Disease activity and vascular involvement in retroperitoneal fibrosis: first experience with fully integrated 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging compared to clinical and laboratory parameters

K. Thuermel[1], I. Einspieler[2], S. Wolfram[1], P. Moog[1], R. Meier[3], M. Schwaiger[2], U. Heemann[1]

[1]Department of Nephrology and Rheumatology, [2]Department of Nuclear Medicine, [3]Department of Diagnostic and Interventional Radiology, Klinikum rechts der Isar, Technical University of Munich, Germany.

*Klaus Thuermel, MD**
*Ingo Einspieler, MD**
Sabine Wolfram, MD
Philipp Moog, MD
Reinhard Meier, Prof.
Markus Schwaiger, Prof.
Uwe Heemann Prof.

**These authors contributed equally to this work*

Please address correspondence to:
Dr Klaus Thuermel,
Department of Nephrology and Rheumatology,
Klinikum rechts der Isar,
Technische Universität München,
Ismaningerstraße 22,
81675 München, Germany.
E-mail: klaus.thuermel@mri.tum.de

Received on February 13, 2016; accepted in revised form on July 1, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S146-S154.

Key words: retroperitoneal fibrosis, large-vessel vasculitis, hybrid [18F]-FDG PET/MRI

Competing interests: none declared.

ABSTRACT

Objective. *The aim of this study was to evaluate the value of fully integrated [18F]-FDG PET/MRI in the assessment of retroperitoneal fibrosis with regard to disease activity, extent and vascular involvement compared to clinical and laboratory parameters.*

Methods. *Seventeen [18F]-FDG PET/MRI examinations were performed in fourteen patients. Qualitative (visual 4-point scale) and quantitative PET parameters (maximum standardised uptake value, SUVmax; target-background ratio, TBR) as well as RF thickness and volume were correlated to clinical and inflammatory parameters and compared between therapy-naïve patients and patients under immunosuppression. Evidence for associated large-vessel vasculitis was examined. Magnetic resonance angiography (MRA) was performed to detect aneurysms or stenoses.*

Results. *Clinical parameters, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) only incompletely displayed inflammatory activity and did not correlate with PET/MRI parameters. In 29% (4/17) resp. 50% (8/16) of PET/MRI examinations active disease was detected although CRP resp. ESR were in the normal range. SUVmax, TBR and volume of the retroperitoneal mass differed significantly between therapy-naïve patients and patients under therapy (SUVmax p=0.004, TBR p=0.015, volume p=0.015), whereas thickness of the retroperitoneal mass did not (p=0.406). Large-vessel vasculitis was detected in 21% (3/14) and aortic aneurysms in 14% (2/14) of patients. Vasculitis occurred apart from the site of RF in two patients.*

Conclusion. *Whole body hybrid [18F]-FDG-PET/MRI is superior to clinical and inflammatory parameters in disease activity assessment of RF. There may be substantial disease activity despite inflammatory parameters in the normal range. Associated large-vessel vasculitis and aneurysms may occur apart from the site of RF.*

Introduction

Retroperitoneal fibrosis (RF) is characterised by the accumulation of fibroinflammatory tissue in the retroperitoneum, potentially leading to serious complications such as ureteral obstruction, hydronephrosis, renal failure and obstruction of large vessels (1). Approximately two thirds of cases are idiopathic, whereas about one third is associated to drugs, malignomas or to various autoimmune diseases (2). Recently, RF has been identified as an IgG4-associated disease in a subset of patients (3). RF may present outside the retroperitoneum, for example in the mediastinum, or, in the case of IgG4 associated disease, in internal organs, lymph nodes or in the orbitae (4-6). There also is evidence of associated large-vessel vasculitis (LVV), potentially causing life-threatening consequences such as vessel stenosis and aneurysms (7-9).

Recently, [18F]-fluorodeoxyglucose ([18F]-FDG) positron emission tomography (PET) has emerged as a new approach in the assessment of RF (10). Although most of the reported experience is retrospective and restricted to small patient numbers, there is growing evidence that [18F]-FDG PET might be useful not only in the diagnosis of RF, but also in estimating the metabolic activity during the course of therapy (11, 12). [18F]-FDG PET is commonly performed in combination with CT as a hybrid PET/CT examination. How-

ever, PET/CT may be associated with substantial radiation exposure, in particular due to CT. Therefore, although CT has been evaluated in retroperitoneal fibrosis (13), CT is conducted as a low-dose examination in most instances, which in turn is not appropriate for diagnostic purposes. In contrast, MRI is superior to CT in matters of soft tissue contrast and offers the advantage of a radiation free examination (14-18). Fully integrated [18F]-FDG PET/MRI allows the conduction of [18F]-FDG/PET and MRI in a one-stop-shop procedure at the same time without changing the patient's position. This allows the precise assignment of PET signals to MRI data, precisely depicting the activity and extent of aortic and periaortic inflammation, as recently shown for large-vessel vasculitis (19).

The aim of this study was to evaluate the value of fully integrated [18F]-FDG PET/MRI in the assessment of RF with regard to disease activity, extent and vascular involvement compared to clinical and laboratory parameters. Visual and quantitative [18F]-FDG PET and MRI parameters including the volume of the retroperitoneal mass were correlated to clinical and inflammatory parameters and compared between therapy naive patients and patients under immunosuppression and between initial and follow-up examinations.

Methods

Patient evaluation

Between March 2013 and April 2015, seventeen [18F]-FDG PET/MRI examinations were performed on fourteen consecutive patients with RF at diagnosis or during follow-up. The study was approved by the local ethics committee and all patients signed informed consent. Clinical workup included detailed history with special regard to symptoms attributable to RF and to systemic inflammatory disease. All patients received further workup to carefully exclude infectious disease and other autoimmune or malignant disorders. Workup included comprehensive history and physical examination, laboratory examination including differential white blood cell count (WBC), serum-electrophoresis, urinary sediment and IgG4. Antinuclear antibodies (ANA) and antineutrophilic antibodies (ANCA) were measured irregularly. Every patient received abdominal ultrasound including ultrasound of the pericardium, the adnex or the prostate respectively.

Clinical and laboratory disease activity

Different arbitrary scenarios of clinical and laboratory activity were defined and compared to PET/MRI results.

Scenario 1: clinical disease activity was assumed, if flank pain or non-mechanical pain in the lower back was present. If flank/lower back pain was absent, the presence of at least 2 symptoms such as unintended weight loss, significant night sweat or raised temperatures without infection was defined as clinically active.

Scenario 2: laboratory activity defined as an elevated C-reactive protein (CRP) (normal ≤0.5 mg/dl) and/or erythrocyte sedimentation rate (ESR) (normal ≤20 mm). Scenario 3: clinical or laboratory activity as defined above.

PET/MRI acquisition

PET/MRI was performed on a Biograph mMR (Siemens Medical Solutions, Erlangen, Germany) which allows whole-body simultaneous acquisition of PET and MRI data. The technical specifications of the PET/MRI scanner used were summarised recently in a performance evaluation paper (20).

Image evaluation

• *Visual activity assessment in PET*

Evaluation of PET data was done in a coregistered way with MRI to allow for precise anatomical assignment in PET/MRI. Scoring was done by consensus by two board certified nuclear medicine physicians on a dedicated workstation and software (syngo MMWP and syngo TrueD, Siemens Medical Solutions) using four visual scores, indicating the intensity of [18F]-FDG uptake in RF in relation to liver uptake: 0, no uptake present; 1, low-grade uptake (uptake present but lower than liver uptake); 2, intermediate-grade uptake (similar to liver uptake); 3, high-grade uptake (higher than liver uptake). Grade 2-3 uptake was assumed to be pathological due to active fibroinflammatory tissue. In contrast, grade 1 and grade 0 uptake were assumed as indeterminate and negative, respectively.

• *Quantitative activity assessment in PET*

Maximum standardised uptake values (SUVmax) for [18F]-FDG were measured on coregistered PET/MRI slices using isocontour volume of interests inluding all voxels above 99% of the maximum. Measurements were normalised for blood pool activity, as previously decribed (19). Target to background ratios (TBR) for each patient were calculated by dividing SUVmax by the blood pool SUV. If MRI did not show a definable retroperitoneal mass, SUV max and TBR were determined as 0.

• *Visual activity assessment and volume calculation in MRI*

MRI was analysed by a board certified radiologist on a workstation using an FDA approved OSIRIX DICOM viewer. The extent and volume (in cm^3) of RF were assessed on axial T1w VIBE sequences by placement and summation of ROIs in consecutive axial slices through the fibrous mass delineating the shape of it. Besides, the presence or absence of oedema within RF was determined on coronal T2w STIR due to its association with active inflammation. Contrast enhancement (CE) intensities were evaluated on axial T1w VIBE between RF and the psoas muscle to determine the degree of inflammation within RF: If the CE intensity was higher in RF compared to the psoas muscle, active disease was assumed. Non-active disease was determined by the lack of RF as well as by a hypointense or isointense presentation of RF without significant CE in relation to the psoas muscle. Disease activity was defined as indeterminate, if none of the above mentioned criteria were attributable.

• *Combination of PET and MRI for determination of disease activity status*

According to the visual analysis of PET and MRI data, combined PET/MRI was considered suggestive for ac-

tive disease, if PET and/or MRI was positive. Non-active disease was assumed, if PET and MRI did not show signs of active disease or indeterminate results. If both PET and MRI showed inconclusive findings, disease status was defined as indeterminate.

• *Assessment of disease extent and LVV*

Analysis of disease extent of RF was performed in a descriptive way, including atypical localisations of RF as well as associated large-vessel vasculitis (LVV). Regarding the latter a grade II-III FDG vessel wall uptake (FDG uptake at least similar or higher in relation to the liver uptake), a significant wall thickening (>3mm) and concomitant mural contrast enhancement of the aorta or its branches or typical long segment vessel stenosis/occlusion were considered suggestive for LVV.

Statistical analysis

Spearman's rank correlation coefficient (r) and Jonckheere-Terpstra trend test were calculated to examine the correlations between PET/MRI parameters (SUVmax, TBR, RF volume, visual score) and inflammatory markers (CRP and ESR). Mann Whitney U and Fisher's exact test were applied to test for correlations between the different disease activity scenarios and PET/MRI parameters as well as disease activity status determined by PET/MRI. In addition, Mann Whitney U was performed to compare PET/MRI parameters and inflammatory biomarkers between examinations rated as active and non-active and between therapy-naïve patients and patients under therapy. A *p*-value below 0.05 was considered significant. Statistical analysis was done with GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) and MedCalc (MedCalc Software, Ostend, Belgium).

Results

Patients

Seventeen examinations were performed in fourteen patients, with one follow-up examination in three patients. The mean age of all patients at the time of examination was 60.0±9.8 years and the mean age of all patients at the time of diagnosis was 56.0±11.1 years. In seven patients the diagnosis of retroperitoneal fibrosis was established at the time when PET/MRI was performed, six of them being therapy-naive. Seven patients already had a previously established diagnosis of RF with a mean disease duration of 10.1±7.8 years. Six out of these had paused immunosuppression at least 6 months before PET/MRI was performed. Overall, five and twelve examinations were performed in patients with and without current immunosuppressive therapy respectively. Biopsy results were available from four patients (patient 1, 2, 8, 11) with diagnosis of IgG4-related disease from biopsy of the lacrimal gland in one patient (patient 2), who also had elevated serum IgG4 levels (171 mg/dl, normal range 10–140 mg/dl). Serum IgG4 were in the normal range in all other patients. For therapy-naive patients serum IgG4 was available from the timepoint of diagnosis. For patients with a current or previous therapy IgG4 was available after diagnosis has been established. History revealed a potential association to asbestos exposure twenty years before diagnosis (patient 1), seminoma and orchiectomy 14 years before diagnosis (patient 10) and pancreatitis due to chronic alcohol abuse with pseudocyst, concrement and pancreaticojejunostomy (patient 13). In the last patient histology from resected tissue was without evidence for IgG4-related disease. In the patient with asbestos exporure no pleuropulmonary asbestosis was detected (21). History, physical examination and further workup showed no evidence for connective tissue disease, vasculitis, infection or malignoma. Immunological parameters were unremarkable. Epidemiological data, clinical symptoms and data about therapy for every patient are shown in Table I. Potential aetiology respectively disease associations, immunological parameters and serum IgG4 levels are provided electronically in Table I in the supplementary material.

Table I. Epidemiological, clinical and therapy data.

Epidemiology			Symptoms	Therapy			
No	Sex	Age	Systemic symptoms	Back pain	current	previous	at last
1	m	57	night sweats	1	no	GC, CYC, AZA	96 months
2*	m	75	0	0	no	no	no
3*	m	56	weight loss	1	no	no	no
4	f	59	0	0	no	GC	Years ago
5a*	f	54	0	1	no	no	no
5b	f	54	0	1	GC (2.73g)	no	no
6*	m	57	0	1	GC (4.67g)	no	no
7	f	82	0	0	no	GC (10.23g), MMF	60 months
8	m	61	0	0	no	GC, MMF	40 months
9*	f	70	weight loss	1	no	no	no
10a	m	54	0	0	no	GC (5.12g)	6 months
10b	m	56	0	0	GC (6.99g), MMF	GC (5.12g)	no
11	m	76	night sweats	0	no	GC (5.12g), MMF	15 months
12	f	64	0	0	GC (7.92g), MMF	no	no
13*	m	46	night sweats	1	no	no	no
14a*	f	52	0	1	no	no	no
14b	f	53	0	0	GC (4.2g), MTX	no	no

*patients with first diagnosis of retroperitoneal fibrosis at the time of examination. Diagnosis confirmed by biopsy in patients 1, 8 and 11. Diagnosis of IgG4-related disease confirmed by biopsy of left lacrimal gland in patient 2.

a, baseline scan and b, follow-up scan in patients undergoing a baseline and a follow-up examination; m: male; f: female; GC: glucocorticoisteroids; the cumulative dose of glucocorticosteroids is shown in brackets, if available; AZA: azathioprine; CYC: cyclophosphamide; MMF: mycophenolatemofetil.

PET/MRI disease activity status vs. clinical and laboratory disease activity

In PET/MRI thirteen (76%) examinations were rated as active, whereas four (24%) were rated as non-active. In fourteen examinations the results of PET and MRI were concordant, with eleven rated as active and three as non-active. In two examinations PET showed in-

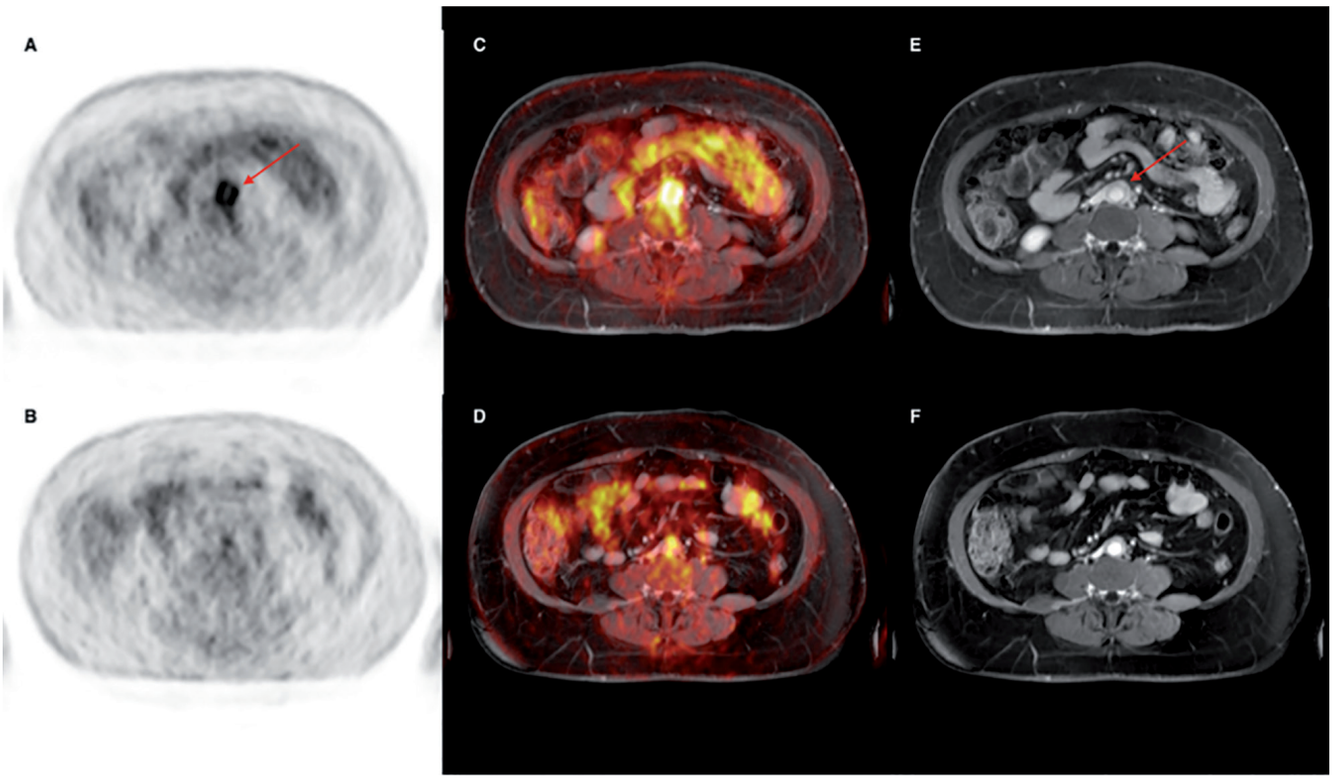

Fig. 1. Patient 14: At initial diagnosis, axial positron emission tomogram shows an intense central 18F-FDG accumulation (red arrow; **A**), which exactly projects onto a periaortic contrast enhanced soft tissue (**C**) seen on axial T1w VIBE (red arrow; **E**) suggesting active retroperitoneal fibrosis. The patient complained about back pain, whereas laboratory biomarkers CRP and ESR were normal. After immunosuppressive treatment, positron emission tomogram and magnetic resonance imaging as well as the combination of both modalities demonstrate regressive functional and morphological inflammatory changes, correlating with disappearing back pain indicating therapy response (**B**, **D** and **F**).

determinate findings, which were rated as active and non-active by MRI, respectively. In one examination, PET suggested active disease, whereas no disease activity was suggested by MRI. With regard to the different clinical and laboratory disease activity scenarios, scenario 1 (disease activity as defined by clinical symptoms) and scenario 2 (disease activity as defined by laboratory parameters) suggested active disease in eight (47%) and eleven (65%) cases, respectively, with concordant judgements in ten cases (59%). Scenario 3 (disease activity as defined by clinical and/or laboratory parameters) suggested active disease in thirteen (76%) examinations and non-active disease in 4 (24%) cases. PET/MRI changed the activity status based on clinical assessment (scenario 1), laboratory parameters (scenario 2) or both (scenario 3) in seven (41%), six (35%) and four (24%) examinations.

Disease activity status based on ESR and CRP alone was changed by PET/MRI in eight of sixteen (50%) and five of seventeen (29%) cases, respectively. In four examinations with CRP in the normal range and in three examinations moderately elevated CRP (0.5 to 1.0 mg/dl) PET/MRI revealed active disease. Six out of these seven examinations showed a high-grade uptake (grade 3, higher than liver uptake) as assessed by visual score. PET/MRI also revealed active disease in eight examinations where ESR was in the normal range. An example of active disease according to MRI and PET despite inflammatory markers in the normal range is given in Figure 1. Table II shows test results for ESR and CRP and assessment of disease activity according to MRI, PET and PET/MRI.

Correlation between clinical and laboratory parameters and PET/MRI

There was no significant association between disease activity status assessed by clinical and/or laboratory parameters (scenario 1 to 3) and disease activity status determined by PET/MRI. ESR and CRP showed a weak to moderate correlation to SUV max, TBR, MRI volume and visual score. Correlations between PET/MRI parameters and disease activity scenarios and inflammatory parameters respectively are provided electronically in Table II in the supplementary material.

SUV max and TBR according to disease activity and therapy status

SUV max and TBR differed significantly between examinations with active and non-active disease and between therapy-naïve patients and patients under current immunosuppressive therapy, whereas ESR and CRP did not. There was a marked difference of visual and quantitative PET parameters between initial and follow-up examinations without an overlap of values (patients 5, 10 and 14). SUV max, TBR and volume of the retroperitoneal mass along with laboratory test results according to disease activity and therapy status are shown in Table III. Image examples for examinations before and after therapy are given in Figure 1 and Figure 2.

Table II. Laboratory, PET, MRI and PET/MRI parameters.

Patient	PET					MRI			Extent			Disease Activity		
No.	ESR (mm)	CrP (mg/dl)	score	SUV	TBR	Thickness (mm)	Volume (cm^3)	STIR	CE	PET	MRI	MRI	PET	PET/ MRI
1	125	9.9	3	13.4	10.14	43	204.75	+	+	r	r	+	+	+
2*#	9	0.1	3	4.3	2.27	10	17.56	-	---	r/il	r/il	-	+	+
3*	16	0.6	3	8.4	5.78	17	38.52	+	+	r/il	r/il	+	+	+
4	18	1.2	0	0.0	0.00	0	0.00	-	-	-	-	-	-	-
5a*	1	3.1	3	9.8	6.15	15	31.25	+	+	r/il	r/il	+	+	+
5b**	5	1.2	2	3.2	2.64	5	7.93	+	+	r/il	r/il	+	+	+
6**	27	0.1	1	2.0	1.79	14	13.97	-	-	-	r/il	-	(-)	-
7	67	1.4	3	3.8	2.73	14	6.69	+	+	r	r	+	+	+
8	9	0.3	3	3.3	2.72	9	9.14	+	+	r/il	r/il	+	+	+
9*	53	5.0	3	11.7	11.94	10	19.13	+	+	r/il	r/il	+	+	+
10a	12	0.9	3	10.6	9.96	14	---	+	+	r/il	r/il	+	+	+
10b**	2	0.2	0	1.0	0.57	4	5.64	-	-	-	r/il	-	-	-
11	16	0.3	0	0.9	1.12	5	4.69	-	-	-	r/il	-	-	-
12**	32	0.6	3	4.2	3.37	28	14.95	+	+	il	il	+	+	+
13*	18	1.0	3	6.3	6.72	11	23.87	+	+	r/il	r/il	+	+	+
14a*	6	0.3	3	11.1	7.96	9	9.88	+	+	r/il	r/il	+	+	+
14b**	---	0.2	1	1.51	1.06	7	4.16	+	+	-	r/il	+	(-)	+

a: baseline scan; b: follow-up scan; *therapy-naïve, **immunosuppressive therapy at the time of examination; #patient refused contrast agent; ---, missing data.
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; score: visual score in PET; SUV: maximum standardised uptake value; TBR: target to background ratio; volume: volume of the retroperitoneal mass; STIR: short τ inversion recovery sequence; CE: contrast enhancement; disease extent: -, no retroperitoneal mass detected; il: iliacal; r: retroperitoneal; disease activity as judged by MRI, PET or PET/MRI: +: active; -: non-active; (-): indeterminate; in examination 10a calculation of MRI volume was not possible due to motion artefacts.

Table III. Comparison of inflammatory markers, PET and MRI parameters between groups.

	Laboratory		PET		MRI	
	ESR (mm)	CrP (mg/dl)	SUV max	TBR	Thickness (mm)	Volume (cm^3)
all examinations	16 (1/125)	1.6 (0.1/9.9)	4.2 (0/13.4)	2.7 (0.0/11.9)	10 (0/43)	11.9 (0.0/204.8)
active (n=13)	14 (1/125)	0.9 (0.1/9.9)	6.3 (1.5/13.4)	5.8 (1.1/11.9)	11 (5/43)	16.3 (4.2/204.8)
non-active (n=4)	17 (2/27)	0.3 (0.1/1.2)	1.0 (0.0/2.0)	0.9 (0.0/1.8)	4 (0/14)	5.2 (0.0/14.0)
p	0.937	0.168	0.001*	0.003*	0.060	0.039*
therapy naive (n=6)	13 (1/53)	0.8 (0.1/5.0)	9.1 (4.3/11.7)	6.4 (2.3/11.9)	11 (9/17)	21.5 (9.9/38.5)
current therapy (n=5)	16 (2/32)	0.2 (1.0/4.3)	2.0 (1.0/4.2)	1.8 (0.6/3.4)	7 (4/28)	7.9 (4.2/15.0)
p	1.000	0.305	0.004*	0.015*	0.406	0.015*
repeater 1st ex. (n=3)	6 (1/12)	0.9 (0.3/3.1)	10.6 (9.8/11.1)	8.0 (6.2/10)	14 (9/15)	20.6 (9.9/31.3)
repeater 2nd ex. (n=3)	4 (2/5)	0.2 (0.2/1.2)	1.5 (1.0/3.2)	1.1 (0.6/2.6)	5 (4/7)	5.6 (4.2/7.9)

Values are shown as median (minimum/maximum). *significant.
Mann-Withney-U test of inflammatory markers, PET and MRI parameters of examinations rated active *versus* non-active by PET/MRI and in therapy naive patients *versus* patients under current therapy. A *p*-value <0.05 was considered statistically significant. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SUV max: maximum standardised uptake value; TBR: target to background ratio; thickness: thickness of the retroperitoneal mass; volume: volume of the retroperitoneal mass.

Disease activity in MRI, thickness and volume of the retroperitoneal mass

MRI revealed active disease in twelve (71%) and non-active disease in five (29%) examinations (in examination 2 contrast agent was refused) (Table II). Volume differed significantly between examinations with active and non-active disease and between therapy-naive patients and patients with current immunosuppression at the time of examination, whereas the thickness of the retroperitoneal mass did not (Table II and III).

Disease extent

PET/MRI showed typical RF manifestations with periaortic and periiliac involvement in 10 patients. Only in two patients (patient 1 and 7) the periaortic retroperitoneum was exclusively involved, whereas in one patient (patient 12) RF was located at the left periiliac region. In one patient with longstanding disease longer than ten years (patient 4), PET/MRI did not detect periaortic, periiliac or atypically located RF, excluding active RF, which was suspected by increased inflammatory biomarkers. All PET/MRI results regarding disease extent are shown in Table II.

Vasculitis and aneurysms

In addition to the extent of RF, PET/MRI showed findings suggestive for LVV in three patients: in patient 7

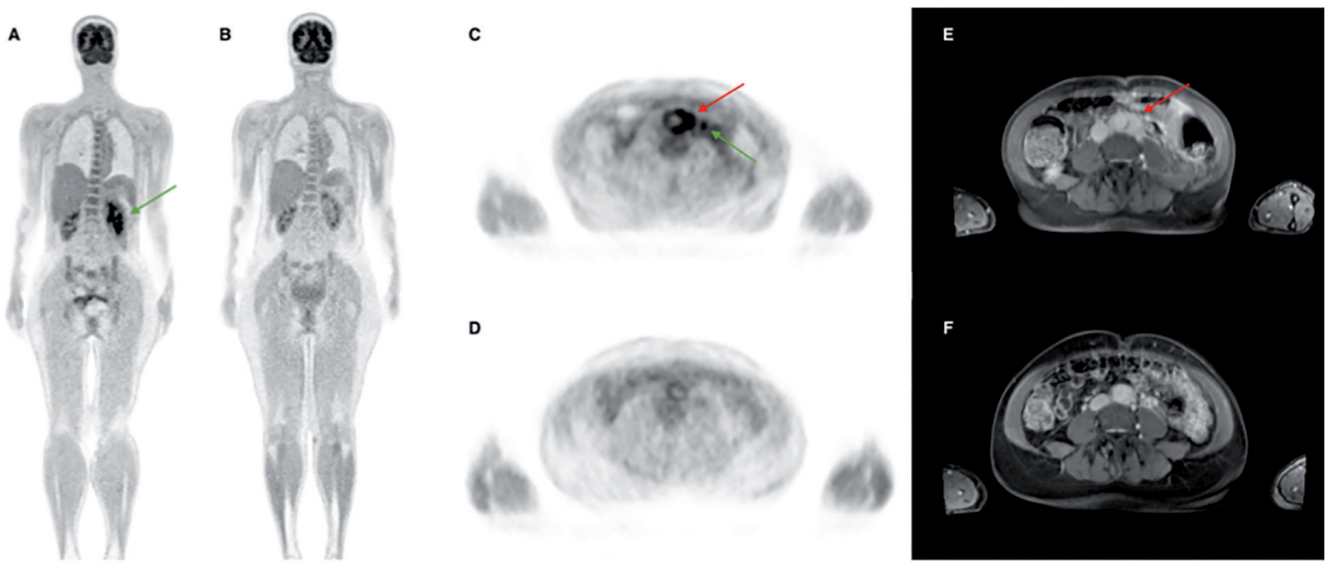

Fig. 2. Patient 5: Baseline axial positron emission tomogram and T1w VIBE after contrast media application show a highly 18F-FDG avid contrast enhanced paraaortal soft tissue (red arrows; **C** and **E**), indicating active retroperitoneal fibrosis. The corresponding coronal and axial positron emission tomograms demonstrate 18F-FDG retention in the left kidney (green arrow; **A**) and left ureter (green arrow; **C**), respectively, due to ureteral obstruction by the retroperitoneal mass. In follow-up, after starting immunosuppressive therapy, tissue volume and 18F-FDG uptake decreased significantly suggesting therapy response (**D** and **F**). Besides, PET/MRI shows decreasing 18F-FDG uptake within the left kidney and ureter, indicating declining ureteral obstruction (**B** and **D**).

both PET and MRI indicated pathologic [18F]-FDG vessel wall uptake of the aortic arch together with substantial wall thickening. In patient 9 PET showed an intense vessel wall uptake in the thoracic aorta demonstrating active inflammation without morphologic vessel wall changes in MRI (Fig. 3). In patient 10 functional und morphological inflammatory changes of the superior mesenteric artery were demonstrated by PET and MRI. Besides, CE-MRA revealed aneurysms of the thoracic and abdominal aorta, the latter without vasculitic activity, in patients 9 and 3, respectively. All four patients had active retroperitoneal fibrosis with retroperitoneal and iliacal, but without thoracic involvement. Both patients with aortic aneurysms had one cardiovascular risk factor, which were former smoking and hyperlipoproteinaemia, respectively.

Discussion

This is the first study investigating fully integrated [18F]-FDG PET/MRI in retroperitoneal fibrosis. PET/MRI provided a comprehensive assessment of RF with regard to disease activity, disease extent, vasculitis and large-vessel morphology. There was substantial influence on activity assessment compared to clinical and laboratory parameters and a clear discrimination between therapy-naïve patients and patients under immunosuppression by SUV max and TBR. In contrast to thickness, the volume of the retroperitoneal mass differed significantly between therapy-naive patients and patients under immunosuppression and decreased markedly in therapy-naive patients after implementation of immunosuppressive therapy. The combination of PET and MRI yielded additional information with regard to disease activity compared to each modality alone.

As a major observation, there was no significant correlation between clinical or laboratory parameters and PET/MRI parameters. PET/MRI changed disease activity status based on clinical or laboratory parameters in 41 percent and 35 percent, respectively. With regard to inflammatory parameters, ESR, but also CRP showed a wide variability among patients with active disease in PET/MRI. In particular, in about the half of examinations inflammatory parameters were in the normal range or only slightly elevated despite clear inflammatory activity in PET/MRI. Of note, this was also the case in most examinations of therapy-naive patients precluding the influence of a previous therapy. Furthermore, inflammatory parameters did not differ significantly between therapy-naive patients and patients under therapy. Published data on the correlation between acute phase reactants and PET parameters in retroperitoneal fibrosis are contradictory. Whereas a significant correlation between CRP and visual PET score has been reported in one prospective study in well selected patients under therapy with tamoxifen (12), a wide range of CRP and a weak correlation between CRP and PET parameters has been reported in several other retrospective and prospective observations (11, 22, 23). This might be explained by heterogenous cohorts with regard to disease stage, therapy and aetiology. Particularly in the setting of previous therapy, inflammatory parameters seem to be less reliable, Furthermore, in a recent study, PET has been shown to detect relapses before a new increase of inflammatory parameters, indicating that also in the setting of previous therapy, inflammatory parameters seem to be less reliable than PET (23). Taken together, the data of this study suggest that inflammatory parameters alone are not sufficient to assess the disease activity of retroperitoneal fibrosis in a substantial proportion of patients and that [18F]-FDG PET/MRI yields additional information regarding disease activity.

In contrast to inflammatory parameters,

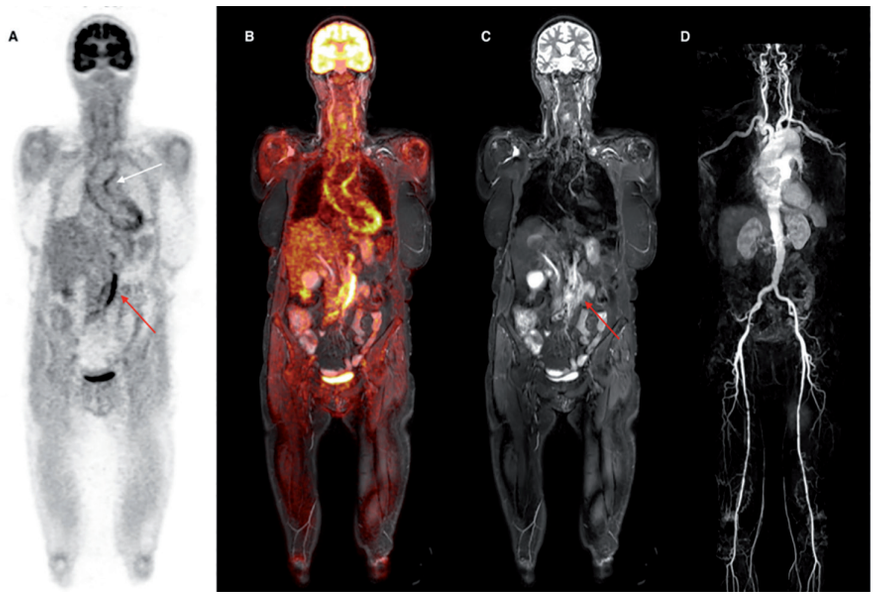

Fig. 3. Patient 9: Coronal positron emission tomogram shows pathologic 18F-FDG uptake within retroperitoneal fibrosis (red arrow; **A**) with oedema on coronal T2w STIR (red arrow; **C**), best seen in the fused PET/MRI images (**B**) indicating active inflammation. Besides, positron emission tomogram shows an increased 18F-FDG radiotracer accumulation in the ascending thoracic aorta suggesting active large-vessel vasculitis with an aneurysm (white arrow; A), whereas T2w STIR and magnetic resonance angiography do not indicate typical findings for vasculitis (**C** and **D**).

the SUV max and the TBR differed significantly between examinations with active and non-active disease and between therapy-naive patients and patients under immunosuppression at the time of examination. This is in accordance with previous studies, which evaluated the SUV max and the TBR in retroperitoneal fibrosis (11, 22, 24, 25). In this study, a SUV max of 4.2 and below correctly identified all patients under immunosuppression and a SUV max of 4.3 and above identified all therapy-naïve patients. All examinations rated as non-active simultaneously by visual assessment in PET and by MRI had an SUV max of 2.0 or below, which is in the range reported from other studies (11). However, one examination with a SUV max of 1.5 which was rated as non-active by visual assessment in PET fulfilled the criteria of disease activity in MRI. This highlights the possibility that 18-F FDG PET and contrast-enhanced imaging methods detect different phases of the inflammatory process. Since this was a follow-up examination, it can not be excluded that there was contrast enhancement due to a disturbed barrier caused by preceding inflammation. However, the clinical relevance of this residual inflammation could only be clarified by biopsy and longitudinal follow-up examinations.

In this study, contrast-enhanced MRI not only allowed the precise allocation of radionuclid-uptake to anatomical structures, but also detected inflammatory activity in addition to [18F]-FDG PET. In a recent study comparing the SUV max of [18F]-FDG PET and CE-CT in disease activity assessment in patients with RF, each modality compared to the other detected disease activity in two additional examinations in a total of thirty-three examinations (11). A similar observation was made for contrast-enhanced MRI in a recent study evaluating [18F]-FDG PET/MRI in large-vessel vasculitis, in which additional information on disease activity was obtained from contrast-enhanced MRI and [18F]-FDG PET in comparison to the other modality, respectively (19). These results are in line with this study, in which contrast-enhanced MRI detected disease activity in one additional examination compared to [18F]-FDG PET and *vice versa*.

Several studies reported the thickness and the craniocaudal extent of the retroperitoneal mass in RF as a parameter for disease extent and activity (12, 22, 26). However, these parameters may only provide an incomplete approximation to the true dimension of the retroperitoneal mass. Therefore, in this study, the volume of the retroperitoneal mass was calculated. The volume differed significantly between examinations with active and non-active disease and between therapy-naive patients and patients with current immunosuppression, whereas the thickness of the retroperitoneal mass did not. Especially in patients with a large disease extent, volume measurement offers the opportunity to better estimate the total inflammatory load of the disease to tailor and guide therapy.

SUV max and TBR's derived from it have been evaluated in disease activity assessment and therapy monitoring of retroperitoneal fibrosis (11, 22, 24, 25). However, they only represent a focal aspect of the disease and do not take into account activity which is not above 99 percent of the maximum. Alternatively, SUV mean and a TBR's derived from it, or metabolic volume measurements with predefined SUV thresholds maybe could better represent global disease status. However, regarding the pattern and shape of retroperitoneal fibrosis, SUV mean measurements are very difficult to standardise and prone to differ between different examinations and observers due to their strong dependency on the size and content of the region of interest (ROI). Considering metabolic volume measurements, a SUV threshold would be needed to discriminate metabolically active from inactive tissue. However, a reliable SUV threshold has not been established yet. Therefore, since SUV max and TBR's derived from it already have been evaluated in retroperitoneal fibrosis, they were used in the present study.

In addition to the detection of inflammation of the retroperitoneal mass there was inflammation of the thoracic aorta in two patients and of the superior mesenteric artery in one patient, which was detected concordantly by MRI and PET in two examinations and only by PET in one examination. Both patients with vasculitic activity of the thoracic aorta had retroperitoneal and iliacal, but no mediastinal involvement in terms of periaortitis, indicating that inflamma-

tion of the large vessels can occur apart from retroperitoneal disease. Furthermore, MRA detected a thoracic and an abdominal aortic aneurysm in one patient each, the latter without signs of vasculitis in [18F]-FDG PET/MRI. Interestingly, in both patients with aneurysms, the initial diagnosis of RF was made at the time of examination and both had an only moderate cardiovascular risk profile. These results are in accordance with previous reports suggesting that large-vessel vasculitis is a common phenomenon in patients with periaortitis (9). They further suggest that aneurysms may be present already at the time of diagnosis, an observation that has also been made in giant cell arteritis (27). As a consequence the search for large-vessel vasculitis and aortic aneurysms not only in the retroperitoneum is essential.

The major limitation of the this study is the small number of patients and examinations, which is mainly due to the rarity of the disease and the relative novelty of hybrid [18F]-FDG PET/MRI. However, the main results were consistent and in line with previous studies. Furthermore, some patients had immunosuppression in the past, possibly causing a bias with regard to inflammatory parameters. In this patient group, there were discordancies between [18F]-FDG PET/MRI results and clinical findings only in two of six examinations. However, in four of six patients without previous therapy inflammatory parameters were in the normal range or only sligthly elevated despite strong inflammation in [18F]-FDG PET/MRI, demonstrating that the discrepancy between inflammatory parameters and the presence of inflammatory activity as assessed by [18F]-FDG PET/MRI exists independently from previous immunosuppression. A further limitation is the lack of a reference method. However, there is no defined standard of reference in retroperitoneal fibrosis and the additional performance of computed tomography (16) was not possible for ethical reasons. Only biopsy can prove that radionuclid uptake or contrast enhancement correspond to inflammatory activity and it has been performed in previous studies evaluating [18F]-FDG PET (12). However, biopsy entails a risk for the patient particularly after the beginning of immunosuppression, when the volume of the retroperitoneal mass decreases. In this study, a biopsy was conducted only in four patients with histological diagnosis of IgG4-related disease in one patient. Although there were no typical findings for retroperitoneal tumours or lymphoma, it has to be kept in mind that imaging alone and even MRI is not able to preclude malignant disease in all cases (28). However, neither PET/MRI itself, nor further workup or follow-up revealed malignant disease in any of the patients. Furthermore, autoantibodies were performed not in all patients. However, none of the patients developed symptoms specific for connective tissue disorders or vasculitis. With regard to potential IgG4-related disease, the normal serum IgG4 values in thirteen patients are difficult to interpret, since six patients had previous and two patients had ongoing immunosuppression potentially leading to false normal values. Furthermore, patients with histologally proven IgG4-related disease may have serum IgG4 in the normal range (29, 30). Therefore, from this study, no conclusion with regard to IgG4-related disease can be drawn.

Conclusion

The main conclusion from the data of this study is that inflammatory parameters do not reliably detect inflammatory activity in retroperitoneal fibrosis even in patients without previous immunosuppression. When the clinical suspicion of retroperitoneal fibrosis arises, the combination of imaging methods and nuclear imaging is advisable to assess disease extent and activity. Because vasculitis and aneurysms may occur apart from the retroperitoneal lesion, whole body assessment is advisable as well. Although [18F]-FDG PET/MRI is not be available as a routine method, this study demonstrates, that whole body hybrid [18F]-FDG-PET/MRI provides a comprehensive workup of RF with regard to inflammatory activity, disease extent, associated vasculitis and vascular alterations in diagnosis and therapy monitoring of RF.

References

1. CORRADI D, MAESTRI R, PALMISANO A *et al*.: Idiopathic retroperitoneal fibrosis: clinicopathologic features and differential diagnosis. *Kidney Int* 2007; 72: 742-53.
2. PIPITONE N, VAGLIO A, SALVARANI C: Retroperitoneal fibrosis. *Best Pract Res Clin Rheumatol* 2012; 26: 439-48.
3. KHOSROSHAHI A, CARRUTHERS MN, STONE JH *et al*.: Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine* 2013; 92: 82-91.
4. WASHINO S, HIRAI M, MATSUZAKI A, KOBAYASHI Y: (18)F-Fluorodeoxyglucose positron emission tomography for diagnosis and monitoring of idiopathic retroperitoneal fibrosis associated with mediastinal fibrosis. *Ann Nucl Med* 2010; 24: 225-9.
5. SA HS, LEE JH, WOO KI, KIM YD: IgG4-related disease in idiopathic sclerosing orbital inflammation. *Br J Ophthalmol* 2015; 99: 1493-7.
6. ZHANG J, CHEN H, MA Y *et al*.: Characterizing IgG4-related disease with (1)(8)F-FDG PET/CT: a prospective cohort study. *Eur J Nucl Med Mol Imaging* 2014; 41: 1624-34.
7. SCHULTZ O, SCHUCHMANN S, BURMESTER GR, BUTTGEREIT F: Case number 26: systemic idiopathic fibrosis associated with aortitis. *Ann Rheum Dis* 2003; 62: 486.
8. PROTOPSALTIS I, SOTIROPOULOS A, FOTEINOS A *et al*.: Chronic periaortitis (retroperitoneal fibrosis) concurrent with giant cell arteritis: a case report. *J Med Case Rep* 2014; 8: 167.
9. SALVARANI C, PIPITONE N, VERSARI A *et al*.: Positron emission tomography (PET): evaluation of chronic periaortitis. *Arthritis Rheum* 2005; 53: 298-303.
10. TREGLIA G, MATTOLI MV, BERTAGNA F, GIUBBINI R, GIORDANO A: Emerging role of Fluorine-18-fluorodeoxyglucose positron emission tomography in patients with retroperitoneal fibrosis: a systematic review. *Rheumatol Int* 2013; 33: 549-55.
11. MORONI G, CASTELLANI M, BALZANI A *et al*.: The value of (18)F-FDG PET/CT in the assessment of active idiopathic retroperitoneal fibrosis. *Eur J Nucl Med Mol Imaging* 2012; 39: 1635-42.
12. JANSEN I, HENDRIKSZ TR, HAN SH, HUISKES AW, VAN BOMMEL EF: (18)F-fluorodeoxyglucose position emission tomography (FDG-PET) for monitoring disease activity and treatment response in idiopathic retroperitoneal fibrosis. *Eur J Intern Med* 2010; 21: 216-21.
13. GAO L, WANG H, XU Y, ZHANG Z: Computed tomography parameters can be used as predictive markers for the improvement of renal function in patients with retroperitoneal fibrosis. *Clin Exp Rheumatol* 2015; 33: 871-6.
14. BROOKS AP, REZNEK RH, WEBB JA, BAKER LR: Computed tomography in the follow-up of retroperitoneal fibrosis. *Clin Radiol* 1987; 38: 597-601.
15. BROOKS AP: Computed tomography of idiopathic retroperitoneal fibrosis ('periaortitis'): variants, variations, patterns and pitfalls. *Clin Radiol* 1990; 42: 75-9.
16. BACHMANN G, BAUER T, RAU WS: [MRI and

CT in diagnosis and follow-up of idiopathic (retroperitoneal) fibrosis]. *Der Radiologe* 1995; 35: 200-7.
17. BRANDT AS, KAMPER L, KUKUK S, PIROTH W, HAAGE P, ROTH S: An aid to decision-making in therapy of retroperitoneal fibrosis: dynamic enhancement analysis of gadolinium MRI. *J Clin Med Res* 2013; 5: 49-56.
18. KAMPER L, BRANDT AS, EKAMP H *et al*.: Diffusion-weighted MRI findings of treated and untreated retroperitoneal fibrosis. *Diagn Interv Radiol* 2014; 20: 459-63.
19. EINSPIELER I, THURMEL K, PYKA T *et al*.: Imaging large vessel vasculitis with fully integrated PET/MRI: a pilot study. *Eur J Nucl Med Mol Imaging* 2015; 42: 1012-24.
20. DELSO G, FURST S, JAKOBY B *et al*.: Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner. *J Nucl Med* 2011; 52: 1914-22.
21. GOLDONI M, BONINI S, URBAN ML *et al*.: Asbestos and smoking as risk factors for idiopathic retroperitoneal fibrosis: a case-control study. *Ann Intern Med* 2014; 161: 181-8.
22. GUIGNARD R, SIMUKONIENE M, GARIBOTTO V, RATIB O: 18F-FDG PET/CT and contrast-enhanced CT in a one-stop diagnostic procedure: a better strategy for management of patients suffering from retroperitoneal fibrosis? *Clin Nucl Med* 2012; 37: 453-9.
23. PICCOLI GB, CONSIGLIO V, ARENA V *et al*.: Positron emission tomography as a tool for the 'tailored' management of retroperitoneal fibrosis: a nephro-urological experience. *Nephrol Dial Transplant* 2010; 25: 2603-10.
24. BERTAGNA F, TREGLIA G, LECCISOTTI L *et al*.: [(1)(8)F]FDG-PET/CT in patients affected by retroperitoneal fibrosis: a bicentric experience. *Jpn J Radiol* 2012; 30: 415-21.
25. NAKAJO M, JINNOUCHI S, TANABE H, TATENO R, NAKAJO M: 18F-fluorodeoxyglucose positron emission tomography features of idiopathic retroperitoneal fibrosis. *J Comput Assist Tomogr* 2007; 31: 539-43.
26. WARNATZ K, KESKIN AG, UHL M *et al*.: Immunosuppressive treatment of chronic periaortitis: a retrospective study of 20 patients with chronic periaortitis and a review of the literature. *Ann Rheum Dis* 2005; 64: 828-33.
27. KERMANI TA, WARRINGTON KJ, CROWSON CS *et al*.: Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis* 2013; 72: 1989-94.
28. CAIAFA RO, VINUESA AS, IZQUIERDO RS, BRUFAU BP, AYUSO COLELLA JR, MOLINA CN: Retroperitoneal fibrosis: role of imaging in diagnosis and follow-up. *Radiographics* 2013; 33: 535-52.
29. HAO M, LIU M, FAN G, YANG X, LI J: Diagnostic value of serum IgG4 for IgG4-related disease: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2016; 95: e3785.
30. SMYRK TC: Pathological features of IgG4-related sclerosing disease. *Current Opin Rheumatol* 2011; 23: 74-9.