Workspace 'IGG4 Related Diseases' in 'PET_CLINICS'

Page 1 (row 1, column 1)

IGG4 RD
(Related Disease)

tissue infiltration by IgG4-positive plasma cells, tissue fibrosclerosis, and elevated serum IgG4 concentration. The most important feature of IgG4-RD is chronic inflammation with multiple organ involvement. IgG4-RD has been found in multiple organs/tissues, including the pancreas (also known as autoimmune pancreatitis), pan- creatobiliary tract, lacrimal gland, salivary gland, lung, retroperitoneal region, and kidney.52 Clini- cally, more than half of the patients have elevated serum IgG4 levels, and the initial response to corticosteroid-based treatment is usually good, although relapses are frequent.5
-Utility of PET/Computed Tomogr...tion and Inflammation Imaging, p.7

18F FDG-PET/CT is useful in patients with IgG4- RD, as it can identify the disease distribution in the whole body
-Utility of PET/Computed Tomogr...ion and Inflammation Imaging, p.7

diffusely elevated 18F FDG uptake in the pancreas and salivary glands, patchy lesions in the retroperitoneal region and vascular wall, and multiorgan involvement that cannot be interpreted as metastasis.
-Utility of PET/Computed Tomogr...ion and Inflammation Imaging, p.7

most commonly affected sites were the lymph nodes followed by submandibular salivary glands.
-Utility of PET/Computed Tomog...n and Inflammation Imaging, p.7

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-Utility of PET/Computed Tomo...on and Inflammation Imaging, p.7

in selecting a biopsy site for the pathologic examination of tissue that is necessary to diagnose or exclude IgG4-RD, which in turn can increase the diagnostic yield.56
-Utility of PET/Computed Tomo...n and Inflammation Imaging, p.7

comprising 20 patients, 7 had 18F FDG uptake in organs not suspected of involvement on a clinical basis alone, which included retroperitoneum, lymph nodes, thoracic aorta, lung, lacrimal glands, and nasopharynx.
-Utility of PET/Computed Tomo...on and Inflammation Imaging, p.7

EXTENDED REPORT

The value of ^{18}F-FDG-PET/CT in identifying the cause of fever of unknown origin (FUO) and inflammation of unknown origin (IUO): data from a prospective study

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Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211687).

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Received 22 April 2017
Revised 24 August 2017
Accepted 8 September 2017
Published Online First
19 September 2017

ABSTRACT

Background Fever of unknown origin (FUO) and inflammation of unknown origin (IUO) are diagnostically challenging conditions. Diagnosis of underlying disease may be improved by ^{18}F-fluorodesoxyglucose positron emission tomography (^{18}F-FDG-PET).

Methods Prospective study to test diagnostic utility of ^{18}F-FDG-PET/CT in a large cohort of patients with FUO or IUO and to define parameters that increase the likelihood of diagnostic ^{18}F-FDG-PET/CT. Patients with FUO or IUO received ^{18}F-FDG-PET/CT scanning in addition to standard diagnostic work-up. ^{18}F-FDG-PET/CT results were classified as helpful or non-helpful in establishing final diagnosis. Binary logistic regression was used to identify clinical parameters associated with a diagnostic ^{18}F-FDG-PET/CT.

Results 240 patients were enrolled, 72 with FUO, 142 with IUO and 26 had FUO or IUO previously (exFUO/IUO). Diagnosis was established in 190 patients (79.2%). The leading diagnoses were adult-onset Still's disease (15.3%) in the FUO group, large vessel vasculitis (21.1%) and polymyalgia rheumatica (18.3%) in the IUO group and IgG_4-related disease (15.4%) in the exFUO/IUO group. In 136 patients (56.7% of all patients and 71.6% of patients with a diagnosis), ^{18}F-FDG-PET/CT was positive and helpful in finding the diagnosis. Predictive markers for a diagnostic ^{18}F-FDG-PET/CT were age over 50 years (p=0.019), C-reactive protein (CRP) level over 30 mg/L (p=0.002) and absence of fever (p=0.001).

Conclusion ^{18}F-FDG-PET/CT scanning is helpful in ascertaining the correct diagnosis in more than 50% of the cases presenting with FUO and IUO. Absence of intermittent fever, higher age and elevated CRP level increase the likelihood for a diagnostic ^{18}F-FDG-PET/CT.

INTRODUCTION

Fever of unknown origin (FUO)[1 2] and inflammation of unknown origin (IUO)[3] are major diagnostic challenges with about 200 differential underlying diagnoses.[4–7] FUO is defined as (1) illness for at least 3 weeks, (2) body temperature over 38.3°C on several occasions and (3) no specific diagnosis despite extended diagnostics.[4–8] Causes for FUO can be divided into four major disease groups: infections, tumours, non-infectious inflammatory diseases (NIIDs) and miscellaneous causes.[8] In developing countries, the major cause of FUO is infection,[9–15] while it is NIID in developed countries. IUO represents chronic inflammation without fever. The aetiology of IUO can vary from malignancy to self-limiting disease.[3 16] The clinical presentation of FUO and IUO might differ, but they often reflect similar disease entities. Therefore, attempts in establishing standardised diagnostic protocols for both diseases should pursue similar strategy.[17–19]

Diagnostic work-up of FUO/IUO includes detailed medical history, physical examination, laboratory tests, blood cultures, urine cultures and standard imaging such as chest radiograph, echocardiography and abdominal ultrasonography. However, often these investigations do not lead to definite diagnosis. Hence, a high proportion of patients with FUO/IUO (in several studies 30%–50%) leave the hospital without specific diagnosis.[17–19] Combination of ^{18}F-fluorodesoxyglucose positron emission tomography (^{18}F-FDG-PET) with CT is considered as a promising diagnostic tool in the work-up for FUO/IUO.[20–31] It combines high spatial resolution with detection of increased glycolysis due to malignancy or inflammation.[21 32–34] Small retrospective studies and only one prospective study have suggested the utility of ^{18}F-FDG-PET/CT in the diagnostic work-up of FUO[35–47] and IUO.[16 48]

To date, larger studies addressing the role of ^{18}F-FDG-PET/CT in the diagnostic work-up of FUO and IOU are still scarce.[49] Importantly, it is unclear which patients with FUO/IUO may profit most from the use of ^{18}F-FDG-PET/CT. Because of its diagnostic effectiveness, ^{8}F-FDG-PET/CT may speed up the diagnostic process, reduce total costs and save patients with FUO/IUO from unnecessary invasive procedures, especially if the underlying disease (1) lacks characteristic symptoms, (2) is not defined by specific serum biomarkers and (3) easily escapes detection by conventional investigation.

PATIENTS AND METHODS

Patients and study design

This prospective study included all adult patients (age ≥18 years) with a diagnosis of FUO or IUO admitted to the ward of the Immunology and Infectious Disease Clinic of the Department of Internal Medicine 3, a tertiary care centre for immunoinflammatory and infectious diseases, between January 2007 and June 2015. FUO[2 4] was defined as a febrile illness with body temperatures >38.3°C

To cite: Schönau V, Vogel K, Englbrecht M, *et al*. *Ann Rheum Dis* 2018;**77**:70–77.

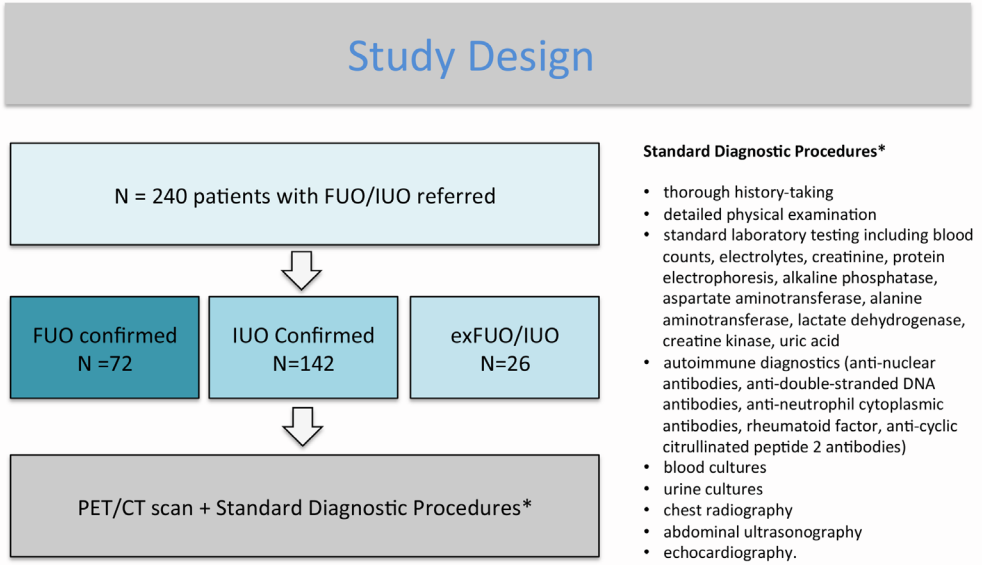


Figure 1 Study design. Patients with either FUO or IUO were referred. At referral, diagnosis of FUO or IUO was confirmed. Patients not fulfilling FUO or IUO criteria at the time of admission were termed patients with exFUO/IUO. All patients received ^{18}F-fluorodesoxyglucose positron emission tomography/CT scanning and a standard diagnostic procedure as outlined. FUO, fever of unknown origin; IUO, inflammation of unknown origin; PET, positron emission tomography.

(>101°F) lasting over at least 3 weeks without achieving diagnosis after thorough history taking, physical examination and standard diagnostic procedures. IUO was defined as illness of at least 3-week duration with body temperatures <38.3°C (101°F) and C-reactive protein (CRP) >7 mg/L and/or erythrocyte sedimentation rate (ESR) >age/2 in men or (age+10)/2 in women and without achieving diagnosis.[15] At admission, the presence of FUO and IUO was tested and patients were classified as FUO, IUO or—in case no signs of FUO or IUO at the time of admission—exFUO/IUO. All patients received a single ^{18}F-FDG-PET/CT scan and defined standard diagnostic work-up (see below) for FUO/IUO during the same hospital stay (figure 1). Patients provided written informed consent for ^{18}F-FDG-PET/CT. The ethics commission of the University Clinic of Erlangen approved the study procedure. All procedures were done according to the Declaration of Helsinki.

^{18}F-FDG-PET/CT scanning

Patients fasted for at least 4 hours before ^{18}F-FDG-PET/CT scans. Because higher blood glucose levels can decrease the FDG uptake,[50 51] patients' blood glucose level had to be <180 mg/dL before 3 MBq/kg of ^{18}F-FDG was injected. Scans were acquired 1 hour after injection. First non-contrast low-radiation-dose CT scan was performed followed by PET scan encompassing the same imaging field using Siemens Biograph TruePoint 64 PET/CT (until September 2011) or Biograph mCT 40 combining lutetium oxyorthosilicate PET with multislice CT.[52] The patients were in supine position and had their arms in elevated position.

Image processing

Images were iteratively reconstructed using standard software shipped with the system and available as PET, CT and fused PET/CT images for evaluation. The data were corrected for attenuated and scattered photons. Scans were independently evaluated at the day of examination by two nuclear medicine specialists (DS and TK) without the knowledge of patients' medical history and classified as 'pathological' and 'non-pathological'. Scans were considered pathological if moderate to high focal tracer uptake (according to Walter and colleagues) was detected additionally to areas of physiological tracer uptake (kidney, brain, heart, urinary bladder, intestinal smooth muscle, liver, spleen and testis).[53–55] Due to the qualitative nature of scan interpretation (localisation, pathological/non-pathological) the inter-reader disagreement was very low (2 cases out of 240; both related to lymph node grading) and no intrareader variability was found.

Standard diagnostic work-up

These procedures included: thorough history taking (previous medical history and medication; drug abuse; travel, family, sexual, inflammation/infection and rheumatologic history; hobbies; occupation; and animal contact), detailed physical examination (special focus on lymph nodes, temporal arteries, eyes, skin, liver and spleen), standard laboratory testing (blood counts, electrolytes, creatinine, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), creatine kinase, uric acid), autoimmune diagnostics (antinuclear antibodies, anti-double-stranded DNA antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, anticyclic citrullinated peptide two antibodies), blood cultures, urine cultures, chest radiography, abdominal ultrasonography and echocardiography.

Comparison of ^{18}F-FDG-PET/CT results and final diagnosis

Final diagnosis was judged by the study team after all results of standard work-up, ^{18}F-FDG-PET/CT scan and later confirmatory procedures (eg, histology) were finalised. Results were grouped according to de Kleijn and colleagues[17] in no diagnosis, malignancy, infection, NIID and other diseases. The judgement whether ^{18}F-FDG-PET/CT was helpful for ascertaining final diagnosis was done by the study team. To assess the predictive value of ^{18}F-FDG-PET/CT, results were additionally divided into four groups.[29] (1) True negatives, if ^{18}F-FDG-PET/CT was normal and no other investigations or clinical follow-up (≥3 month) revealed any underlying disease. (2) True positives, if ^{18}F-FDG-PET/CT detected a specific disease process causing of FUO/IUO, which was then confirmed by additional investigations

(eg, histology or response to treatment). (3) False negatives, if ^{18}F-FDG-PET/CT was normal but a specific disease process could be detected with another diagnostic test or response to specific treatment. (4) False positives, if ^{18}F-FDG-PET/CT showed tracer uptake that could not be identified as the cause of FUO/IUO by additional tests. For example, pathological FDG uptake in the large arteries or para-aortic tissue was considered helpful in establishing the diagnosis of large vessel vasculitis or IgG_4-related disease, respectively. In contrast, FDG uptake only in the bone marrow and lymph nodes in a patient with the final diagnosis of Still's disease was classified as non-helpful (see also online supplementary table 1). Negative ^{18}F-FDG-PET/CT scans were generally not considered as being helpful for ascertaining final diagnosis.

Statistical analysis

For summarising data, descriptive statistical analysis was applied, including calculation of arithmetic means and SD for interval data and frequency analysis for categorical data. Furthermore, we also calculated the positive predictive value (PPV), negative predictive value (NPV) as well as sensitivity and specificity in order to evaluate the correct classification and prediction quality of ^{18}F-FDG-PET/CT. A binary logistic regression model using forced entry method adding all independent variables and an intercept to the model at a single step was used to identify independent clinical parameters that are related to helpful ^{18}F-FDG-PET/CT. According to previous studies[26 35 37] and taking into account the typical manifestations of FUO and IUO, the following parameters were chosen as predictors for setting up the regression model: sex (male; female), age (<50 years; >50 years), fever (>38.2°C; absence; presence); CRP (<30 mg/L; >30 mg/L), diabetes (absence; presence), immunosuppressive treatment in medical history (absence; presence), corticosteroids prior to PET-CT (absence; presence), leukocytosis (<10 000 cells/µL; >10 000 cells/µL), anaemia (haemoglobin <11 mg/dL; >11 mg/dL) and elevated LDH (<250 U/L; >250 U/L). All statistical analyses were calculated using SPSS Software Package (IBM SPSS Statistics 21 for Windows, IBM Corporation). p Values ≤0.05 were considered statistically significant.

RESULTS

Patients' characteristics

A total of 240 patients were enrolled (117 male, 123 female): 72 patients were classified as FUO (46 male, 26 female; age range: 18–84 years, median age: 51.7 years), 142 as IUO (56 male, 86 female; age range: 18–86 years, median age: 61.3 years) and 26 (15 male, 11 female; age range: 19–73 years, median age: 50.8 years) did not fulfil FUO/IUO criteria at the time of ^{18}F-FDG-PET/CT but were admitted to hospital because of FUO or IUO diagnosed in the referring centre. We subsequently used the term exFUO/IUO for this group. Acute phase parameters were elevated in FUO (CRP 95.3±76.5 mg/L; ESR 63.5 mm±31.4 mm) and IUO (48.3±53.2 mg/L and 54.4±29.0 mm, respectively). Fifty-nine patients (24.6%) had received glucocorticoids prior to the ^{18}F-FDG-PET/CT scan (minimum dose 2.5 mg/d; maximum dose 240 mg/day). Glucocorticoids and antibiotics were discontinued at day of hospital administration. A summary of patients' characteristics is given in table 1.

Table 1 Characteristics of FUO, IUO and exFUO/IUO groups

	FUO	IUO	exFUO/IUO
Sex: male/female (N)	46/26	56/86	15/11
Age (years; mean±SD)	51.7±19.5	61.3±14.3	50.8±12.5
CRP (mg/L; mean±SD)	95.3±76.5	48.3±53.2	2.0±0.74
ESR (mm; mean±SD)	63.5±31.4	54.4±29.0	12.1±7.5
Haemoglobin (g/dL; mean±SD)	11.8±1.9	12.1±1.7	13.8±1.3
LDH (U/L; mean±SD)	27.4±148.5	250.7±91.2	220.4±82.8
Leukocytes (G/L; mean±SD)	9.5±5.0	9.9±4.0	7.1±2.4
Glucocorticoids use (%)	13.9 (10/72)	31.7 (45/142)	15.4 (4/26)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FUO, fever of unknown origin; IUO, inflammation of unknown origin; LDH, lactate dehydrogenase.

Diagnosis

Diagnosis could be made in 190 patients (79.2%), while in the remaining 50 patients (20.8%) the cause of illness remained undefined. Out of the 190 patients with diagnosis, 132 had NIID (69.5%), 27 had infections (14.2%), 20 malignancies (10.5%) and 11 other diseases (5.6%). Online supplementary table 2 gives an overview on the various diagnoses in the patients with FUO, IUO and exFUO/IUO. NIID contributed slightly more often to diagnosis in patients with IUO (61.9%) than patients with FUO (48.6%) and exFUO/IUO (40.0%) (table 2). Infections were only found in patients with FUO and IUO, whereas the diagnosis of other diseases were most frequent in patients with exFUO/IUO. The latter finding was mostly attributed to cases of IgG_4-related disease in patients with exFUO/IUO. Malignancies were distributed evenly among the three groups.

When looking at individual diagnoses, we found a clear separation between patients with FUO, IUO and exFUO/IUO. Although each clinical presentation was associated with a large variety of different diagnoses (online supplementary table 2), the most prevalent cause of FUO was adult-onset Still's disease (15.3%) (defined by Yamaguchi criteria plus lab values) by far, while in IUO, large vessel vasculitis (defined by American College of Rheumatology (ACR) criteria) was the leading diagnosis (21.1%) followed by polymyalgia rheumatica (18.3%) (defined by Rice criteria). IgG_4-related disease (ascertained by IgG_4-positive plasma cells in histology) was the most prevalent diagnosis (15.4%) in the patients with exFUO/IUO (figure 2A).

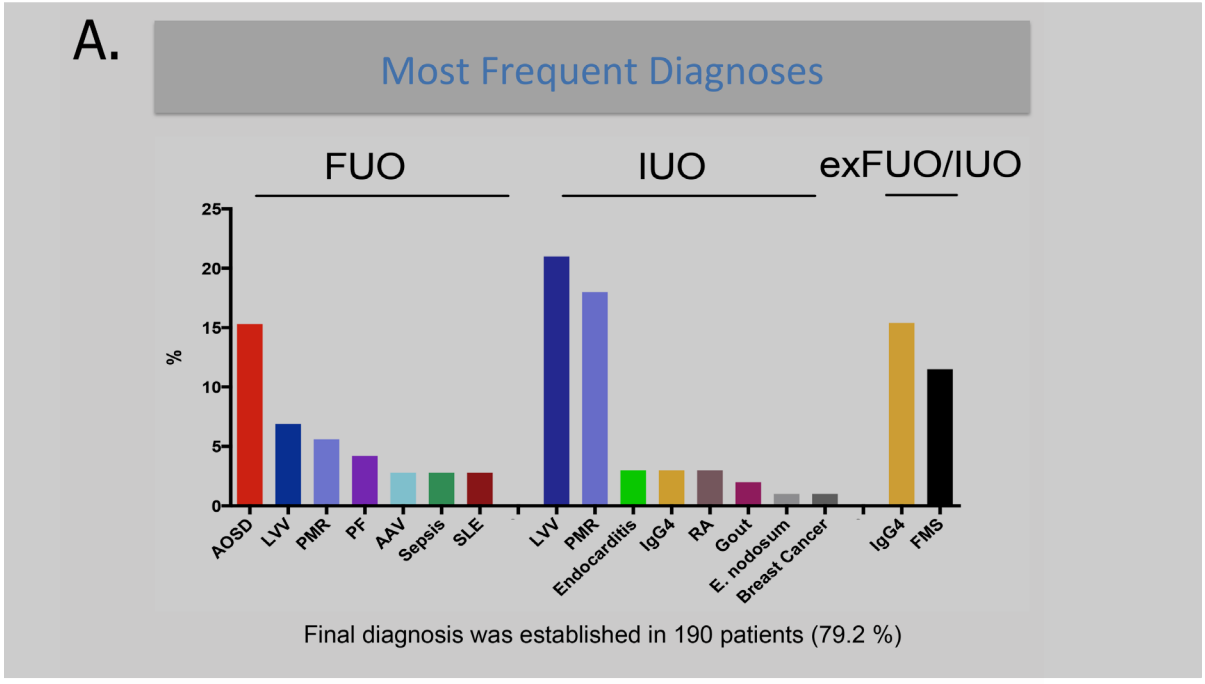
Diagnostic contribution of ^{18}F-FDG-PET/CT

We next asked whether ^{18}F-FDG-PET/CT scan is helpful in finding the diagnosis. Positive ^{18}F-FDG-PET/CT scans leading to diagnosis (true positive) were found in 136 patients (56.7% of all patients and 71.6% of the patients with a diagnosis) (figure 2B). The most common diagnoses in the true positive group were large vessel vasculitis (n=29), followed by infections (n=24), polymyalgia rheumatica (n=21), malignancies (n=19) and IgG_4-related disease (n=9) (figure 3). True negative results, meaning a negative ^{18}F-FDG-PET/CT scan and no final

Table 2 Diagnostic groups according to clinical presentation

	FUO	IUO	exFUO/IUO
Chronic inflammatory disease, n (%)	34 (47.2)	88 (62.0)	10 (38.5)
Infection, n (%)	11 (15.3)	16 (11.3)	0 (0)
Malignancy, n (%)	6 (8.3)	12 (8.5)	2 (7.7)
Miscellaneous disease, n (%)	1 (1.4)	3 (2.1)	7 (26.9)
No diagnosis, n (%)	20 (27.8)	23 (16.2)	7 (26.9)
Total, n (%)	72 (100)	142 (100)	26 (100)

FUO, fever of unknown origin; IUO, inflammation of unknown origin.



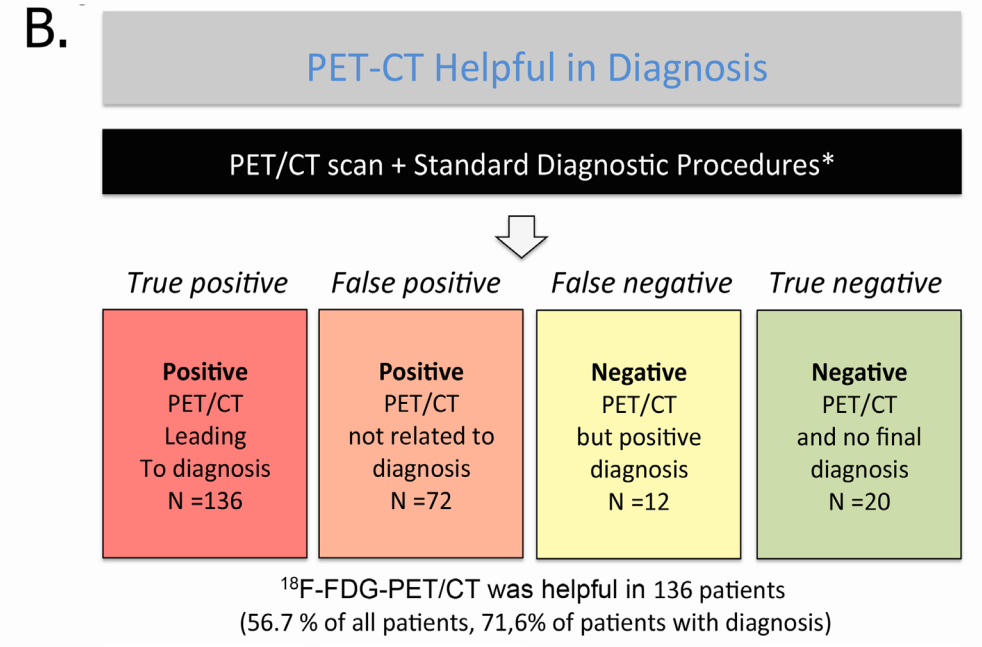


Figure 2 Most prevalent diagnoses and helpfulness of PET-CT. (A) Most prevalent diagnoses: bar graph showing the most prevalent diagnoses in patients with FUO, IUO or exFUO/IUO. Only diagnoses a more than one patient are shown. A complete list of diagnoses is shown in online supplementary table 2. (B) Helpfulness of PET-CT: classification of ^{18}F-FDG-PET/CT scanning results in relation to final diagnosis. (1) 'True positives' if the ^{18}F-FDG-PET/CT detected a specific disease process causing of FUO or IUO, which was then confirmed by additional investigations or a response to a medical treatment. (2) 'False negatives' if ^{18}F-FDG-PET/CT was normal, but a specific disease process could be detected with another diagnostic test or if there was response to a specific treatment. (3) 'False positives' if the ^{18}F-FDG-PET/CT showed an FDG uptake or disease process that could not be identified as the cause of FUO or IUO by additional tests. (4) 'True negatives' if neither ^{18}F-FDG-PET/CT nor standard diagnostic procedure found the cause for FUO/IUO. ^{18}F-FDG-PET, ^{18}F-fluorodesoxyglucose positron emission tomography; AAV, ANCA-associated vasculitis; AOSD, adult-onset Still's disease; E. nodosum, erythema nodosum; FMS, fibromyalgia; FUO, fever of unknown origin; IgG_4, IgG_4-associated syndrome; IUO, inflammation of unknown origin; LVV, large vessel vasculitis; PF, periodic fever; PMR, polymyalgia rheumatic; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

diagnosis and no diagnosis after at least a 3-month follow-up, were found in 20 patients (8.3%). In 72 patients (30.0%), we detected a tracer uptake in addition to the physiological uptake that was not explained by the final diagnosis or no diagnosis could be made. Hence, these patients were categorised as false positive. In few (n=12) patients, we had false negative (5.0%) scans, but the disease could be detected with other diagnostic tests or was responsive to specific treatment. Four of them had

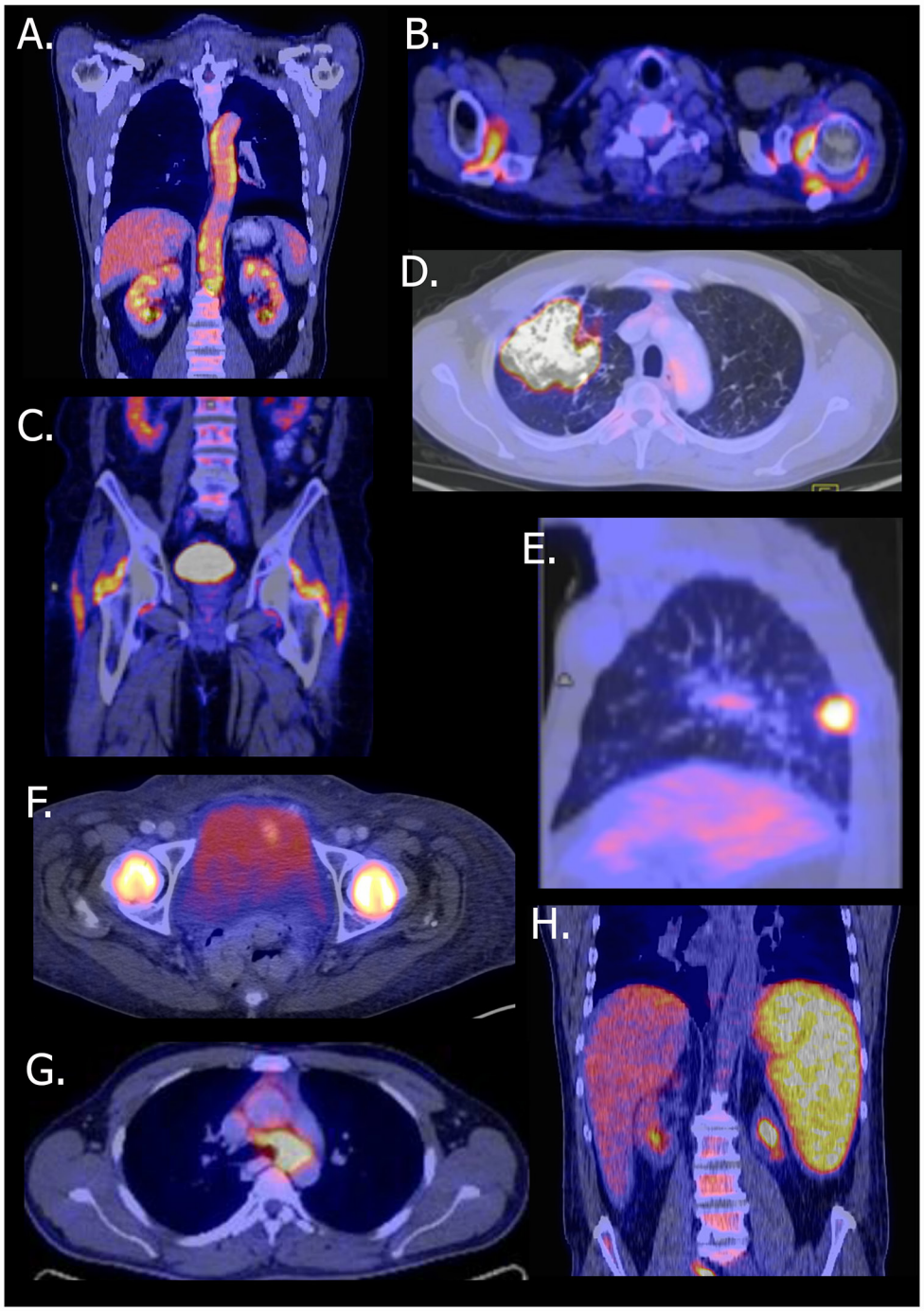


Figure 3 PET-CT examples. Examples of diagnostic ^{18}F-fluorodesoxyglucose positron emission tomography/CT scans resembling different disease categories: (A) giant cell arteritis with aortic tracer uptake; (B, C) polymyalgia rheumatic with tracer uptake in the periarticular tissue of the shoulder (B) and the hip (C) joints; (D) pulmonary tracer uptake based on bronchial carcinoma confirmed by histology; (E) pulmonary tracer uptake of a lung lesion of histologically confirmed IgG_4 syndrome; (F) tracer uptake in the bone marrow of the femoral heads based on histologically confirmed Erdheim-Chester's disease; (G) tracer uptake in the mediastinal lymph nodes due to histology and bacteriology confirmed tuberculosis; (H) tracer uptake in the spleen based on histology-proven lymphoma of spleen.

either large vessel vasculitis or isolated temporal arteritis. The PPV of ^{18}F-FDG-PET/CT was 65.4% with an NPV of 62.5% and a diagnostic accuracy of 65%. The sensitivity was high with 91.1%, while the specificity was low at 21.7%.

Clinical predictors for helpful ^{18}F-FDG-PET/CT

For analysing which parameters predict positive ^{18}F-FDG-PET/CT scans leading to diagnosis, data from 237 patients could be analysed. Three patients were excluded because of incomplete data on clinical parameters. When performing binary logistic regression model, the variables that could predict diagnostic ^{18}F-FDG-PET/CT were age over 50 years (p=0.019), CRP level over 30 mg/L (p=0.002) and absence of fever (p=0.001). In figure 4, we plotted the likelihood for a diagnostic ^{18}F-FDG-PET/CT scan in patient groups with or without fever and the subgroups according to CRP level (<30 mg/L vs >30 mg/L)

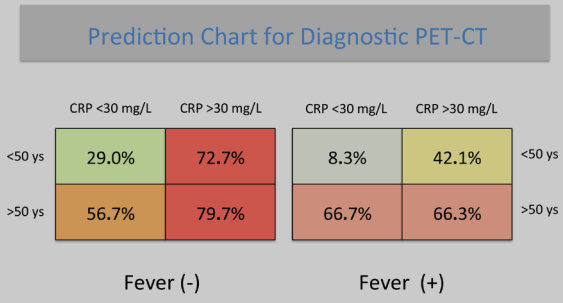


Figure 4 Prediction chart for diagnostic PET/CT. The chart shows the likelihood (%) of a diagnostic ^{18}F-fluorodesoxyglucose positron emission tomography/CT scanning in patients with fever of unknown origin or inflammation of unknown origin dependent on age, C-reactive protein level and the presence/absence of fever. CRP, C-reactive protein; PET, positron emission tomography.

and age (<50 years vs >50 years). Patients with elevated CRP, higher age and no fever had an almost 80% chance for diagnostic ^{18}F-FDG-PET/CT, while the chance in younger patients with fever and lower CRP level was very low (8.3%).

DISCUSSION

FUO and IUO remain diagnostic challenges. The percentage of undiagnosed cases ranges from 9% to 50% in FUO[6–15] and 11% to 60% in IUO.[16 48] Different diagnostic approaches have been suggested in FUO and IUO.[17–19] Only small retrospective studies and one prospective study have addressed the diagnostic performance of ^{18}F-FDG-PET/CT in FUO (online supplementary table 3),[35–47] and very limited data exist in IUO.[16 48] Our study is the so far largest with the advantage of (1) a prospective setting, (2) the inclusion of both FUO and IUO, (3) thorough diagnostic work-up before referral and (4) evaluation in a 'real-life' clinical setting as all patients admitted to our ward were evaluated.

Investigating 240 patients with FUO and IUO, we show that ^{18}F-FDG-PET/CT is helpful in identifying underlying diseases. Scans led to diagnosis in 56.7% of all patients and 71.6% of those patients with final diagnosis. This values are comparable to published studies on FUO varying between 26% and 75%[35–47] and studies on IUO.[16 48] Moreover, ^{18}F-FDG-PET/CT was sometimes helpful in finding the diagnosis in patients with 'exFUO/IUO' such as IgG_4 syndrome and large vessel vasculitis.[56–60] Nonetheless, data obtained in this group need to be seen with some caution as we could not predict the frequency of patients with exFUO/IUO and their numbers were actually rather small. To assess its role in defining diagnosis, ^{18}F-FDG-PET/CT scans were rated as true positive, true negative, false positive and false negative results in relation to the final diagnosis. Scans were 'true positive' in 136 patients (56.7%) with a PPV of 65.4% and an NPV of 62.5%. Comparable to other studies, sensitivity was 91.8%. Few scans (n=12) were 'false negative', 4 of which had large vessel vasculitis (3 temporal artery arteritis; 1 Takayasu's arteritis), suggesting the limitation of ^{18}F-FDG-PET/CT in isolated temporal artery arteritis. Negative scans ('true' and 'false' negative) were generally not considered as being helpful in ascertaining the correct diagnosis. Nonetheless, a negative scan may still point to a certain direction as it makes some diagnoses (eg, tumours or abscesses) more unlikely.

We observed a rather high number of 'false positive' scans (30%) reducing specificity to 21.7% and diagnostic accuracy to 65%. This observation, however, may be attributed to the rigorous definition of 'false positive' as a tracer uptake in addition to the physiological uptake being not helpful for diagnosis. This definition also includes tracer uptake in the bone marrow and lymph nodes as sign of inflammation. A substantial improvement in specificity can be reached when classifying increased bone marrow and lymph nodes uptake resembling unspecific signs of inflammation as 'true negative' increasing specificity to 53.8% with sensitivity remaining at 91.8%. Then, also PPV (76%), NPV (80.6%) and diagnostic accuracy (77.1%) were increased. Because classification into the different groups (true positive, false positive, true negative and false negative) varies between studies, we summarised in online supplementary table 3 whether ^{18}F-FDG-PET/CT contributed to ascertaining diagnosis (PET/CT helpful or PET/CT not helpful). ^{18}F-FDG-PET/CT was helpful in finding the underlying disease responsible for FUO in 42%–92% of cases,[35–47] while it was possible in 36%–74% of IUO cases[16 48] (online supplementary table 3). Data from our study (57%) are accordance with these findings.

Searching for clinical parameters associated with helpful ^{18}F-FDG-PET/CT, we found that age over 50 years, CRP level over 30 mg/L and absence of fever predicted helpfulness of ^{18}F-FDG-PET/CT. This finding confirms other studies showing elevated CRP level associated with diagnostically helpful scan.[61] In contrast to Crouzet *et al*[37] and Gafter-Gvili *et al*[26] we did not find that anaemia, lymphadenopathy or male sex correlated with diagnostic ^{18}F-FDG-PET/CT. The better performance of ^{18}F-FDG-PET/CT in patients older than 50 years and those without fever is most likely attributed to the higher prevalence of large vessel vasculitis as major diagnostic entity responsible for IUO. However, fever and younger age is often associated with adult-onset Still's disease, which usually yields negative results in ^{18}F-FDG-PET/CT. We think that such easy-to-use predictors for helpful ^{18}F-FDG-PET/CT scans will allow more tailored and cost-effective use of ^{18}F-FDG-PET/CT in the diagnostic work-up of patients with FUO/IUO.[33] Such approach may also help to implement a fast track to ^{18}F-FDG-PET/CT as shown in the diagnostic work-up trees for patients with FUO/IUO based on the concepts of Mulders-Manders and colleagues.[10] Such tree is depicted in figure 5.

Limitations of this study are related to the referral of the patients to a clinic specialised to immunology and infectious diseases. Hence, referral bias towards immune-mediated diseases cannot be excluded and may account for the lower prevalence of malignancies in this population and underestimation of cancer prevalence in the patients with FUO/IUO. However, cancer often goes along with organ-specific symptoms in addition to fever and inflammation, and therefore, selective diagnostics with ultrasound or CT are employed earlier. In consequence, such patients are not anymore 'FUO/IUO' patients and ^{18}F-FDG-PET/CT is rather done for staging than diagnostics. In addition, the study reflects the real-life situation in a referral centre for immune-mediated diseases and is therefore of relevance for the rheumatologic community. A second limitation is that we do not know whether and to what extent consequent application of whole-body CT before ^{18}F-FDG-PET/CT would contribute to correct diagnosis. While the latter appears to be the diagnostic technique of choice in larger centres with good access to ^{18}F-FDG-PET/CT, whole-body CT can be seen as an alternative approach for ascertaining diagnosis at least in some patients (see figure 5) and should be performed if no ^{18}F-FDG-PET/CT is available. Finally, a third limitation of the study is that the general applicability of the results in all ethnicities, since the overwhelming ethnical background of the population studied herein was Caucasian.

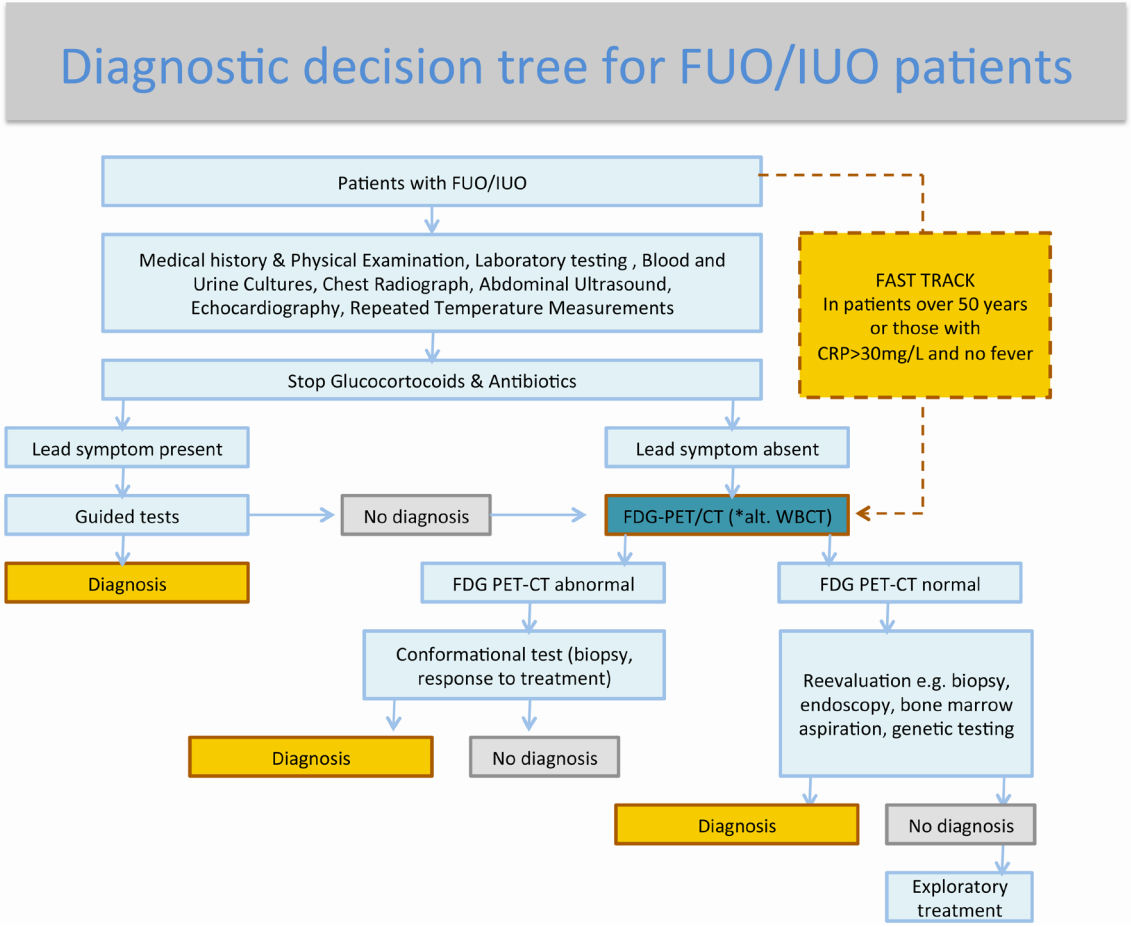


Figure 5 Decision tree for diagnosis in patients with FUO/IUO. Decision tree showing the integration of ^{18}F-FDG-PET/CT scanning into diagnosis of FUO or IUO. A fast track for patients with a high likelihood for a diagnostic ^{18}F-FDG-PET/CT is integrated into the diagnostic tree. Asterisk indicates that conventional WBCT represents an alternative procedure, if no ^{18}F-FDG-PET/CT is available. ^{18}F-FDG-PET, ^{18}F-fluorodesoxyglucose positron emission tomography; FUO, fever of unknown origin; IUO, inflammation of unknown origin; WBCT, whole-body computed tomography.

In summary, this large prospective study in patients with FUO/IUO showed that the ^{18}F-FDG-PET/CT allows ascertaining diagnosis in 56.7% of the patients, substantially improving correct diagnosis in FUO/IUO. The likelihood to identify the underlying disease is higher in patients older than 50 years, those with elevated CRP and those without fever.

Acknowledgements This study was supported by the Deutsche Forschungsgemeinschaft (SPP1468-IMMUNOBONE; CRC1181), the Bundesministerium für Bildung und Forschung (project METARTHROS), the TEAM project of the European Union and the project BTCure funded by Innovative Medicines Initiative. The study was part of the academic requirements for the MD thesis of KV and will be published in a different format in the Faculty of Medicine of the University Erlangen-Nuremberg.

Contributors VS, KV, JW and BM collected the data. DS and TK read the scans. VS, KV, BM and GS analysed the data. ME performed statistical analyses. VS and GS wrote the manuscript.

Competing interests None declared.

Ethics approval University of Erlangen-Nuremberg.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Petersdorf RG. Fever of Unknown Origin. *Arch Intern Med* 1992;152:21–2.
2 Durack DT, Street AC. Fever of unknown origin—reexamined and redefined. *Curr Clin Top Infect Dis* 1991;11:35–51.
3 Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008;454:428–35.
4 Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine* 1961;40:1–30.
5 Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet* 1997;350:575–80.
6 Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. *J Intern Med* 2003;253:263–75.
7 Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. *Arch Intern Med* 1996;156:618–20.
8 Tolia J, Smith LG. Fever of unknown origin: historical and physical clues to making the diagnosis. *Infect Dis Clin North Am* 2007;21:917–36.
9 Yamanouchi M, Uehara Y, Yokokawa H, *et al*. Analysis of 256 cases of classic fever of unknown origin. *Intern Med* 2014;53:2471–5.
10 Mulders-Manders C, Simon A, Bleeker-Rovers C. Fever of unknown origin. *Clin Med* 2015;15:280–4.
11 Saltoglu N, Tasova Y, Midikli D, *et al*. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. *J Infect* 2004;48:81–5.
12 Chin C, Chen YS, Lee SS, Ssj L, *et al*. Fever of unknown origin in Taiwan. *Infection* 2006;34:75–80.
13 Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. *Scand J Infect Dis* 2006;38:632–8.
14 Mansueto P, Di Lorenzo G, Rizzo M, *et al*. Fever of unknown origin in a Mediterranean survey from a division of internal medicine: report of 91 cases during a 12-year-period (1991–2002). *Intern Emerg Med* 2008;3:219–25.
15 Robine A, Hot A, Maucort-Boulch D, *et al*. Fever of unknown origin in the 2000s: evaluation of 103 cases over eleven years. *Presse Med* 2014;43:e233–e240.
16 Vanderschueren S, Del Biondo E, Ruttens D, *et al*. Inflammation of unknown origin versus fever of unknown origin: two of a kind. *Eur J Intern Med* 2009;20:415–8.
17 de Kleijn EM, van Lier HJ, van der Meer JW, *et al*. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. *Medicine* 1997;76:401–14.

18 Affronti M, Mansueto P, Soresi M, *et al*. Low-grade fever: how to distinguish organic from non-organic forms. *Int J Clin Pract* 2010;64:316–21.
19 Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med* 2003;163:545–51.
20 Meller J, Sahlmann CO, Scheel AK. 18F-FDG PET and PET/CT in fever of unknown origin. *J Nucl Med* 2007;48:35–45.
21 Kouijzer IJ, Bleeker-Rovers CP, Oyen WJ. FDG-PET in fever of unknown origin. *Semin Nucl Med* 2013;43:333–9.
22 Tokmak H, Ergonul O, Demirkol O, *et al*. 18)F-FDG-PET/CT in fever of unknown origin. *Int J Infect Dis* 2014;19:53–8.
23 Love C, Tomas MB, Tronco GG, *et al*. FDG PET of infection and inflammation. *Radiographics* 2005;25:1357–68.
24 Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. *Nucl Med Commun* 2001;22:779–83.
25 Buysschaert I, Vanderschueren S, Blockmans D, *et al*. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. *Eur J Intern Med* 2004;15:151–6.
26 Gafter-Gvili A, Raibman S, Grossman A, *et al*. [18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin. *QJM* 2015;108:289–98.
27 Sioka C, Assimakopoulos A, Fotopoulos A. The diagnostic role of (18)F fluorodeoxyglucose positron emission tomography in patients with fever of unknown origin. *Eur J Clin Invest* 2015;45:601–8.
28 Meller J, Sahlmann CO, Gürocak O, *et al*. FDG-PET in patients with fever of unknown origin: the importance of diagnosing large vessel vasculitis. *Q J Nucl Med Mol Imaging* 2009;53:51–63.
29 Brodmann M, Lipp RW, Passath A, *et al*. The role of 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography in the diagnosis of giant cell arteritis of the temporal arteries. *Rheumatology* 2004;43:241–2.
30 Bleeker-Rovers CP, Vos FJ, Corstens FH, *et al*. Imaging of infectious diseases using [18F] fluorodeoxyglucose PET. *Q J Nucl Med Mol Imaging* 2008;52:17–29.
31 Lensen KJ, Voskuyl AE, van der Laken CJ, *et al*. 18F-fluorodeoxyglucose positron emission tomography in elderly patients with an elevated erythrocyte sedimentation rate of unknown origin. *PLoS One* 2013;8:e58917.
32 Pauwels EK, Sturm EJ, Bombardieri E, *et al*. Positron-emission tomography with [18F] fluorodeoxyglucose. Part I. Biochemical uptake mechanism and its implication for clinical studies. *J Cancer Res Clin Oncol* 2000;126:549–59.
33 Deichen JT, Prante O, Gack M, *et al*. Uptake of [18F]fluorodeoxyglucose in human monocyte-macrophages in vitro. *Eur J Nucl Med Mol Imaging* 2003;30:267–73.
34 Kubota R, Yamada S, Kubota K, *et al*. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med* 1992;33:1972–80.
35 Balink H, Collins J, Bruyn GA, *et al*. F-18 FDG PET/CT in the diagnosis of fever of unknown origin. *Clin Nucl Med* 2009;34:862–8.
36 Buch-Olsen KM, Andersen RV, Hess S, *et al*/18F-FDG-PET/CT in fever of unknown origin: clinical value. *Nucl Med Commun* 2014;35:955–60.
37 Crouzet J, Boudousq V, Lechiche C, *et al*. Place of (18)F-FDG-PET with computed tomography in the diagnostic algorithm of patients with fever of unknown origin. *Eur J Clin Microbiol Infect Dis* 2012;31:1727–33.
38 Ergül N, Halac M, Cermik TF, *et al*. The diagnostic role of FDG PET/CT in patients with fever of unknown origin. *Mol Imaging Radionucl Ther* 2011;20:18–25.
39 Federici L, Blondet C, Imperiale A, *et al*. Value of (18)F-FDG-PET/CT in patients with fever of unknown origin and unexplained prolonged inflammatory syndrome: a single centre analysis experience. *Int J Clin Pract* 2010;64:55–60.
40 Ferda J, Ferdová E, Záhlava J, *et al*. Fever of unknown origin: a value of (18) F-FDG-PET/CT with integrated full diagnostic isotropic CT imaging. *Eur J Radiol* 2010;73:518–25.
41 Kei PL, Kok TY, Padhy AK, *et al*. [18F] FDG PET/CT in patients with fever of unknown origin: a local experience. *Nucl Med Commun* 2010;31:788–92.
42 Keidar Z, Gurman-Balbir A, Gaitini D, *et al*. Fever of unknown origin: the role of 18F-FDG PET/CT. *J Nucl Med* 2008;49:1980–5.
43 Kim YJ, Kim SI, Hong KW, *et al*. Diagnostic value of 18F-FDG PET/CT in patients with fever of unknown origin. *Intern Med J* 2012;42:834–7.
44 Manohar K, Mittal BR, Jain S, *et al*. F-18 FDG-PET/CT in evaluation of patients with fever of unknown origin. *Jpn J Radiol* 2013;31:320–7.
45 Pedersen TI, Roed C, Knudsen LS, *et al*. Fever of unknown origin: a retrospective study of 52 cases with evaluation of the diagnostic utility of FDG-PET/CT. *Scand J Infect Dis* 2012;44:18–23.
46 Pelosi E, Skanjeti A, Penna D, *et al*. Role of integrated PET/CT with [18F]-FDG in the management of patients with fever of unknown origin: a single-centre experience. *Radiol Med* 2011;116:809–20.
47 Sheng JF, Sheng ZK, Shen XM, *et al*. Diagnostic value of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin. *Eur J Intern Med* 2011;22:112–6.
48 Balink H, Bennink RJ, Veeger N, *et al*. 18)F-FDG PET/CT in inflammation of unknown origin. *Clin Nucl Med* 2014;39:419–25.
49 Balink H, Tan SS, Veeger NJ, *et al*. 18F-FDG PET/CT in inflammation of unknown origin: a cost-effectiveness pilot-study. *Eur J Nucl Med Mol Imaging* 2015;42:1408–13.
50 Bleeker-Rovers CP, Vos FJ, Mudde AH, *et al*. A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. *Eur J Nucl Med Mol Imaging* 2007;34:694–703.
51 Wahl RL, Henry CA, Ethier SP. Serum glucose: effects on tumor and normal tissue accumulation of 2-[F-18]-fluoro-2-deoxy-D-glucose in rodents with mammary carcinoma. *Radiology* 1992;183:643–7.
52 Langen KJ, Braun U, Rota Kops E, *et al*. The influence of plasma glucose levels on fluorine-18-fluorodeoxyglucose uptake in bronchial carcinomas. *J Nucl Med* 1993;34:355–9.
53 Weissleder R, Ross BD, Rehemtulla A, *et al*; *Molecular Imaging: Principles and Practice*. Shelton, Connecticut, USA: People's Medical Publishing House, 2010.
54 Cook GJ, Wegner EA, Fogelman I. Pitfalls and artifacts in 18FDG PET and PET/CT oncologic imaging. *Semin Nucl Med* 2004;34:122–33.
55 Ahmad Sarji S. Physiological uptake in FDG PET simulating disease. *Biomed Imaging Interv J* 2006;2:e59–56.
56 Schäfer VS, Warrington KJ, Williamson EE, *et al*. Delayed diagnosis of biopsy-negative giant cell arteritis presenting as fever of unknown origin. *J Gen Intern Med* 2009;24:532–6.
57 Hooisma GA, Balink H, Houtman PM, *et al*. Parameters related to a positive test result for FDG PET(/CT) for large vessel vasculitis: a multicenter retrospective study. *Clin Rheumatol* 2012;31:861–71.
58 Zerizer I, Tan K, Khan S, *et al*. Role of FDG-PET and PET/CT in the diagnosis and management of vasculitis. *Eur J Radiol* 2010;73:504–9.
59 Zhang J, Chen H, Ma Y, *et al*. Characterizing IgG4-related disease with 18F-FDG PET/CT: a prospective cohort study. *Eur J Nucl Med Mol Imaging* 2014;41:1624–34.
60 Löffler C, Hoffend J, Benck U, *et al*. The value of ultrasound in diagnosing extracranial large-vessel vasculitis compared to FDG-PET/CT: A retrospective study. *Clin Rheumatol* 2017;5:1–8.
61 Balink H, Veeger NJ, Bennink RJ, *et al*. The predictive value of C-reactive protein and erythrocyte sedimentation rate for 18F-FDG PET/CT outcome in patients with fever and inflammation of unknown origin. *Nucl Med Commun* 2015;36:604–9.