consider ordering ^{18}F-FDG PET-CT and the indications where it was deemed to add more value as compared with conventional imaging. Although 81.1% would consider performing ^{18}F-FDG PET-CT for the study of fever of unknown origin (FUO), only 52.8% believed this was the indication where ^{18}F-FDG PET-CT had more added value compared to conventional tests. In contrast, ^{18}F-FDG PET-CT was considered to add the most value in detecting silent sites of involvement (61.1%) and in differentiating active from residual lesions (60.6%).

The question about the timing for performing a follow-up ^{18}F-FDG PET-CT to monitor the response to antifungal therapy obtained variable responses (Fig. 3), although the majority considered it should be performed at 6 (53.7%) or 12 weeks (42.9%) after starting antifungals.

Based on the results of the ^{18}F-FDG PET-CT follow-up, many clinicians agreed they would change the management of the patient. Clinicians would shorten antifungal therapy if there were no FDG uptake (56.7%) or if there were a clear decrease in FDG uptake (even if had not totally disappeared) (29.2%). However, if FDG uptake persisted, 55.6% would prolong antifungal therapy. If there were an

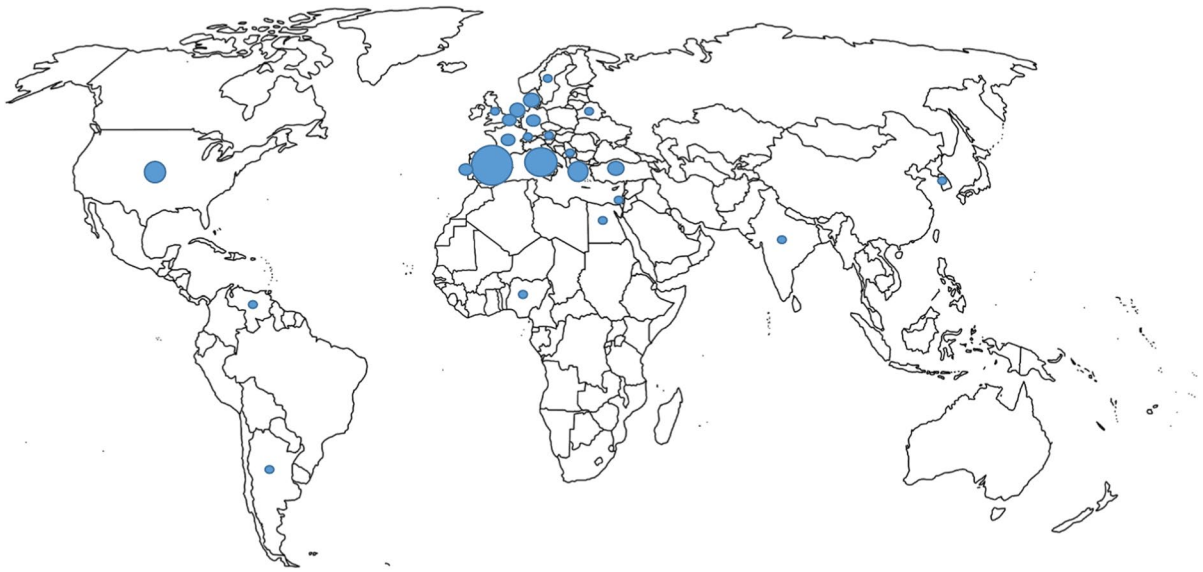

Fig. 1 Distribution of the countries of practice of the survey respondents

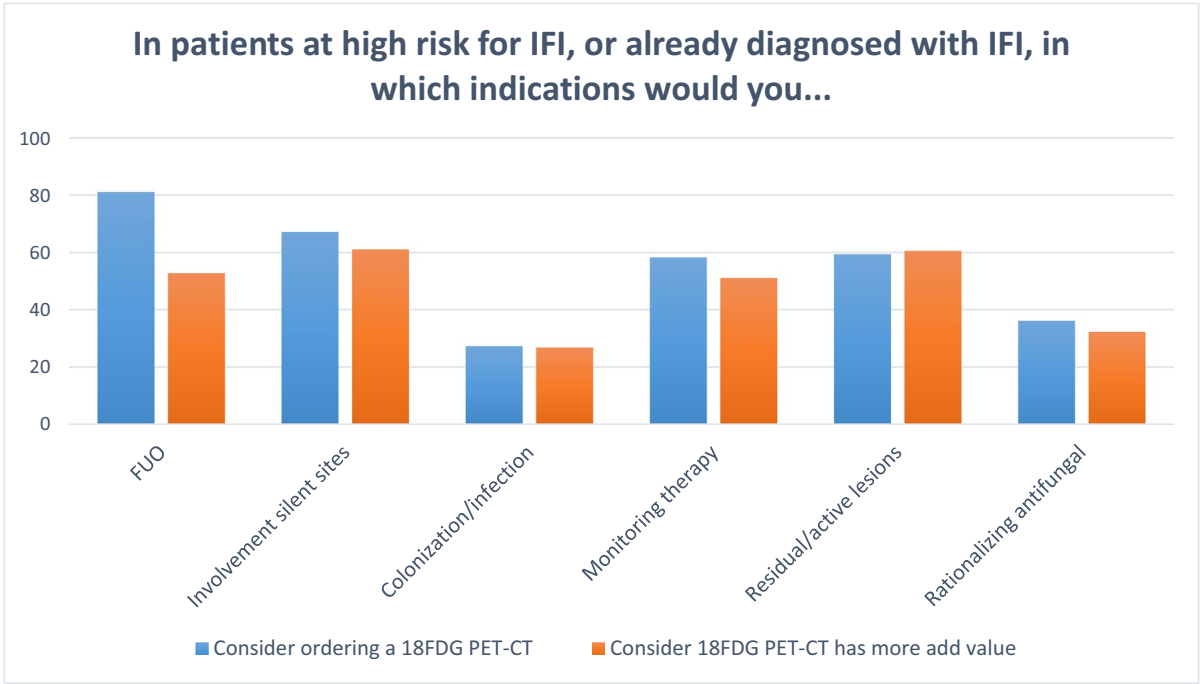

Fig. 2 Usefulness of 18F-FDG PET/CT for invasive fungal infection

increase in uptake or new lesions, 62.9% would consider performing new diagnostic tests and 61.2%

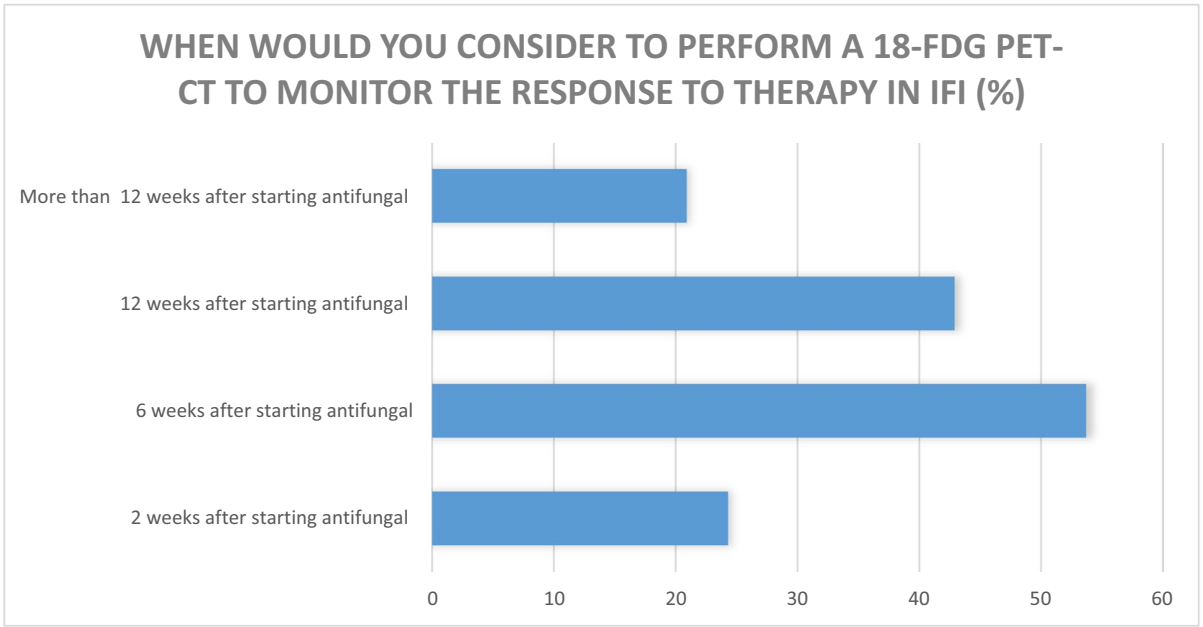

Fig. 3 When to perform 18F-FDG PET/CT to monitor the response to therapy in a patient with IFI

would consider a change in the therapeutic strategy. Only 3.9% would not modify it.

Fungal Endocarditis

Regarding ^{18}F-FDG PET-CT usefulness in candidemia to diagnose or rule out *Candida* endocarditis in the event of inconclusive echocardiography, 61.5% would use ^{18}F-FDG PET-CT in case of prosthetic endocarditis, 59.8% in case of cardiac device-associated endocarditis and 50.3% to unveil septic metastasis. Only 31.3% would perform ^{18}F-FDG PET-CT in all cases of candidemia and 5% would not use ^{18}F-FDG PET-CT and would prefer a different imaging technique.

Technical Aspects of 18F-FDG PET/CT Uptake

The responses regarding the duration of glucose uptake of fungal lesions in ^{18}F-FDG PET-CT when therapy is effective were very diverse, however, most respondents (44.8%) agreed on the influence of the patient's immunological status on persistence of uptake. In this sense, 91.6% believed that ^{18}F-FDG PET-CT could be useful in spite of the patient being neutropenic.

The ability of ^{18}F-FDG PET-CT to discern between different etiologies was enquired. Almost 50% believed it is possible to differentiate malignancy from fungal infection according to FDG uptake, while almost 50% (48.9%) believed that it is not. When evaluating the ability of ^{18}F-FDG PET-CT to distinguish bacterial from fungal infection using ^{18}F-FDG PET-CT, the agreement was greater, with a vast majority (86.6%) of respondents considering this is not possible. Nevertheless, a similar agreement was not found when asking about the possibility of different FDG uptake by different fungal species in ^{18}-FDG PET-CT, 46.9% believe that the uptake is different depending on the species versus 53.1% who believe it is not.

Radiation exposure can be a matter of concern. Compared to high-resolution CT (HRCT), 39.7% were unsure of the degree of radiation exposure, while the remaining answers were distributed between 29.6% who thought that radiation exposure in ^{18}F-FDG PET-CT is significantly less than HRCT; and 22.9% who considered that it has a slightly higher or a significantly higher 13 (7.3%) radiation exposure than a standard chest HRCT.

Personal Experience of the Respondents with the Use of 18-FDG PET-CT

The most common use of ^{18}F-FDG PET-CT was for Oncology indications (85.8%). A large proportion of the respondents (57.3%) used it commonly for infection management, but only 16.7% used it commonly specifically for IFI management. However, up to 80.9% reported an occasional use in this indication.

The experience in the use of ^{18}F-FDG PET-CT for the management of IFI is summarized in Figs. 4 and 5. The main indications for requesting a ^{18}F-FDG PET-CT in this setting were FUO (58.7%) followed by assessment of the response to antifungal therapy (48%), while uncovering occult lesions (52%) and diagnosis/exclusion of endocarditis 92 (52.7%) were the situations in which ^{18}F-FDG PET-CT was considered to have been the most useful.

The main barriers to the use of ^{18}F-FDG PET-CT for the management of IFI were the concern about cost-effectiveness (54.5%), lack of knowledge of its added value as compared to conventional imaging (39.6%), on site unavailability (19%), authorization only for Oncology indications (13.2%) or the fear of exposing patients to additional radiation (10.7%).

Discussion

The present survey sheds light on the areas of uncertainty regarding ^{18}F-FDG PET-CT usefulness for IFI management, underlines the need for spreading the available information to take advantage of its added value and reveals barriers to the use of ^{18}F-FDG PET-CT in this indication.

Demographics and Access to ^{18}F-FDG PET/CT

The majority of the respondents of the survey belong to the target population that takes care of patients with IFI: practitioners who work in third level hospitals with Oncology and Hematology units, or that care for solid organ transplantation recipients or manage ICU patients. A large proportion were senior specialists experienced with the use of ^{18}F-FDG PET-CT. Consequently, their answers reflect the current

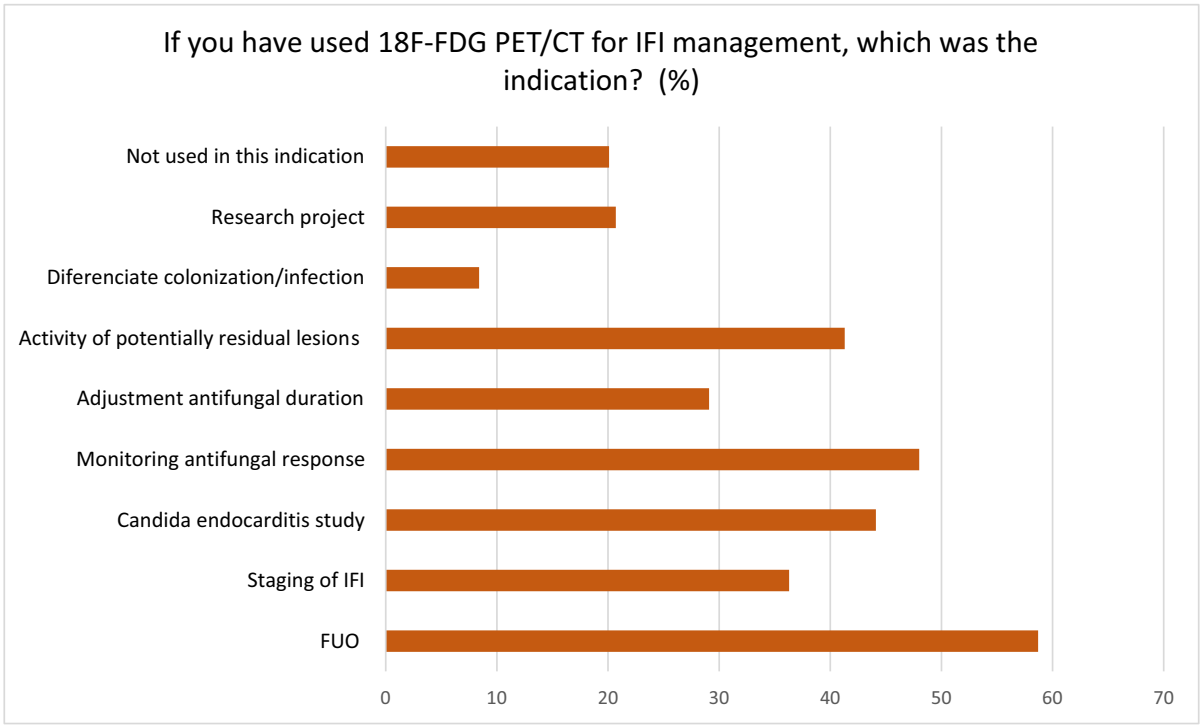

Fig. 4 Personal experience on the use of 18F-FDG PET/CT: Indication

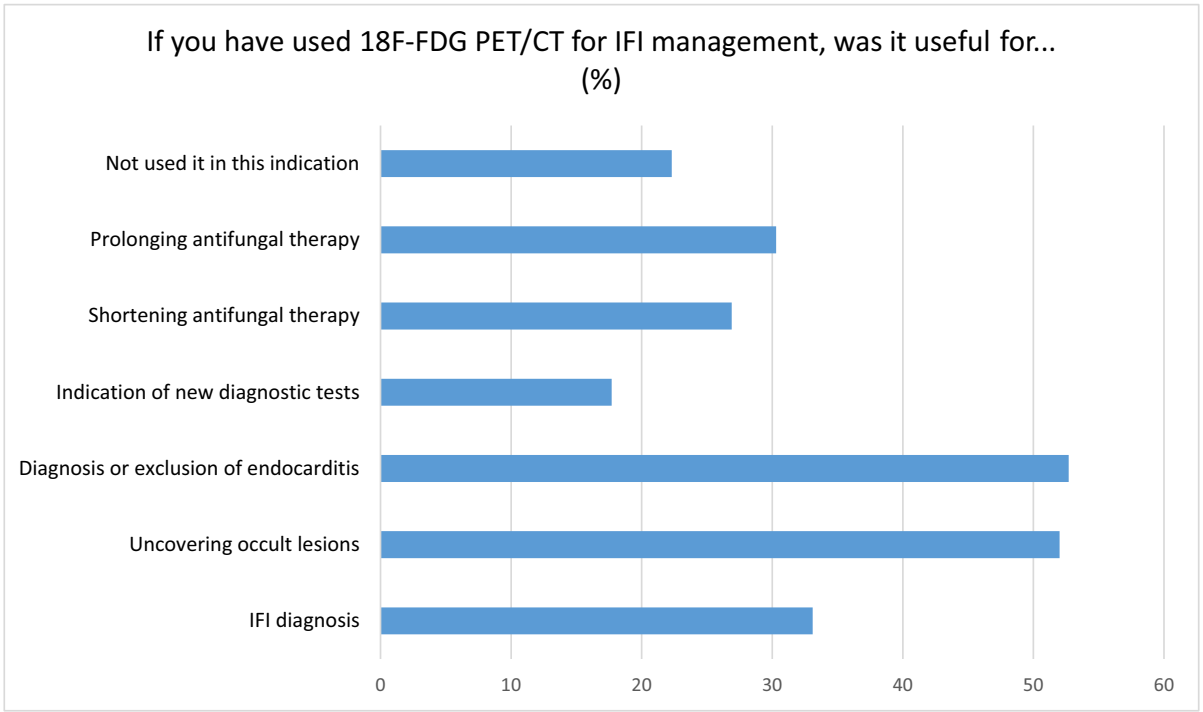

Fig. 5 Personal experience on the use of 18F-FDG PET/CT: Usefulness

access to ^{18}F-FDG PET-CT, and the knowledge and experience of physicians on this indication in developed countries.

Access to ^{18}F-FDG PET/CT

^{18}F-FDG PET-CT was accessible to almost all the respondents, but there is a need to implement its use for infection, and to reduce the delay to get it done in a timely manner. This delay can lead to a decrease in its performance. Despite data from several studies increasingly supporting the usefulness of ^{18}F-FDG PET-CT for the management of infection in immunocompromised patients [2, 5, 16–18], practitioners encountered barriers such as disagreement regarding the indication and, in some cases, lack of reimbursement. Likewise, a survey conducted in Australia obtained similar results regarding access to ^{18}F-FDG PET-CT for the management of infection [19] in spite of the clinicians considering it useful. There is little data on the cost-effectiveness of ^{18}F-FDG PET-CT compared to conventional imaging. A cost-effectiveness analysis of the PIPPIN study has recently been published that reflects that ^{18}F-FDG PET-CT is cost effective when compared to CT for investigation of neutropenic fever in high-risk patients, providing further support for incorporation of ^{18}F-FDG PET-CT into clinical guidelines [20].

Indications of ^{18}F-FDG PET-CT in Invasive Fungal Infection

Diagnosis/Exclusion and Rationalization of Antifungals

Several studies, mostly retrospective, have demonstrated the usefulness of ^{18}F-FDG PET-CT for IFI diagnosis in high risk patients [12, 21], in particular in non-neutropenic patients whose lower fungal burden and amount of necrosis hinder the diagnosis [18], or cases that are clinically silent or involve extrapulmonary sites [14]. A high proportion of respondents would consider performing ^{18}F-FDG PET-CT in this scenario. However, only a small percentage would consider performing ^{18}F-FDG PET-CT to distinguish colonization from invasion, in spite of some evidence in this area [22].

Regarding neutropenic patients, the vast majority of the respondents were aware of ^{18}F-FDG PET-CT usefulness in patients with neutropenia, in accordance with previous studies that demonstrate that it is a reliable technique even in patients with severe neutropenia [4, 9]. In view of the growing evidence in this area, institutions should facilitate the use of ^{18}F-FDG PET-CT as part of the study of FN, and in particular to exclude IFI.

Less than 40% of clinicians were aware that despite only a small proportion of high risk patients being eventually diagnosed with IFI, the negative ^{18}F-FDG PET-CT results allow to discontinue empirical antifungals, and so, rationalize antifungal use, as shown by a recent clinical trial that compares an ^{18}F-FDG PET-CT-based strategy to the standard imaging-based strategy [5]. So far, studies comparing ^{18}F-FDG PET-CT versus conventional techniques head to head in the same patient are lacking [12]. More prospective, comparative studies are needed to better determine its role.

Staging (Dissemination/Endocarditis)

IFI presentation may vary depending on the immune status (e.g. neutropenic versus non neutropenic), and fever may be the only manifestation of persisting infection. Dissemination with multiple organ involvement is not uncommon, especially in immunocompromised patients, often remaining clinically silent. The detection of these silent lesions can modify patient management, especially when considering a stem cell transplant or initiation of chemotherapy, as in the setting of further immunosuppresion, fungal infection can reactivate from previously silent sites. However, staging is not a clearly established practice in routine evaluation of IFI. Despite the available literature, less than half of those surveyed considered performing ^{18}F-FDG PET-CT at the time of diagnosis for staging the infection, and a large percentage did not consider that it provided an added value in this setting. Regarding both mold and yeast infections, several authors have shown the superiority of ^{18}F-FDG PET-CT over CT scan to detect silent lesions [10] or lesions outside the regions imaged by the anatomy-based studies in almost 50% of the cases [1].

In the case of fungemia, staging includes the evaluation for endocarditis. In this indication, only one third of those surveyed, and up to 62% in specific circumstances, would use ^{18}F-FDG PET-CT. According to the guidelines, ^{18}F-FDG PET-CT does have a role in patients with prosthetic valves [15, 23]. It has proven useful to detect septic metastases [24, 25], and especially helpful in cases with dubious or negative echocardiography [14], but the available evidence on ^{18}F-FDG PET-CT use in candidemia is still scarce and based in retrospective single center studies.

Monitoring the Response (Duration/Residual/Active)

The optimal antifungal treatment duration is a controversial issue [24, 25]. The assessment of the response to antifungal therapy is typically based on clinical signs, fungal biomarkers and imaging. Conventional imaging can be confusing when it comes to differentiate active from residual lesions. There is data in favor of ^{18}F-FDG PET-CT for the assessment of the activity of residual lesions [1, 2, 10, 14].

Although more than 80% of respondents considered that ^{18}F-FDG PET-CT could be of help for monitoring the response to antifungal therapy, and around 60% considered that one of its main contributions is precisely the ability to distinguish active from residual lesions, there was no consensus on when would be the optimal moment to perform a follow-up ^{18}F-FDG PET-CT to monitor response to treatment. The majority pointed to 6 or 12 weeks from the start of the antifungals. Two ongoing prospective studies that will perform systematic ^{18}F-FDG PET-CT at different time points in different subsets of patients with IFI will hopefully help clarify this issue (OPTIFIL study, https://ichgcp.net/es/clinical-trials-registry/NCT02955966; PETIFI PROJECT29, Clinical trials.gov identifier NCT05688592 [3].

More than half of the clinicians that answered the survey would take into account the results of the ^{18}F-FDG PET-CT to make changes in treatment or order new diagnostic tests. However, as validated by the answers of 45% of the respondents, the patient's immunological status is likely to influence the duration of the glucose uptake, presumably reflecting the fungal activity [26]. Different duration of activity of fungal lesions has been observed in different types of hosts [14]. The natural history of the ^{18}F-FDG PET-CT imaging of IFI is still unknown, and the optimal uptake threshold to safely discontinue antifungal needs to be determined.

Other Technical Aspects of ^{18}F-FDG PET/CT Uptake

Cancer lesions present typically a high glucose uptake in ^{18}F-FDG PET-CT. Historically, a SUV of 2.5 or higher was considered to be indicative of malignant tissue; however, there has been a wide range of SUVs reported for other diseases [27]. Uncertainty about the different ^{18}F-FDG PET-CT uptake by lesions of diverse etiology was reflected in the responses to the survey, with 50% believing that it would be possible to differentiate neoplasia from infection, or considering that different fungal species could have different glucose uptake intensities. On the contrary, a large majority believed that it is not possible to distinguish bacterial from fungal infection based on glucose uptake. Interestingly, several publications suggest that glucose uptake by fungal lesions is often above the 2.5 SUV threshold, and that it could vary depending on the fungal species [2, 14]. Further studies on IFI characteristics in ^{18}F-FDG PET-CT will improve evaluation of Oncology and Hematology patients at risk for IFI.

^{18}F-FDG PET-CT generates somewhat more radiation than CT since patients are receiving not only radiation from the CT component of the examination but also lingering radiation from the radiopharmaceutical, ^{18}F-FDG [28, 29]. In this sense, inconsistent answers from the survey indicate lack of awareness of this issue by the majority of the respondents. Only 23% indicated the correct option, that is, that ^{18}F-FDG PET-CT has a slightly higher exposure than HRCT, similar to the answers in the survey carried out among Australian practitioners [19]. Awareness of this only small increase in radiation exposure might help eliminate barriers for the use of ^{18}F-FDG PET-CT.

Experience of Participants in the Use of ^{18}F-FDG PET-CT

Despite the availability of ^{18}F-FDG PET-CT among the respondents, slightly more than half used it regularly for infection management, but only 17% specifically for IFI management, compared to a widespread use in Oncology indications. This results are similar to those of a European survey on the treatment of invasive aspergillosis [25] and the Australian survey [19].

Barriers to the use of ^{18}F-FDG PET-CT for IFI, in addition to the aforementioned access and funding difficulties, consist in unawareness of existing evidence in some aspects and insufficient evidence in others, reflected by the percentage of respondents who doubted about its added value as compared to conventional techniques or believed that it did not provide relevant information, and a great proportion who reported concerns about its cost-effectiveness in this indication. Additionally, the survey showed some concern of exposure to additional radiation.

Evidence regarding ^{18}F-FDG PET-CT usefulness for IFI management is based mainly in retrospective single center studies. Although ^{18}F-FDG PET-CT has long been used in patients at high risk for IFI, and its results in monitoring the response to antifungals are promising, there are still many areas of uncertainty (Table 2). Prospective multicenter studies that compare head to head ^{18}F-FDG PET-CT to conventional imaging in the same patient are needed, especially regarding natural history of IFI from ^{18}F-FDG PET-CT perspective, follow-up timing and criteria to safely end antifungal therapy.

Limitations of the Survey

Only 10.4% of those to whom the survey was sent responded and, almost 69% of the questions had incomplete answers, in line with other surveys [19]. However, the characteristics of the respondents correspond to the target population of physicians managing patients with IFI, so that we can consider that the results are generalizable to clinicians working in hospitals of similar characteristics. The majority of the respondents come from southern European countries, though there was a considerable representation of a variety of other mainly western countries. Another limitation of the study is in the interpretation of the questions and, therefore, in how the doctors responded. This may have influenced the variability of some of the responses.

Conclusion

Although many clinicians consider that ^{18}F-FDG PET-CT could be better than conventional techniques for IFI management, there remain many areas of uncertainty to be resolved regarding its role in this

Table 2 Areas of uncertainty regarding usefulness of ^{18}F-FDG PET-CT for IFI management to be addressed by future research

Area	Evidence gap/research question	Required investigations
Diagnosis	Value of ^{18}F-FDG PET-CT for the differential diagnosis between colonization and infection in patients with positive cultures from non-sterile sites	Prospective study that analyzes the results of performing ^{18}F-FDG PET-CT to assess active lesions in patients with fungal isolates and whether it determines modification of management
	Value of ^{18}F-FDG PET-CT for the differential diagnosis between bacterial and fungal infection	Multicenter registry that compares the type of uptake of the different etiologies
	Value of ^{18}F-FDG PET-CT for the differential diagnosis between fungal species infection	Multicenter registry that compares the type of uptake of the different fungal species
	Value of ^{18}F-FDG PET-CT for the differential diagnosis between cancer and fungal infection	Multicenter registry that compares the type of uptake of the different etiologies
Staging	Added value of ^{18}F-FDG PET-CT performed at diagnosis to rule out or confirm dissemination	Head to head comparison with conventional techniques
Follow-up	Normal duration of glucose uptake in ^{18}F-FDG PET-CT in the case of a good outcome, and to what extent is it influenced by immunological status	Serial ^{18}F-FDG PET-CT at different time points in patients with different types of underlying immunocompromise and correlation with outcome
	Optimal timing of follow-up ^{18}F-FDG PET-CT	Protocolized ^{18}F-FDG PET-CT at different time points of IFI follow-up
	Optimal glucose uptake threshold to stop antifungals	Correlation of ^{18}F-FDG PET-CT SUV values with clinical parameters and fungal biomarkers
Prognosis	^{18}F-FDG PET-CT parameters such as TLG (total lesion glycolysis) and MV (metabolic volume) showed the ability to predict whether a patient will achieve a complete metabolic response	Prospective study that analyzes patient´s outcome through these parameters
Efficiency	Disagreement about the indication of ^{18}F-FDG PET-CT for IFI as compared to conventional imaging	Cost-effectiveness studies
	Lack of reimbursement of ^{18}F-FDG PET-CT in this indication	

indication. Unawareness of existing evidence, and lack of good quality evidence in other areas, hamper its generalized use. The present survey unveils the need to generate evidence to establish a protocolized use of ^{18}F-FDG PET-CT that helps clinicians in their day-to-day decision making to improve IFI management in a cost-effective way.

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Declarations

Conflict of interest The authors declares that they have no conflicts of interest.

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