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ORIGINAL ARTICLE

FDG PET/CT imaging in detecting and guiding management of invasive fungal infections: a retrospective comparison to conventional CT imaging

A. P. Douglas[1,2,3] · K. A. Thursky[1,2,3,4,5] · L. J. Worth[1,2,3,5] · E. Drummond[6] · A. Hogg[6] · R. J. Hicks[2,6] · M. A. Slavin[1,2,3,4]

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Abstract

Purpose Invasive fungal infections (IFIs) are common in immunocompromised patients. While early diagnosis can reduce otherwise high morbidity and mortality, conventional CT has suboptimal sensitivity and specificity. Small studies have suggested that the use of FDG PET/CT may improve the ability to detect IFI. The objective of this study was to describe the proven and probable IFIs detected on FDG PET/CT at our centre and compare the performance with that of CT for localization of infection, dissemination and response to therapy.

Methods FDG PET/CT reports for adults investigated at Peter MacCallum Cancer Centre were searched using keywords suggestive of fungal infection. Chart review was performed to describe the risk factors, type and location of IFIs, indication for FDG PET/CT, and comparison with CT for the detection of infection, and its dissemination and response to treatment.

Results Between 2007 and 2017, 45 patients had 48 proven/probable IFIs diagnosed prior to or following FDG PET/CT. Overall 96% had a known malignancy with 78% being haematological. FDG PET/CT located clinically occult infection or dissemination to another organ in 40% and 38% of IFI patients, respectively. Of 40 patients who had both FDG PET/CT and CT, sites of IFI dissemination were detected in 35% and 5%, respectively ($p < 0.001$). Of 18 patents who had both FDG PET/CT and CT follow-up imaging, there were discordant findings between the two imaging modalities in 11 (61%), in whom normalization of FDG avidity of a lesion suggested resolution of active infection despite a residual lesion on CT.

Conclusion FDG PET/CT was able to localize clinically occult infection and dissemination and was particularly helpful in demonstrating response to antifungal therapy.

Keywords Positron emission tomography · Computed tomography · Cancer · Invasive fungal infections · Diagnosis

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✉ A. P. Douglas
abby.douglas@petermac.org

1 Department of Infectious Diseases, Peter MacCallum Cancer Centre, 305 Grattan St, Parkville, Melbourne, VIC, Australia

2 University of Melbourne, Melbourne, Australia

3 The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Australia

4 Victorian Infectious Diseases Service, The Peter Doherty Institute for Immunity and Infection, Royal Melbourne Hospital, Melbourne, Australia

5 The National Centre for Antimicrobial Stewardship, Melbourne, Australia

6 Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia

Introduction

Invasive fungal infections (IFIs) are common in immunosuppressed patients, particularly patients with haematological malignancy, occurring in up to 30% of those with acute leukaemia and following 20% of stem cell transplants without prophylaxis [1–3]. Breakthrough IFIs also occur despite prophylaxis [4]. Furthermore, the population at risk of IFI is ever-expanding [5] and patients are living for longer than previously, with consequently longer periods at risk of infection [6]. Mortality rates attributable to IFI are high, in the order of 35–100% in invasive mould infection (IMI) [7–11]. Importantly, it has been shown that early treatment of IFI can improve outcomes [12]; hence early detection of IFI is desirable. However, the current standard diagnostics for early detection of IFI, which include high-resolution CT (HRCT), are suboptimal due to variable sensitivity [13, 14]. Early IFI diagnosis still eludes us, particularly in haematology patients who may lack distinct clinical and radiographic features of IFI [15].

There has been recent interest in the use of FDG PET/CT in the early diagnosis of IFI and as a means of following response to treatment [16–18]. ^{18}F-Fluorodeoxyglucose positron emission tomography combined with X-ray computed tomography (FDG PET/CT) utilizes radiolabelled glucose to localize areas of increased cellular metabolism on PET with low-dose CT to localize abnormalities. FDG PET/CT is a functional imaging technique that allows whole-body scanning that is of particular value when attempting to identify clinically occult and disseminated infections. Small studies have shown promising results indicating that FDG PET/CT has higher sensitivity in the identification of IFI than conventional CT [13, 17, 19], and demonstrates benefit in identifying areas of clinically occult infection and dissemination [13, 18–22]. Although the presence of active malignancy can be a confounding factor in differentiating infective foci from tumour involvement, the pattern of abnormality and correlative CT findings can generally allow assignment of the relative likelihoods of each process [23].

The optimal duration of antifungal therapy for IFI can be difficult to determine in immunocompromised patients. Accordingly, long treatment courses are prescribed because of the concern for relapse and associated morbidity and mortality. Conventional CT imaging may show persistent changes beyond resolution of infection and hence is a poor guide to the duration of antifungal therapy [24, 25]. Small studies have indicated that FDG PET/CT may provide guidance on the duration of antifungal treatment given its functional imaging capacity, with the potential to differentiate active infection from residual scar tissue [17, 18, 22, 26–29]. These reports, however, are either case reports or small case series, mostly describing yeast or dimorphic fungal infection only, with mould infection relatively under-examined.

The Peter MacCallum Cancer Centre is a large quaternary referral centre in Melbourne, Australia, which specializes in the management of haematological malignancy, haematopoietic stem cell transplant (HSCT) and solid tumours. As a PET/CT referral centre for other hospitals in metropolitan Melbourne including the Royal Melbourne Hospital, it also receives patients without confirmed malignancy. From this diverse referral base, collection of a large, multicentre cohort with IFI is possible. We describe the FDG PET/CT findings of a broad range of IFIs detected through our PET centre, compare these to the findings on conventional CT imaging and assess the ability of both modalities to detect clinically occult sites of infection and dissemination, and guide antimicrobial management.

Materials and methods

This was a retrospective study of proven or probable IFIs detected or evaluated by FDG PET/CT imaging performed at the Peter MacCallum Cancer Centre, Melbourne over a 10-year period from May 2007 to May 2017. The definitions of proven and probable IFI are complex, but in brief, proven IFI refers to the confirmed identification of fungal infection in a sterile site by culture, cryptococcal antigen detection or histopathology, or evidence of fungal tissue invasion on histopathology from needle aspiration or biopsy. Probable infection refers to the isolation of fungus or galactomannan at a site in conjunction with host predisposition and clinical features [30].

PET/CT database and case finding

All FDG PET/CT reports are stored in a radiology information system (RIS). This RIS (Karisma; Kestral Pty Ltd., Perth, Australia) was queried for the keywords: fungal, fungus, fungi, mould, mycosis, aspergillus, aspergillosis, mucormycosis, mucor, candida, candidiasis, cryptococcus and cryptococcosis. The search was refined to include only adult patients (18+ years of age). Reports were reviewed for mention of a potential IFI as a differential diagnosis, and irrelevant reports were excluded. A review of the medical record in those remaining was performed and only those with a proven or probable IFI according to EORTC/MSG criteria [30] were included.

Data collection and definitions

Medical records were reviewed to capture uniform data regarding: patient demographics, details of any underlying malignancy and its treatment, other risk factors for IFI, use of antifungal prophylaxis, characteristics of IFI (mould or yeast, genus and species of fungi), method of diagnosis, EORTC/MSG classification [30] and site of infection, IFI treatment and duration and 12-week survival. Neutropenia was defined as polymorphonuclear neutrophils <0.5 cells/L, lymphopenia <1.0 cells/L and panleucopenia as concomitant neutropenia, lymphopenia and monocytopenia (<0.2 cells/L) for >10 days during the month preceding IFI diagnosis.

FDG PET/CT data

The indication for FDG PET/CT was extracted from the request slip and patient history and classified into staging/restaging of malignancy, for assessment of fever of unclear focus, for characterization of an abnormality detected by other imaging or evaluation of a previously diagnosed infection. The site of infection and maximum standardized uptake value (SUVmax) were recorded. FDG PET/CT was classified as contributing to management if it localized infection, revealed a clinically occult site of infection (e.g. in those with fever of unclear focus, or on staging) or detected dissemination. Findings on CT performed within a month of FDG PET/CT were recorded as for FDG PET/CT except for SUVmax (not measurable on CT). Findings on follow-up FDG PET/CT and CT were recorded if available.

FDG PET/CT performance

According to our standard oncological acquisition protocol, patients fasted for a minimum of 4 h prior to FDG administration. Patients with a blood glucose level (BGL) of >10 mmol/L underwent a dedicated protocol to reduce the level to <10 mmol/L. This included either further fasting or administration of short-acting insulin and an observation period of at least 60 min until the BGL had reached a nadir and had started to rise again, indicating loss of exogenous insulin effects. All studies were acquired on a combined PET/CT scanner (GE Discovery STE, GE Discovery 690, GE Discovery 710 or Biograph mCT). The CT scan was acquired from the vertex of the scalp to at least the mid-thigh, but generally to the toes if occult infection was suspected. The CT scan (as part of the combined PET/CT scan) was generally acquired without oral or intravenous administration of contrast agent and as a low-dose study. The PET scan included the same axial field of view and was processed using an iterative reconstruction algorithm (OSEM) with standard corrections for scatter and randoms.

If a prior or contemporaneous diagnostic CT scan had been performed, the PET imaging specialists had access to the images and report from this scan for correlative purposes, as in conventional clinical practice.

Patient work-up

Standard work-up for a pulmonary parenchymal abnormality suspicious for IFI included bronchoscopy with cytology, bacterial and fungal microscopy and culture, *Aspergillus* PCR and galactomannan, respiratory virus and *Pneumocystis jirovecii* PCR. The results from bronchoscopy performed within 2 weeks of imaging were recorded.

Statistical analysis

IFI detection, identification of disseminated infection, and demonstrated response to antifungal therapy are reported as proportional outcomes for each investigative arm (PET/CT and conventional CT). Outcomes were compared using the chi-squared or Fisher's exact test, as appropriate, with $p < 0.05$ deemed statistically significant (Stata v12; StataCorp, College Station, TX). The study was approved by the Peter MacCallum Human Research Ethics Committee (approval no.: HREC/17/PMCC/142).

Results

Over the 10-year period of this study, approximately 67,000 PET/CT scans were performed at our centre. The keyword search of the RIS reports yielded 419 individual patients: 374 were excluded as either the report was not suggestive of IFI (most commonly due to identification of the phrase "mycosis fungoides"), or the findings on diagnostic work-up did not fulfil the EORTC criteria for proven or probable IFI. Thus 45 patients were eligible for analysis.

Demographics and risk factors

In the cohort of 45 studied patients, 48 separate IFI episodes were diagnosed . The demographics, malignancy type, treatment for malignancy including transplantation and the indication for FDG PET/CT are shown in Table 1. Overall, 96% of patients had a malignancy with 78% of all patients having a haematological malignancy. Of the 45 patients, 12 (27%) had received autologous HSCT and 8 (18%) allogeneic HSCT. Other risk factors for IFI are shown in Fig. 1. Of the 45 patients, 12 (27%) were neutropenic and 29 (64%) had neutropenia, lymphopenia or both within a month of IFI diagnosis on PET. The respiratory virus copathogens identified on bronchoscopy PCR included rhinovirus (six episodes), and parainfluenza 3, influenza A and B and adenovirus (one each). Nonrespiratory viral coinfections included nontuberculous mycobacteria (in two patients), *Pneumocystis jirovecii* (in two), *Nocardia* (in one) and both a mould and a yeast identified (in one). Of the IFIs detected on FDG PET/CT, 18% were incidental findings on staging or restaging scans with the remainder detected as part of work-up for infection or for characterization of an abnormality detected on other imaging. Nine patients were on mould-active prophylaxis and experienced breakthrough IMI (Table 2).

Aetiology of IFIs

Of the 48 separate IFI episodes, 19 were proven and 29 were probable. There were 41 IMIs and 7 invasive yeast infections (IYIs; Table 3). The majority of IMIs were aspergillosis ($n = 31$), but several patients had *Lomentospora*/*Scedosporium* infections ($n = 7$).

Sites of infection

The majority of IFIs involved only the lungs (34 of 48 infections, 71%), but eight infections involved the lungs together with other organs (17%), including lymph node (LN) infection (four), central nervous system (CNS) infection (one), CNS infection and fungaemia (one), CNS infection and sinusitis

Table 1 Demographics and underlying malignancy of the 45 patients with IFI seen on FDG/PET scan

Characteristic	Value
Age (years)	
Range	19–80
Mean	57.1
Median	61
Sex	
Male	29 (64%)
Female	16 (36%)
Underlying malignancy	
Haematological malignancy	35 (78%)
Non-Hodgkin's lymphoma	10
Multiple myeloma	6
Chronic lymphocytic leukaemia	6
Acute myeloid leukaemia	5
Acute lymphoblastic leukaemia	4
Myelofibrosis	1
Hodgkin's disease	1
Hairy cell leukaemia	1
Chronic myeloid leukaemia	1
Oncological malignancy[a]	8 (18%)
No malignancy[b]	2 (4%)
Treatment for malignancy	
Chemotherapy	39 (87%)
High-dose steroids[c]	9 (20%)
Autologous HSCT	12 (27%)
Allogeneic HSCT[d]	8 (18%)
Radiotherapy	4 (9%)
Extracorporeal photopheresis	2 (4%)
Indication for FDG PET/CT	
Staging/restaging of malignancy	8 (18%)
Abnormality on other imaging modality	4 (9%)
Fever of unclear focus	10 (22%)
Evaluation of known infection	23 (51%)

[a] Four patients had lung cancer, one each had melanoma, colorectal cancer, adrenocortical carcinoma and breast cancer plus immune thrombocytopenic purpura

[b] One patient had common variable immune deficiency, one patient had severe chronic obstructive pulmonary disease

[c] >20 mg prednisone/day for >1 month

[d] Six matched related donors, one matched unrelated donor, one cord transplant

(one), and hepatosplenic collections (one). The six infections without lung involvement are described below.

Of patients with invasive aspergillosis, 90% had pulmonary involvement only, two patients had pulmonary and LN involvement and one had CNS and sinoorbital involvement only (Fig. 2). Of seven patients with *Lomentospora*/*Scedosporium* infections, three had pulmonary involvement only, two had sinus involvement only, one had fungaemia with pulmonary and hepatosplenic dissemination (Fig. 2), and one had pulmonary, CNS and sinus involvement. Of four patients with invasive cryptococcosis, all had lung involvement, one had mediastinal LN involvement, two had concomitant meningitis and one had fungaemia. All patients with invasive candidiasis had candidaemia, with urinary, hepatosplenic or intraabdominal foci (*see* Supplementary Table 1 for details of the sites of infection by pathogen).

Characteristics of fungal lesions

The FDG avidity of lesions based on SUVmax is summarized, by pathogen, in Table 3. All invasive *Cryptococcus* and *Candida* lesions had an SUVmax greater than 2.5.

FDG PET/CT versus conventional CT

Table 4 summarizes the findings on FDG PET/CT and on conventional CT. CT did not localize IFI as well as FDG PET/CT, typically because CT showed nonspecific pulmonary consolidation in contrast to the clear nodularity and focal FDG avidity seen on FDG PET/CT. Overall, FDG PET/CT was able to locate clinically occult infection or dissemination to another organ or tissue in 40% and 38% of IFI infections, respectively. In those who had both FDG PET/CT and CT scans, sites of IFI dissemination were detected in 35% and 5%, respectively ($p < 0.001$). Examples of extrapulmonary abnormalities detected solely on FDG PET/CT were FDG-avid LNs (six patients), hepatosplenic and intraabdominal collections (three patients), bony and muscular lesions (two patients), and CNS and orbital involvement (one patient).

Follow-up FDG PET/CT was performed at a median of 2.5 months after initial FDG PET/CT (range 0.5 to 13 months). Of the 18 patients who had both FDG PET/CT and CT follow-up imaging, the findings were discordant in 11 (61%), where the normalization of FDG avidity of a lesion suggested that the active infection had resolved, yet the CT scan showed a persisting lesion (Fig. 2).

Treatment and mortality

All patients with a diagnosed IFI were treated with recommended antifungal therapy. Overall mortality at 12 weeks was 9/45 (20%), with mortality of 2/7 (29%) and 8/39 (21%) in those with IYI and IMI, respectively, including one patient who died with both IYI and IMI.

Discussion

This study provided important data on the role of FDG PET/CT in the diagnosis and management of IFI. Notably, FDG

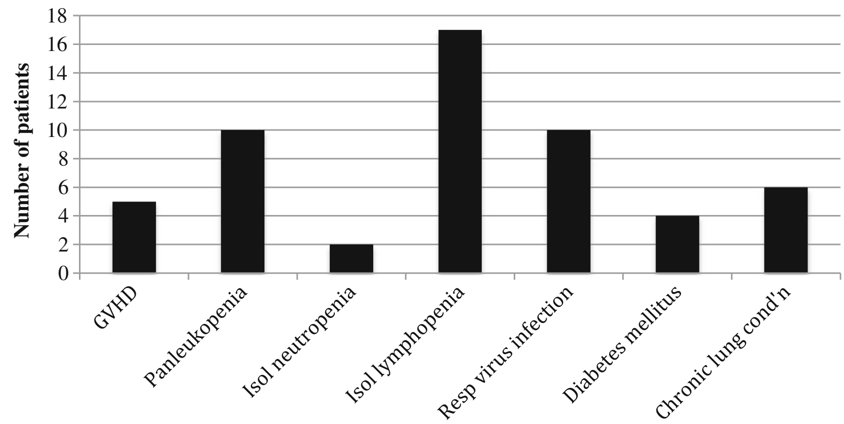

Fig. 1 Other risk factors for invasive fungal infection. Respiratory virus coinfections included rhinovirus (6), parainfluenza 3 (1), influenza A (1), influenza B (1), and adenovirus (1). Chronic lung conditions included pulmonary fibrosis, bronchiectasis, COPD and lung cancer. *GVHD* graft versus host disease, *isol* isolated, *resp* respiratory, *cond'n* condition

PET/CT performed well even in patients with severe neutropenia. Further, FDG PET/CT detected IFI in patients where CT did not, and particularly detected areas of dissemination significantly more frequently than CT, and provided important information regarding response to antifungal therapy. Our findings support those of smaller studies indicating the value of FDG PET/CT in IFI management. A small study in haematological patients with neutropenic fever comparing the sensitivity of FDG PET/CT and CT in the detection of IFI showed that FDG PET/CT was 100% sensitive [13]. A prospective single-centre study in 30 adults and children with probable or proven IFI showed similar results [17]. Our findings are also consistent with those of studies identifying occult infection and dissemination, that showed particular benefit of FDG PET/CT in identifying intraabdominal infection including hepatosplenic dissemination [13, 17].

Importantly, in this study follow-up FDG PET/CT was found to be particularly useful in assessing response to antifungal therapy. Frequently, there was clear resolution of FDG avidity on FDG PET/CT but with a residual lesion on CT indicative of a scar or inactive granuloma. This suggests that FDG PET/CT may be more useful than CT for informing decisions regarding cessation of antifungal therapy. Only one other small study in patients with IMIs found that FDG PET/CT was more useful than CT in 36% of patients [18], and other case series have shown more restricted benefit in the identification of invasive yeast infections, and particularly in monitoring hepatosplenic candidiasis therapy [17, 24, 31, 32]. The utility of FDG PET/CT for guiding decisions on the duration of therapy is significant, given the cost of antifungal therapy and therefore its potential to reduce unnecessary overall healthcare costs related to the management of IFIs [21].

In this study, proven and probable IFI was detected incidentally in 18% of patients, with all requiring antifungal treatment and therefore with implications for the timing of treatment of the underlying malignancy. This study also demonstrates the inherent issue with the use of SUVmax alone to stratify lesions on FDG PET/CT as probably benign or malignant. Traditionally, pulmonary lesions with an SUVmax of 2.5 or greater have been thought likely to be malignant [33]. However, this study highlights the tendency of pulmonary IFIs to be highly FDG-avid and more often than not to have an SUVmax of ≥2.5. Clearly, tissue diagnosis is required in those lesions suspicious of pulmonary malignancy. In this context, we recommend nonsurgical methods of diagnosis such as endobronchial sampling on bronchoscopy or percutaneous CT-guided biopsy as a first diagnostic step, particularly if IFI is a possibility since these methods can identify specific organisms.

Table 2 Antifungal prophylaxis in patients experiencing breakthrough invasive fungal infection

Antifungal prophylaxis	Antifungal agent	Infective species	No. of patients with breakthrough
Mould-active	Posaconazole	*Aspergillus* spp.	2
		Aspergillus niger	1
		Lomentospora prolificans	1
		Scedosporium apiospermum	1
	Voriconazole	*Lomentospora prolificans*	2
		Scedosporium apiospermum	1
	Amphotericin B	*Aspergillus terreus*	1
Yeast-active	Fluconazole	*Candida krusei*	1
	Posaconazole	*Candida glabrata*	1

Table 3 Invasive fungal infections by genus and species, with description of SUVmax distribution per genus

Fungal infection	Number (% of overall moulds/yeasts)	SUVmax	
		Median (range)	Percentage above 2.5
Moulds (*n* = 41)			
Aspergillus spp.	31 (76%)	6.5 (1.5–21.9)	94%
A. fumigatus	14		
Species only	11		
A. niger	3		
A. flavus	2		
A. terreus	1		
Lomentospora/*Scedosporium* spp.	7 (17%)	4.0 (2.2–4.9)	86%
L. prolificans	5		
S. apiospermum	2		
Mucormycetes	2 (5%)	6.1 (2.2–10.0)	50%
Rhizopus microsporum	1		
Cunninghamella betholletiae	1		
Mould NOS	1 (2%)	8.2	100%
Yeasts (*n* = 7)			
Candida spp.	3 (43%)	4.7 (4.4–9.0)	100%
C. albicans	1		
C. glabrata	1		
C. krusei	1		
Cryptococcus	4 (57%)	7.2 (3.8–15.8)	100%
C. neoformans	3		
Cryptococcus NOS	1		

NOS not otherwise specified

The limitations of this study include its retrospective nature, and the fact that single-centre experience was evaluated, potentially limiting generalizability to other groups. Further, we cannot comment on the overall sensitivity of FDG PET/CT for proven or probable IFI as overall IFI diagnoses was not the denominator used here. Thirdly, FDG PET/CT is associated

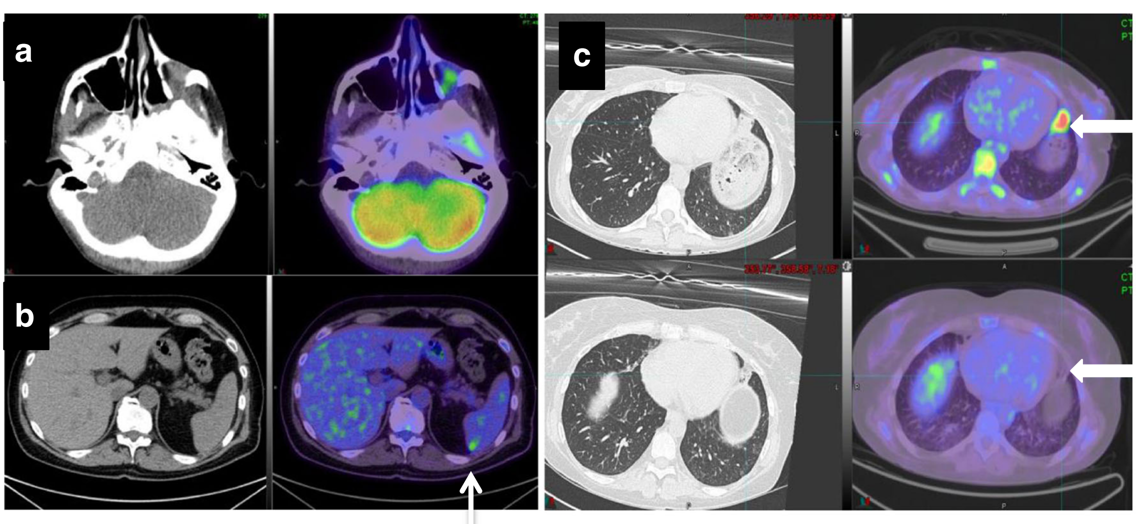

Fig. 2 Selected FDG PET/CT images illustrating appearances of IFI. **a** Low-dose CT and fused PET/CT images of sinoorbital infection with *Aspergillus*. **b** Low-dose CT and fused PET/CT images of disseminated scedosporiosis with FDG-avid splenic lesion (*thin arrow*). **c** Typical pulmonary *Aspergillus* lesion in the left lower lobe (*top* low-dose CT and fused PET/CT images), and images after antifungal treatment (*bottom* low-dose CT and fused PET/CT images) demonstrating discordant PET/CT and CT responses (*thick arrows*)

Table 4 Yield of FDG PET/CT and conventional CT

	PET/CT (*n* = 40)	CT (*n* = 40)	*p* value
Identification of clinically occult infection	17 (48%)	15 (38%)	0.765[b]
Yield of CT vs. PET	–	15/17 (88%)	
Identification of dissemination	14 (35%)	2 (5%)	<0.001[b]
Yield of CT vs. PET	–	2/14 (14%)	
Response to antifungal therapy on follow-up imaging[a]			
All scans	30/32 (94%)	14/25 (56%)	<0.001[b]
PET and CT	18/18 (100%)	7/18 (39%)	<0.001[c]
Discordance between PET and CT	–	11/18 (61%)	

[a] 18 patients had follow-up PET and CT scans; therefore treatment response could be compared

[b] Chi-squared test

[c] Fisher's exact test

with slightly higher radiation exposure than HRCT; however, one could argue that it removes the need for sequential imaging with multiple modalities (e.g. HRCT followed by PET/CT) and also enables localization of nonpulmonary occult infection and dissemination which would require a more extensive diagnostic CT scan (i.e. sinus, chest, abdomen and pelvis). The strengths of this study are in the size of the reported cohort and its attention on the detection of occult IFI and its dissemination and the examination of response to therapy, all of which are important management issues in heavily immunocompromised patients requiring ongoing treatment for their malignancy.

Conclusion

This study indicated that FDG PET/CT could be used to detect IFI in immunocompromised patients with persistent fever when conventional CT is noncontributory. Furthermore, incidental findings on FDG PET/CT that are suggestive of infection should be pursued for a diagnosis as clinically significant IFI that will affect the cancer management plan and survival may be detected. FDG PET/CT could be a useful way to monitor response to IFI treatment, particularly when the patient has clinically responded, has had adequate duration of empirical therapy, and CT suggests persistent lesions. Further large-scale prospective and multicentre evaluation of these recommendations is required.

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