

¹⁸F-FDG PET/CT for diagnosing infectious complications in patients with severe neutropenia after intensive chemotherapy for haematological malignancy or stem cell transplantation

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Abstract

Purpose Between 30 and 50% of febrile neutropenic episodes are accounted for by infection. C-reactive protein (CRP) is a nonspecific parameter for infection and inflammation but might be employed as a trigger for diagnosis. The aim of the study was to evaluate whether ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT can be used to detect inflammatory foci in neutropenic patients with elevated CRP and whether it helps to direct treatment.

Methods Twenty-eight consecutive patients with neutropenia as a result of intensive chemotherapy for haematological malignancies or myeloablative therapy for haematopoietic stem cell transplantation were prospectively included. ¹⁸F-FDG PET/CT was added to the regular diagnostic workup once the CRP level rose above 50 mg/l.

Results Pathological FDG uptake was found in 26 of 28 cases despite peripheral neutrophil counts less than $0.1 \times 10^9/l$ in 26 patients: in the digestive tract in 18 cases, around the tract of the central venous catheter (CVC) in 9 and in the lungs in 7 cases. FDG uptake in the CVC tract was associated with coagulase-negative staphylococcal bacteraemia ($p < 0.001$) and deep venous thrombosis ($p = 0.002$). The number of patients having *Streptococcus mitis* bacteraemia appeared to be higher in patients with grade 3 oesophageal FDG uptake ($p = 0.08$). Pulmonary FDG uptake was associated with the presence of invasive fungal disease ($p = 0.04$).

Conclusion ¹⁸F-FDG PET/CT scanning during chemotherapy-induced febrile neutropenia and increased CRP is able to detect localized foci of infection and inflammation despite the absence of circulating neutrophils. Besides its potential role in detecting CVC-related infection during febrile neutropenia, the high negative predictive value of ¹⁸F-FDG PET/CT is important for avoiding unnecessary diagnostic tests and therapy.

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Introduction

Fever frequently develops during the profound neutropenia induced by intensive chemotherapy but is not always related to infection. It has long been the standard of care to start treatment with broad-spectrum antibiotics promptly once fever is observed because infection can be life-threatening. Between 30 and 50% of febrile episodes are

caused by infection. Most cases are caused by bacteraemia, but invasive fungal pulmonary disease also occurs, and this is the most important infectious cause of death in stem cell recipients with mortality rates varying between 50 and 90% [1–3]. Inflammation of the mucosa of the digestive tract induced by cytotoxic treatment of haematological malignancies manifests itself as mucositis and also leads to elevated C-reactive protein (CRP) levels and fever, often preceding certain types of bacteraemia typically with *Streptococcus mitis* [4, 5].

Coagulase-negative staphylococcal (CoNS) bacteraemia is seen in 30% of recipients of haematopoietic stem cell transplantation (HSCT), and the central venous catheter (CVC) usually implanted to manage most patients is assumed to be the source of this bacteraemia. Transient bacteraemia secondary to mucosal barrier injury, however, may also lead to infection of the CVC and to catheter-related thrombi [6–8].

Early recognition of infection contributes to better patient outcomes [2, 9]. Unnecessary treatment, on the other hand, is associated with side effects, the development of resistant microorganisms and increased costs [10–12]. Hence, it is important to attempt to distinguish fever due to mucosal barrier injury and fever caused by infection whenever possible. ^{18}F -Fluorodeoxyglucose (FDG) positron emission tomography (PET) proved capable of detecting localized infectious and noninfectious inflammatory foci in immunocompetent patients often before any anatomical changes could be detected by conventional radiological techniques [13–16]. Since ^{18}F -FDG PET/CT depends not only on neutrophils, it was hypothesized that this technique can also be used in severely neutropenic patients [17–19].

We therefore performed a prospective observational study among patients given myeloablative chemotherapy for haematological malignancies. The aim of the study was to determine whether ^{18}F -FDG PET/CT allows detection of inflammatory foci in patients with severe neutropenia. We also explored the possibility of using ^{18}F -FDG PET/CT to direct treatment of infectious complications in patients with elevated CRP levels during neutropenia. ^{18}F -FDG PET/CT was also evaluated for pathological FDG uptake in the digestive tract because of expected mucosal barrier injury.

Materials and methods

This was a prospective, descriptive study in which the relationship between clinically defined infection (CDI) and microbiologically defined infection (MDI) with ^{18}F -FDG PET/CT findings was defined. The Regional Ethics Committee granted approval (CMO nr 11231).

Patients

All consecutive patients admitted between November 2006 and June 2007 to the Department of Haematology for remission induction or consolidation chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS), or for a HSCT following myeloablative therapy, were eligible provided treatment was expected to result in neutropenia of more than 7 days duration. CRP levels (upper limit of normal 10 mg/l) were determined twice weekly and an ^{18}F -FDG PET/CT scan was made as soon as the CRP concentration exceeded 50 mg/l. Patients were withdrawn from the study when there was evidence of haemodynamic instability, diabetes mellitus if insulin had to be administered within 4 h before the ^{18}F -FDG PET/CT scan or when glucose levels exceeded 15 mmol/l at the time of ^{18}F -FDG PET/CT. The study ended when the patient was discharged. All patients gave written informed consent.

^{18}F -FDG PET/CT

An integrated PET/CT scanner (Siemens Biograph, Knoxville, TN, USA) was used for data acquisition. ^{18}F -FDG PET/CT was performed according to the European Association of Nuclear Medicine (EANM) guidelines [20]. Before FDG injection, patients fasted and glucose or insulin-containing intravenous infusions were discontinued for 6 h. One hour after intravenous injection of 3.5 MBq/kg FDG (Covidien, Petten, The Netherlands), a low-dose CT of the area between the proximal femora and the base of the skull was made for anatomical correlation and attenuation correction of the PET data. Subsequently, emission images of the same area were acquired. FDG uptake in the digestive tract was compared to liver uptake. The digestive tract was divided into three anatomical regions: oesophagus, small bowel and colon. Lack of FDG uptake was graded as 0, FDG uptake less than that in the liver was designated grade 1, equal to liver uptake as grade 2 and as grade 3 when uptake was more than that in the liver [21].

Low dose CT versus high-resolution CT (HRCT) of the thorax

^{18}F -FDG PET/CT was combined with HRCT of the thorax when HRCT of the thorax was indicated because of suspected invasive pulmonary fungal disease [10, 22–24]. The trigger for ordering HRCT for high-risk patients included the following: signs or symptoms of pulmonary disease, abnormal chest X-ray, a plasma galactomannan index of >0.5 or fever persisting for >4 days despite broad-spectrum antibiotic treatment.

Regular patient monitoring

Monitoring of patients was performed according to standard clinical practice. CRP determination was the only additional test to the regularly scheduled laboratory tests. ^{18}F -FDG PET/CT was included in the regular diagnostic workup when CRP exceeded 50 mg/l. Additional investigations to confirm ^{18}F -FDG PET/CT findings were only performed when clinically justified. Epidemiological data, the number, type and results of all diagnostic tests and treatment data were registered in an electronic case record form (File-Maker Pro 9.0).

Confirmation of ^{18}F -FDG PET/CT findings

^{18}F -FDG PET/CT reading was performed by two nuclear medicine physicians. The low-dose CT provided anatomical reference for ^{18}F -FDG PET abnormalities and was not used for diagnostic purposes. On the same day, this was reported to the attending physician. To be included in patient management, ^{18}F -FDG PET/CT findings had to be supported by clinical evidence, microbiological tests and routine radiology. Invasive techniques such as biopsy, bronchoscopy or endoscopy were only performed when clinically indicated.

The ^{18}F -FDG PET/CT assessments were independently re-evaluated (F.V. and W.O.) without knowledge of the final diagnosis or the outcome. At a later stage, a differential diagnosis of febrile neutropenia was made independently without knowledge of the ^{18}F -FDG PET/CT assessment by an infectious disease specialist (F.V.) and a specialist in infectious diseases in haematology (P.D.).

Clinical features

Bacteraemia was defined by the recovery of a microorganism from a single percutaneous blood culture, except for members of the skin commensal flora such as CoNS or coryneforms in which case an identical isolate had to be recovered from two simultaneous sets of percutaneous blood cultures, or from each lumen of a three- or four-lumen CVC. Bacteraemia was deemed persistent when blood cultures drawn on at least 2 separate days yielded growth of the same isolate.

Catheter exit site infection was defined by the development of any of the following manifestations within 2 cm of the exit site: erythema or tenderness or induration or seropurulent discharge (CDI). When any potential pathogen was isolated from a specimen of the exit site or >15 colony-forming units (cfu) were isolated in pure culture from segment A (the external catheter) or segment B (the subcutaneous part of the catheter), the infection was

deemed an MDI. Tunnel infection was defined by the development of any of the following along the subcutaneous tract: cellulitis, erythema or tenderness or induration with or without an exit site infection. In the absence of a specimen of the tunnel infection, the cause was assumed to be the same as that of an exit site infection when one existed. Septic thrombophlebitis at the site of a CVC was defined as persistent bacteraemia, and deep venous thrombosis as diagnosed by ultrasound or venography, and no other source of infection explaining the persistence of bacteraemia [25]. No specific testing for mucosal bowel injury was performed. Citrulline levels, however, have shown to be a reproducible measure for intestinal villous mass [26]. Measurement of citrulline levels had been performed in the majority of the patients. Citrulline levels below 10 $\mu\text{mol/l}$ have been interpreted as severe mucosal bowel injury in other studies and replace other indirect functional tests to assess cytotoxic effects of chemotherapy [27]. Invasive fungal disease (IFD) was classified as possible, probable and proven according to European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) guidelines [10].

Outcome parameters

The primary outcome parameter was the ability of ^{18}F -FDG PET/CT to locate an inflammatory (infectious or noninfectious) focus during neutropenia. Secondary outcome parameters were the ability of ^{18}F -FDG PET/CT to be used to direct treatment of infectious complications in patients with elevated CRP levels during neutropenia and the ability of ^{18}F -FDG PET/CT to depict mucosal barrier injury.

Statistical analysis

Descriptive statistics were done to compare ^{18}F -FDG PET/CT with current practice regarding identification of infectious or inflammatory foci explaining fever or other potential signs of infection. Per anatomical area patients with or without pathological FDG uptake were assessed for the presence of a clinically and microbiologically defined illness. Differences between patients with or without pathological FDG uptake were tested using Fisher's exact tests for categorical variables. Differences were considered to be statistically significant when the p value was less than 0.05 (two-sided).

Results

A total of 37 eligible patients provided written consent. CRP levels remained below 50 mg/l in six cases, one

Table 1 Patient characteristics

Patient, sex, age (years), haematological disease	Clinical, microbiological and radiological diagnoses						Citruiline (µmol/l)	FDG uptake			
	Persistent CoNS bacteraemia	<i>Strep. mitis</i> bacteraemia	DVT subclavian vein	IFD	Other			CVC tract	Lung	Colon (grade 3)	Oesophagus (grade 3)
1, M, 66, AML	Yes		N/A		Typhlitis		No CVC	Yes	Yes		
2, F, 63, MM			N/A			4.4		Yes	Yes		
3, F, 33, AML	Yes		Yes			4.3	Yes	Yes			
4, M, 54, AML	Yes		Yes			7.0	Yes				
5, F, 42, AML	Yes		No	Yes (possible)	Typhlitis	6.9		Yes	Yes		
6, M, 62, NHL			N/A			4.5					
7, M, 48, NHL		Yes	N/A			4.9		Yes	Yes		
8, M, 59, MM		Yes	N/A			4.4		Yes	Yes		
9, M, 41, MM			N/A	Yes (probable)			No CVC	Yes			Thyroid lesion
10, M, 50, MDS			N/A		<i>Candida</i> abscess thyroid gland	6.9					
11, M, 58, NHL			N/A								
12, F, 57, MDS		Yes	N/A	Yes (possible)	Typhlitis	2.9		Yes	Yes		
13, M, 54, MDS	Yes		Yes	Yes (possible)		6.6	Yes	Yes			
14, M, 44, NHL		Yes	No	Yes (possible)		6.3		Yes	Yes		
15, M, 52, NHL			N/A	Yes (possible)		18.7		Yes			
16, M, 40, ALL	Yes		Yes			6.0	Yes		Yes		
17, M, 59, AML		Yes	N/A			3.5		Yes	Yes		
18, M, 31, HL			N/A			9.3			Yes		
19, F, 49, AML			N/A			7.1			Yes		
20, F, 48, CMML	Yes		Yes			5.8			Yes		
21, F, 59, MDS	Yes		Yes			10.7	Yes	Yes			
22, F, 45, AML	Yes		No			8.1	Yes		Yes		
23, M, 45, MDS	Yes		N/A			11.6			Yes		
24, M, 55, AML	Yes		N/A		Typhlitis		Yes		Yes		
25, M, 36, ALL	Yes		No	Yes (probable)			Yes	Yes			
26, M, 62, MM			N/A								
27, M, 52, MM		Yes	N/A						Yes		
28, F, 44, AML	Yes	Yes	Yes				Yes		Yes		

CoNS coagulase-negative staphylococcal, DVT deep venous thrombosis, IFD invasive fungal disease, CVC central venous catheter, N/A ultrasound not performed, no clinical signs of thrombosis, AML acute myeloid leukaemia, MM multiple myeloma, NHL non-Hodgkin's lymphoma, MDS myelodysplastic syndrome, ALL acute lymphatic lymphoma, HL Hodgkin's lymphoma, CMML chronic myelomonocytic leukaemia

patient who experienced clinical deterioration withdrew consent before ^{18}F -FDG PET/CT could be performed and ^{18}F -FDG PET/CT could not be performed in a further two cases due to technical problems. Hence, 28 cases were evaluated (Table 1).

On average, CRP reached 50 mg/l on day 12 after starting chemotherapy. In 26 of 28 (93%) patients this was accompanied by fever. ^{18}F -FDG PET/CT was performed a mean of 14 days after starting chemotherapy when all patients were still profoundly neutropenic: 26 had peripheral neutrophil counts less than $0.1 \times 10^9/\text{l}$. Pathological FDG uptake was found in 26 of 28 cases (93%) (Table 1). Grade 3 uptake was found in the digestive tract in 18 cases, uptake in the CVC tract was seen in 9 cases and abnormal pulmonary uptake was found in 7 cases. In one case, localized FDG uptake in the right thyroid lobe was found during the neutropenic phase (Fig. 1) although the patient had no localizing symptoms. He deteriorated 1 week later due to persistent candidemia. A second ^{18}F -FDG PET/CT scan, made 3 weeks after the first scan, indicated abscess formation in the right thyroid lobe, which was confirmed by surgical drainage and culture.

FDG uptake in the CVC tract and CoNS bacteraemia

Of the 28 patients included in the study, 26 had a CVC. FDG uptake in the CVC tract was only seen in nine patients, all of whom had persistent CoNS bacteraemia ($p < 0.001$). The presence of FDG uptake in the CVC tract was not related to clinical signs of exit site or tunnel infection. Ultrasounds were only performed in the presence of local complaints, such as swelling of the arm, to exclude deep venous thrombosis. An ultrasound of the subclavian vein was performed in 11 of 26 (42%) patients, amongst whom all 9 patients with FDG uptake in the CVC tract. In case of deep venous thrombosis alone without concomitant persistent CoNS bacteraemia, FDG uptake in the CVC tract was never seen (see Table 1). Confirmed

deep venous thrombosis in combination with persistent CoNS bacteraemia (septic thrombophlebitis) was present in seven patients. Increased FDG uptake in the subclavian tract was found in six of these seven cases with confirmed septic thrombophlebitis. In three patients FDG uptake in the CVC tract was present without confirmed septic thrombophlebitis. Persistent CoNS bacteraemia was present in all three of them, but an ultrasound deep venous thrombosis was ruled out in two of them and was not performed in the last patient.

In the patients without FDG uptake in the CVC tract septic thrombosis was ruled out either by an ultrasound ruling out thrombosis in 1 patient or the absence of persistent bacteraemia in 14 patients. In only one patient could septic thrombophlebitis not be ruled out definitely as despite the presence of persistent CoNS bacteraemia no ultrasound was performed. However, no clinical signs of thrombosis were present. The positive predictive value of ^{18}F -FDG PET/CT for the presence of septic thrombophlebitis was 67% and the negative predictive value 94%.

In four of these six cases with septic thrombophlebitis delineated by ^{18}F -FDG PET/CT the first ultrasound was negative and thrombosis could only be confirmed by a second ultrasound, whereas ^{18}F -FDG PET/CT had been positive at the time of the first ultrasound (Fig. 2).

FDG uptake in the intestinal wall and *Streptococcus mitis* bacteraemia

FDG uptake grade 2 or more was found in the digestive tract, irrespective of the localization, in 24 of 28 (86%) cases. Citrulline levels were known in 20 of 28 patients (see Table 1). In two of the four patients in whom no pathological FDG uptake was found in the digestive tract citrulline levels were measured and below $10 \mu\text{mol/l}$. FDG uptake grade 2 or more in the oesophagus and colon were not concomitant ($p = 1.0$). Grade 3 FDG uptake in the wall of the oesophagus was seen in 11 cases. Endoscopy was not performed in these patients. Of these 11 patients, 7

Fig. 1 Patient 10 with a *Candida* abscess in the right thyroid lobe, already present on the first (left) ^{18}F -FDG PET/CT scan and increased on a second scan (right)



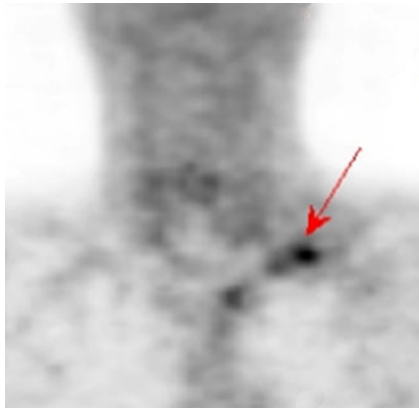


Fig. 2 Patient 4 with a swollen arm showed FDG uptake in the left subclavian tract. Thrombosis of the subclavian vein was rejected by normal ultrasound and he was discharged from the hospital 4 days later. Two days later, the patient was readmitted for progressive swelling of his arm. Deep venous thrombosis was confirmed by a repeat ultrasound and blood cultures after removal of the CVC remained positive for CoNS. The diagnosis of septic thrombophlebitis of the subclavian vein was further supported by CT

(64%) had retrosternal complaints consistent with oesophagitis (Fig. 3). Only one of the patients with retrosternal complaints did have *Streptococcus mitis* bacteraemia. On the other hand there appeared to be an association between *Streptococcus mitis* bacteraemia and grade 3 oesophageal FDG uptake ($p=0.08$), as five of seven patients with *Streptococcus mitis* bacteraemia did have grade 3 FDG uptake in the oesophagus (Table 2). Grade 3 FDG uptake in the wall of the colon was found in 13 cases, but there was no correlation with *Streptococcus mitis* bacteraemia ($p=0.2$). Four patients had severe abdominal complaints consistent with typhlitis and grade 3 colonic FDG uptake was found in each case (Fig. 4).

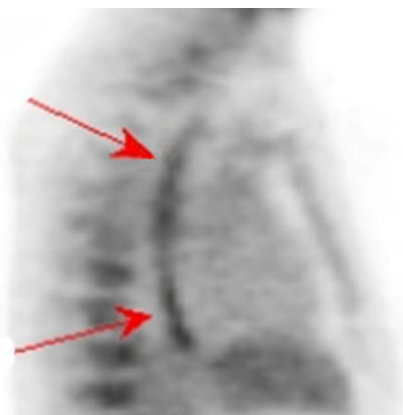


Fig. 3 Grade 3 FDG uptake in the oesophagus in patient 8. He developed *Streptococcus mitis* bacteraemia during the neutropenic phase

Table 2 *Streptococcus mitis* bacteraemia and FDG uptake in the digestive tract

	<i>S. mitis</i> bacteraemia present ($n=7$)	<i>S. mitis</i> bacteraemia absent ($n=21$)
FDG uptake oesophagus grade 3	5*	6
FDG uptake oesophagus <grade 3	2	15
FDG uptake colon grade 3	5	8
FDG uptake colon <grade 3	2	13

Streptococcus mitis bacteraemia is most often found in patients with grade 3 oesophageal FDG uptake

* $p=0.076$

Pulmonary FDG uptake and IFD

Proven invasive pulmonary fungal disease was not found, but five patients had possible and two patients had probable IFD (Fig. 5). Pulmonary FDG uptake was present in both cases of probable IFD and in 3 of the 5 cases with possible IFD and in only 2 of 21 patients without IFD. Pulmonary FDG uptake therefore is associated with the presence of IFD ($p=0.04$). Probable IFD was never present in the absence of pulmonary FDG uptake.

Discussion

This study shows that localized foci of infection or inflammation can be visualized by ^{18}F -FDG PET/CT during severe neutropenia. It has been shown before that

Fig. 4 ^{18}F -FDG PET/CT images of patient 1 during severe right side abdominal pain, diarrhoea and signs of local peritonitis on physical examination, showing grade 3 FDG uptake in the entire colonic wall



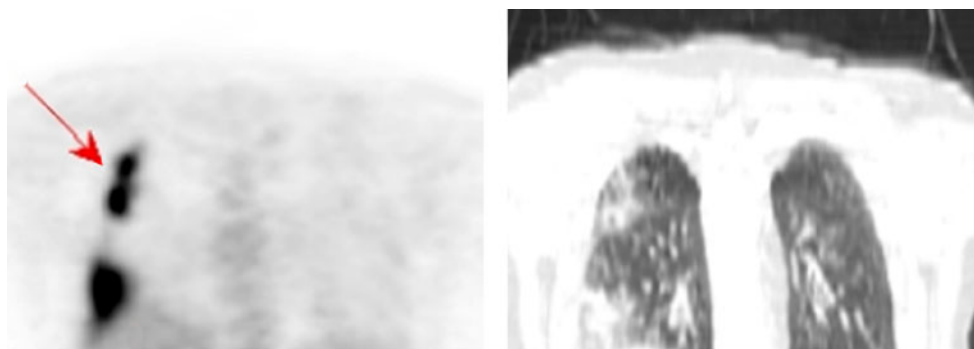


Fig. 5 ^{18}F -FDG PET/CT images during the neutropenic phase after allogeneic stem cell transplantation of patient 9 treated for multiple myeloma. The ^{18}F -FDG PET/CT scan shows extensive pulmonary FDG uptake in both lungs (image shows pathological uptake in the right lung). A chest X-ray made because of fever during the

neutropenic phase was unremarkable 3 days earlier. The HRCT scan performed on the same day as the ^{18}F -FDG PET/CT showed bilateral consolidations, with a surrounding halo of ground glass supporting probable IFD

^{18}F -FDG PET/CT is capable of visualizing localized areas of inflammation by using the accelerated metabolism of different activated inflammatory cells, other than neutrophils, such as macrophages and monocytes [17–19, 28]. This suggests that not only activated neutrophils, but also other inflammatory cells play a role in visualizing localized infection or inflammation by ^{18}F -FDG PET/CT. Some retrospective studies have reported the possibility of visualizing infectious foci by ^{18}F -FDG PET/CT in neutropenic patients, but only a minority of these patients were deeply neutropenic at the time ^{18}F -FDG PET/CT was performed in contrast to all of our study patients [25, 29, 30]. In the largest study so far among patients with multiple myeloma ($n=248$), ^{18}F -FDG PET/CT was performed for disease staging in most patients ($n=199$) and for infection workup in the remaining 49 patients [29]. In total, 165 infectious foci were detected in that study. Neutropenia ($<1.0 \times 10^{-9}/\text{l}$) was present in only 27 of 248 (11%) patients, however. Most probably FDG uptake in other activated inflammatory cells is the explanation for the visualization of inflammatory foci on ^{18}F -FDG PET/CT in the vast majority of patients in our study despite neutrophil counts below $0.1 \times 10^9/\text{l}$ [17, 18].

We found a clear correlation between FDG uptake in the CVC tract and septic thrombophlebitis of the subclavian vein. This supports the results of another study on the value of ^{18}F -FDG PET/CT in the diagnosis of septic thrombophlebitis in which ^{18}F -FDG PET/CT was prospectively conducted in patients with suspected septic thrombophlebitis [25, 30]. ^{18}F -FDG PET/CT showed pathological tracer uptake in all nine patients with proven septic thrombophlebitis. Control patients in that study were collected from a retrospective cohort of patients with deep venous thrombosis without signs of infection in whom an ^{18}F -FDG PET/CT was performed for other reasons. Selection bias in that study makes it impossible to calculate positive and negative predictive values of ^{18}F -FDG PET/CT regarding detection

of septic thrombophlebitis. A caveat in our study is, however, that ultrasound was only performed on clinical grounds, so we might have missed asymptomatic deep venous thrombosis. The negative predictive value of ^{18}F -FDG PET/CT for the presence of septic thrombophlebitis, however, can be estimated to be high (94%) as in only one patient with persistent bacteraemia was a deep venous thrombosis ruled out solely on the absence of clinical signs. The positive predictive value (67%) regarding septic thrombophlebitis on the other hand might be underestimated in our study, because ultrasound was not performed in all patients precluding these patients from fulfilling the definition of septic thrombophlebitis. In three patients with FDG uptake in the subclavian tract and persistent bacteraemia only one ultrasound was performed. This is important as strikingly ^{18}F -FDG PET/CT seemed to precede detection of the abnormalities on ultrasound of the subclavian vein in four cases of septic thrombophlebitis. Therefore, pathological FDG uptake in the CVC tract in patients with febrile neutropenia should not be ignored as it might have important consequences in CVC management, e.g. line removal, particularly when persistent bacteraemia is diagnosed.

Pulmonary FDG uptake was frequently seen in this study and was related with possible or probable IFD. In the absence of pulmonary FDG uptake probable or definite IFD was never the cause of fever at the time ^{18}F -FDG PET/CT was performed. An adequate comparison with HRCT, which already has an added value in the early recognition of life-threatening IFD, was not possible in our study because ^{18}F -FDG PET/CT and HRCT were not performed within a time frame of several days in enough patients [22–24]. Data show, however, that IFD can be visualized despite profound neutropenia.

Metastatic infection was diagnosed in only one patient with a *Candida* abscess in the thyroid gland. No other metastatic foci were diagnosed by clinical symptoms or

signs or other imaging techniques in our study. Consequently, the negative predictive value of ^{18}F -FDG PET/CT for excluding clinically relevant metastatic foci of infection is likely to be high assuming that these foci reveal themselves due to intensive monitoring for symptoms and signs when left untreated.

Substantial FDG uptake in the digestive tract was seen in almost every case, but digestive tract uptake is contentious as it is known to yield false-positive results [31]. A visual grading for gastrointestinal activity was chosen due to the variability in distribution and extent of the enhanced FDG uptake in the gut. Theoretically, chemotherapy may have influenced FDG uptake in the liver, which was chosen as the organ of reference. However, all patients were scanned at approximately the same point in time during the course of treatment, thus reducing the possibility of chemotherapy-induced variability in liver uptake. Furthermore, none of the patients was receiving metformin at the time the ^{18}F -FDG PET/CT was performed, excluding another important cause of increased FDG uptake [32]

We specified uptake according to the anatomical region and graded uptake comparing it to liver uptake to circumvent this problem as has been done by others for staging disease activity in colitis, which then showed a firm correlation with disease activity [21, 33]. An interesting finding was the possible correlation between oesophageal FDG uptake and *Streptococcus mitis* bacteraemia, which was not seen in colonic FDG uptake. These findings support the theory that *Streptococcus mitis* bacteraemia originates from oesophageal mucosal barrier injury [34]. Increased FDG uptake may be the result of mucositis with or without infection since this has been shown to be associated with thickening of the oesophagus [35]. Besides mucosal barrier injury, there may be an additional local factor such as infection due to *Streptococcus mitis* of the mucosa, resulting in increased FDG uptake [36]. Surprisingly no FDG uptake was found in the digestive tract in some patients despite citrulline levels below $10\ \mu\text{mol/l}$. Probably this supports the presence of an additional inflammatory factor. Further studies on this subject, however, should be performed.

Conclusion

^{18}F -FDG PET/CT during chemotherapy-induced febrile neutropenia and increased CRP is able to visualize localized foci of infection and inflammation despite the absence of neutrophils in the peripheral blood. Besides the potential role of ^{18}F -FDG PET/CT in early detection and managing specific infectious complications during febrile neutropenia, i.e. septic thrombophlebitis and metastatic infection, its high negative predictive value may help in avoiding unnecessary diagnostics and therapy.

Conflicts of interest None.

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