Diffusion-weighted MRI findings of treated and untreated retroperitoneal fibrosis

Lars Kamper, Alexander Sascha Brandt, Hendrik Ekamp, Nadine Abanador-Kamper, Werner Piroth, Stephan Roth, Patrick Haage

PURPOSE
We aimed to evaluate diffusion-weighted imaging (DWI) findings in patients with treated and untreated retroperitoneal fibrosis (RPF).

METHODS
We analyzed magnetic resonance imaging examinations of 44 RPF patients (36 male, 8 female), of which 15 were untreated and 29 were under therapy. Qualitative DWI and T1 postcontrast signal intensities and the largest perivascular extent of RPF were compared between treated and untreated groups and correlated to erythrocyte sedimentation rate and C-reactive protein values. Quantitative DWI signal intensities and apparent-diffusion-coefficients were calculated in regions-of-interest, together with a relative index between signal intensities of RPF and psoas muscle in 15 untreated patients and 14 patients under treatment with remaining perivascular fibrosis of more than 5 mm.

RESULTS
The extent of RPF in untreated patients was significantly larger compared with the extent of RPF in treated patients ($P < 0.0001$). DWI signal intensities were significantly higher in untreated patients than in patients under therapy (mean, 27 s/mm^2 vs. 20 s/mm^2; $P = 0.009$). The calculated DWI-index was significantly higher in untreated patients than in patients under therapy ($P = 0.003$).

CONCLUSION
Our data show significant differences in the DWI findings (b800 signal intensities and relative DWI-index) of patients with treated and untreated RPF. DWI is a promising technique in the assessment of disease activity and the selection of patients suitable for medical therapy.

From the Departments of Diagnostic and Interventional Radiology (L.K. ✉ lars.kamper@helios-kliniken.de, H.E., W.P., P.H.), Urology (A.S.B., S.R.), and Cardiology (N.A.-K.), HELIOS Medical Center Wuppertal, University Hospital Witten/Herdecke, Wuppertal, Germany; the Center for Clinical Medicine (L.K., A.S.B., H.E., N.A.-K., W.P., S.R., P.H.), Witten/Herdecke University Faculty of Health, Wuppertal, Germany.

Retroperitoneal fibrosis (RPF) is a rare disease affecting the retroperitoneal space (1–3). It presents as retroperitoneal proliferation of fibrous tissue surrounding the retroperitoneal vascular structures and abutting the medial aspect of the ureters. Clinical findings of RPF are nonspecific; the most common symptom is chronic back pain. Further symptoms include lower extremity edema, deep vein thrombosis, oliguria, and urinary tract infection (3). Computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred imaging modalities for the diagnosis of RPF (3). Retroperitoneal fibrosis shows contrast enhancement of gadolinium containing contrast media in MRI (4). Medical treatment is classically based on steroids like prednisone (3). Recent studies suggested tamoxifen as another safe and effective treatment alternative (5).

The assessment of disease activity is relevant for planning of further medical or surgical therapy (6, 7). Nowadays the disease activity is assessable by positron emission tomography tracer uptake (3), with a relatively low resolution and the need of ionized radiation. As an alternative, dynamic contrast-enhanced MRI was suggested for the evaluation of disease activity (7, 8). However, gadolinium may be contraindicated in patients with impaired renal function due to the potential development of nephrogenic systemic fibrosis (NSF) (9). This is especially relevant in RPF patients with postrenal failure due to ureteral compression. For those cases a supplemental method for the determination of disease activity would be helpful.

Diffusion-weighted imaging (DWI) is a radiation-free unenhanced MRI modality that has been applied for the detection of bowel inflammation in patients with chronic inflammatory bowel diseases (10, 11), as well as for oncological retroperitoneal and abdominal applications (12–14). Therefore, we aimed to evaluate the application and findings of DWI in patients with treated and untreated RPF disease.

Methods

Study protocol

Our local institutional ethics committee approved the study. Between June 2011 and January 2013, we retrospectively analyzed MRI examinations of 44 consecutive patients (36 male, 8 female; mean age, 55 years; range, 37–82 years) with idiopathic RPF in typical lumbar location (Fig. 1). These included 15 untreated patients with newly diagnosed disease and 29 patients under medical therapy, according to the standardized treatment protocol of our Urology Department (15).

Clinical symptoms together with typical imaging and laboratory findings established the diagnosis of idiopathic RPF, after careful exclusion of malignancy. In uncertain cases diagnosis was confirmed by histology,
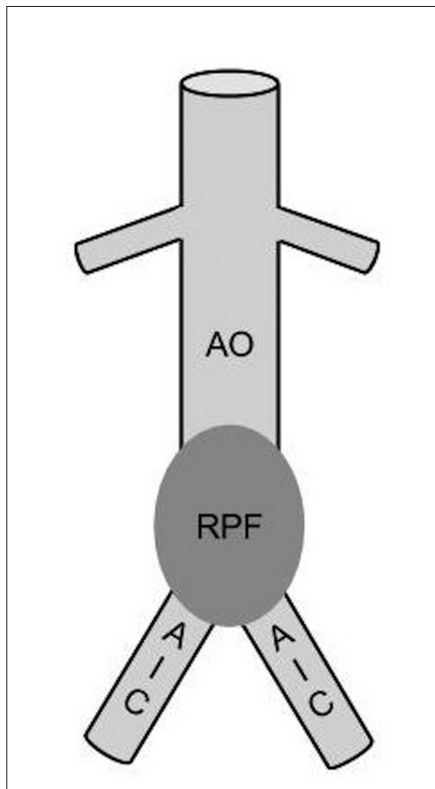
Figure 1. Schematic illustration of typical lumbar location for retroperitoneal fibrosis (RPF) ventral to the aortic bifurcation. AO, aorta; AIC, common illiac artery.

which was necessary in nine of 15 patients with untreated RPF and 18 of 29 patients with treated RPF.

We excluded 15 patients with perivascular fibrosis of less than 5 mm from the quantitative examination to avoid interference from artefacts caused by aortic pulsation and partial volume averaging. Parallel to each MRI examination we documented erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels.

MRI procedure

MRI examinations were performed after written informed consent of the patients. Renal function was determined by serum creatinine and glomerular filtration rate (GFR) to prevent the development of NSF. Patients with GFR 30–60 mL/min were informed about the increased risk of NSF. No gadolinium-based contrast agent was applied in three patients due to impaired renal function with calculated GFR below 30 mL/min.

We used a 1.5 Tesla MRI scanner (Siemens MAGNETOM Avanto, Siemens Medical Systems, Erlangen, Germany) with a standard body array coil. Steady-state free precession sequences (TRUE-FISP) in transversal, coronal, and sagittal orientations were used to localize the extent of RPF. We performed transversal T1-weighted sequences with fat suppression (TR 170 ms, TE 4.76 ms, flip angle 70°, resolution 256, slice thickness 8.0 mm, bandwidth 150 kHz and a pre-pulse for the fat saturation) before and 5 min after injection of weight-adapted Gadoteridol contrast (0.2 mmol/kg, ProHance, Altana Pharma, Konstanz, Germany). Axial single-shot echo-planar DWI sequence using tridirectional gradients and b-values of 50, 400, and 800 s/mm² (TR 5.300 ms, TE 75 ms, flip angle 90°, resolution 192, slice thickness 6.0 mm) with in-line reconstruction of apparent diffusion coefficient (ADC) maps were used as DWI sequences. Due to retroperitoneal focus, no respiratory motion correction was applied. The total acquisition time of all sequences was approximately 15 min, including 3.28 min for the DWI sequences.

Image analysis

Qualitative image analysis was performed in consensus by two radiologists with five and 10 years of experience in MRI using our picture archiving system (Centricity PACS 3.1.1.4, GE Healthcare, Milwaukee, Wisconsin, USA). The readers were blinded to patients' treatment status, but were aware of the RPF diagnosis. The RPF configuration, extent, and relative contrast uptake was assessed in each examination. The size of the retroperitoneal tissue was acquired by the largest perivascular diameter in the axial plane. The relative contrast uptake of RPF was assessed visually in the T1-weighted images with fat suppression compared to psoas muscle.

The qualitative signal intensity of RPF in DWI was evaluated visually. DWI signal was considered as visually high if a hyperintense perivascular mass or rim was delineable from unaffected retroperitoneal tissue. The qualitative contrast uptake was assessed visually in comparison to the psoas muscle.

Quantitative examination was performed in 15 untreated and 14 treated patients with remaining perivascular fi-brosis of more than 5 mm, by ellipsoid regions-of-interest (ROI) with identical position and size in the b-800 DWI and the ADC maps. We selected the largest possible extent on a single slice for the ROI position, avoiding outer margins and areas of artefact to reduce partial volume averaging. In addition, we examined a relative DWI-index in the b-800 images, by dividing signal intensities within RPF and the psoas muscle. For better visualization of the DWI data we generated fusion images from the T1-weighted images with fat suppression and the b800 images using a commercial software package (AW-Server 2.0-5.5, GE Healthcare).

Data storage and statistics

All patients gave written consent to storage and examination of their personal and disease-related data. Patients' data were recorded in the Else Kröner-Fresenius Registry of Retroperitoneal Fibrosis in Germany, a nationwide registry for RPF patients headquartered in our Department of Urology (16). For data storage we used a MySQL database in pseudo-anonymous form, concordant with the standards of the local ethics committee. Median values and ranges were used for descriptive analysis. Statistical comparisons were performed using Mann-Whitney U test for continuous data and Fisher's exact test for categorical data, with $P < 0.05$ considered significant for all tests. Pearson's correlation coefficient was used for the correlation between the DWI parameters (b800, ADC) and the laboratory inflammation markers (ESR, CRP).

Statistical analysis was performed using a commercial software tool (XL-STAT, Addinsoft, New York City, New York, USA).

Results

The extent of RPF was significantly higher in untreated patients (mean, 25 mm; range, 9–40 mm) than in treated patients (mean, 7 mm; range, 3–29 mm).

Qualitatively, we observed a visually high signal intensity of the retroperitoneal fibrosis in all of the 15 untreated patients and 21 of 29 patients under medical therapy. Visually low ADC was found in 13 of 15 untreated and 13 of 29 treated patients (Table). There was a statistically significant

Table. Comparison between untreated and treated patients

	Untreated	Treated	*P*
RPF extent (mm)	25±23 (9–40)	7±7 (3–29)	<0.0001[a]
DWI visually high, % (n/N)	100 (15/15)	72 (21/29)	0.037[b]
ADC visually low, % (n/N)	87 (13/15)	45 (13/29)	0.01[b]
DWI (b800) signal intensity (s/mm²)[c]	26.6±5.3 (17–35)	20.1±6.4 (9–30)	0.009[a]
DWI index (RPF/Psoas)[c]	2.2±0.4 (1.6–2.8)	1.5±0.5 (0.8–2.5)	0.003[a]
ADC (×10⁻³ mm²/s)[c]	0.88±0.18 (0.54–1.21)	1.1±0.3 (0.74–1.64)	0.096[a]
Contrast enhancement, % (n/N)[d]	100 (14/14)	55.6 (15/27)	0.003[b]
ESR (mm/1h)	45.7±31.9 (12–99)	15.7±11.8 (5–56)	<0.0001[a]
ESR (mm/2h)	64.9±27.2 (23–105)	31.9±21.6 (7–99)	<0.0001[a]
CRP (mg/dL)	2.6±3.9 (0.1–13.2)	0.6±0.6 (0.1–2.7)	0.043[a]

Data are given as mean±SD (range) unless otherwise noted.
RPF, retroperitoneal fibrosis; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
[a]Mann-Whitney U test.
[b]Fisher's exact test.
[c]Calculated for 14 of 29 patients under therapy with persisting retroperitoneal fibrous tissue (>5 mm).
[d]No contrast agent was applied in one patient with untreated RPF and two patients with treated RPF, due to impaired renal function (GFR <30).

difference between the two groups for visually high DWI (*P* = 0.037) and visually low ADC (*P* = 0.01). Exemplary cases for untreated and treated patients are shown in Fig. 2. Quantitative analyses revealed significantly higher DWI signal intensities (*P* = 0.009) and significantly higher DWI index (*P* = 0.003) in patients with newly diagnosed RPF compared with 14 treated patients with remaining perivascular fibrosis of more than 5 mm (Table). Signal intensities of the psoas muscle displayed no differences (*P* = 0.47). Mean values for ADC intensities were lower in the untreated group, but without statistical significance (*P* = 0.096). The untreated group showed a significantly higher extent of perivascular fibrous tissue and higher contrast uptake (Table).

In addition, untreated patients had higher ESR and CRP values compared with treated patients (Table). ESR values after one and two hours showed statistically significant differences between the two groups, while CRP differences reached no statistical significance.

We found no correlation between the DWI parameters (b800, ADC) and the laboratory markers of inflammation (ESR, CRP) using Pearson's correlation coefficient.

Discussion

The presented DWI data demonstrate significant differences in the RPF signal intensities between treated and untreated patients. In addition, we found significant differences for the quantitative and qualitative signal intensities in b800 images and ADC maps in the individual follow-up.

So far, morphological cross sectional imaging is essential to evaluate the response to treatment of RPF (3,17,18). Gadolinium-enhanced MRI provides high contrast discrimination between RPF and surrounding retroperitoneal tissue. However, the development of gadolinium-associated NSF must be carefully considered (9), especially in RPF patients with impaired renal function due to ureteral compression. In this context, the independence of DWI from intravenous contrast media is especially advantageous. DWI sequences are increasingly used for the evaluation of other extracranial diseases and can be added to abdominal MRI protocols without relevant prolongation of the examination time (10–14). In the retroperitoneum DWI allowed the clear delineation of an inflammatory abdominal aortic aneurysm (19). Nakayama et al. (20) found significantly different ADC values between malignant and benign retroperitoneal le-

sions with lower values for lymphoma and carcinoma.

Rosenkrantz et al. (21) suggested that DWI may also be helpful in the differentiation between RPF and lymphoma. They observed higher ADC values in 22 patients with RPF compared with nine patients with retroperitoneal lymphoma, regardless of RPF stage and therapy. Further studies are necessary to clarify the potential role of DWI in the differentiation of malignant and non-malignant retroperitoneal masses.

Vivas et al. (22) observed a higher T2 signal intensity in the early stage of the disease in a retrospective MRI analysis of 30 patients. This may be due to edema and hypercellularity in active fibrosis. In contrast, more "mature" RPF shows a reduced T2 signal, presumably caused by predominant composition of a collagen matrix and fewer cells. We did not evaluate T2 signals in this study, but the concept of hypercellularity in active fibrosis may be supported by our results showing significantly higher DWI signals in untreated patients than in patients with treated RPF. Best results were observed for a relative index of the quantitative RPF signal compared to psoas muscle in the b800 DWI. However, for ADC values, only qualitative analyses displayed significant differences between the two groups. Quantitatively, ADC signal intensities showed lower median values in the untreated group, without reaching a statistically significant difference. Larger studies would be helpful to prove the potential of ADC values in this rare disease and the value of T2-signals for the differentiation of treated and untreated RPF.

We observed significant difference in DWI signals between the two groups of patients. In contrast, the laboratory values (CRP and ESR) reached no statistical difference. Additionally, no correlation was observed between the inflammation markers and the DWI parameters. This may support the results of Magrey et al. (23) who observed no correlation between CRP or ESR and the radiological response in patients with good therapeutic response and a second group of patients with no therapeutic response.

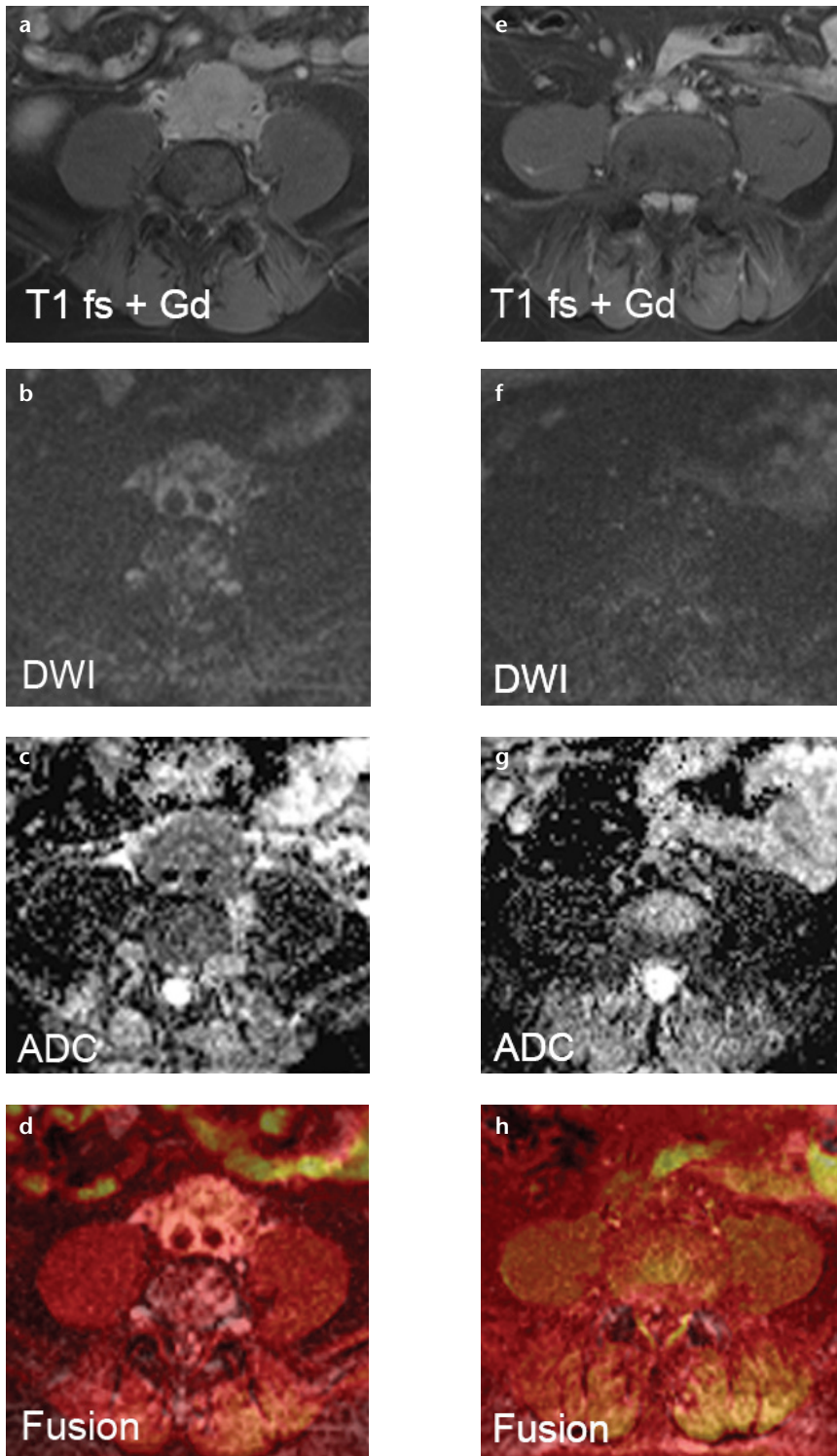The necessity of a primary biopsy in RPF patients is controversial. Histolog-

a
T1 fs + Gd

e
T1 fs + Gd

b
DWI

f
DWI

c
ADC

g
ADC

d
Fusion

h
Fusion

Figure 2. a–h. Exemplary transverse sections directly below the aortic bifurcation for two male patients: a 51-year-old patient with untreated RPF **(a–d)** and a 58-year-old patient with treated RPF **(e–h)**. Contrast-enhanced T1-weighted image with fat suppression shows distinct contrast uptake of fibrosis compared with psoas muscle in the untreated patient **(a)**. DWI (b800) **(b)** shows excellent delineation between normal retroperitoneal and inflammatory fibrosis. ADC-map **(c)** shows relatively low RPF signal. The fusion image of native fat-suppressed T1-weighted image and DWI (b800) **(d)** displays corresponding extent of fibrous tissue and impaired diffusion. RPF shows significantly smaller extent and no elevated contrast uptake compared with the psoas muscle in a patient undergoing treatment **(e)**. DWI (b800) shows a hypointense presentation of the RPF without impaired diffusion **(f)** and a hyperintense signal in the ADC-map **(g)**. The fusion image of the treated RPF patient **(h)** displays the remaining fibrosis without impaired diffusion. T1 fs + Gd, T1-weighted gadoteridol contrasted image with fat saturation; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

ical diagnosis is mandatory in patients with an atypical formation, signs of malignancy, progression of fibrosis under medical therapy, or in institutions with limited experience (3). Accordingly, we established the diagnosis of RPF by a combination of clinical symptoms and typical imaging findings. In 27 of 44 cases diagnosis was confirmed by histology. This approach led to a limitation of our study with missing histological proof in some patients. However, in patients under medical therapy the diagnosis was supported by disease regression compared with previous imaging studies. The quantitative assessment of signal intensities by ROI may be limited in patients with inhomogeneous DWI signal intensity, and in patients with small fibrotic plaque size. Since only patients with typical RPF location were included in the present study, further research is required for the evaluation of atypical RPF locations. Different slice thickness used in anatomical T1 imaging and the DWI-sequences is a limitation for fusion images. However, fusion images were used only for visualisation, and qualitative and quantitative analyses were performed in the original sequences. Another limitation is that the signal intensities in treated patients usually cannot be correlated with histology, since repetitive para-aortic biopsy cannot be justified in patients with or without improved clinical symptoms and reduced RPF extent.

In conclusion, DWI signal intensities and relative DWI index between RPF and psoas muscle were significantly different in treated and untreated RPF. Further examinations are necessary to evaluate the potential of DWI in assessment of RPF disease activity and for individual follow-up.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Dineen J, Asch T, Pearce JM. Retroperitoneal fibrosis. An anatomic and radiologic review with a report of four new cases and an explanation of pathogenesis. Radiology 1960; 75:380–390. [CrossRef]

2. 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; 33:535–552. [CrossRef]

3. Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. Lancet 2006; 367:241–251. [CrossRef]

4. Geoghegan T, Byrne A, Benfayed W, McAuley G, Torreggiani W. Imaging and intervention of retroperitoneal fibrosis. Australas Radiol 2007; 51:26–34. [CrossRef]

5. Van Bommel EFH, Pelkmans LG, van Damme H, Hendriksz TR. Long-term safety and efficacy of a tamoxifen-based treatment strategy for idiopathic retroperitoneal fibrosis. Eur J Intern Med 2013; 24:444–450. [CrossRef]

6. Brandt AS, Soares SB, Fehr A, et al. "Retroperitoneal Fibrosis" (RPF) Urologic Cooperation and Research Project. Urologe A 2007; 46:1302–1304. [CrossRef]

7. Burn PR, Singh S, Barbar S, Boustead G, King CM. Role of gadolinium-enhanced magnetic resonance imaging in retroperitoneal fibrosis. Can Assoc Radiol J 2002; 53:168–170.

8. Kamper L, Brandt AS, Scharwächter C, et al. MR evaluation of retroperitoneal fibrosis. Rofo 2011; 183:721–726. [CrossRef]

9. Prince MR, Zhang HL, Prowda JC, Grossman ME, Silvers DN. Nephrogenic systemic fibrosis and its Impact on abdominal imaging. Radiographics 2009; 29:1565–1574. [CrossRef]

10. Oto A, Zhu F, Kulkarni K, Karczmar GS, Turner JR, Rubin D. Evaluation of diffusion-weighted MR imaging for detection of bowel inflammation in patients with Crohn's disease. Acad Radiol 2009; 16:597–603. [CrossRef]

11. Kilickesmez O, Soylu A, Yasar N, et al. Is quantitative diffusion-weighted MR imaging a reliable method in the assessment of the inflammatory activity in ulcerative colitis? Diagn Interv Radiol 2009; 16:293–298.

12. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007; 188:1622–1635. [CrossRef]

13. Niwa T, Aida N, Fujita K, et al. Diffusion-weighted imaging of retroperitoneal malignant peripheral nerve sheath tumor in a patient with neurofibromatosis type 1. Magn Reson Med Sci 2008; 7:49–53. [CrossRef]

14. Padhani AR, Liu G, Mu-Koh D, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009; 11:102–125.

15. 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.

16. Brandt AS, Kamper L, Kukuk S, Haage P, Roth S. Associated findings and complications of retroperitoneal fibrosis in 204 patients: results of a urological registry. J Urol 2011; 185:526–531. [CrossRef]

17. Heckmann M, Uder M, Kuefner M, Heinrich M. Ormond's disease or secondary retroperitoneal fibrosis? An overview of retroperitoneal fibrosis. Rofo 2009; 181:317–323. [CrossRef]

18. Kamper L, Brandt AS, Winkler SB, et al. Imaging of retroperitoneal fibrosis. Med Klin (Munich) 2010; 105:582–584. [CrossRef]

19. Orta Kilickesmez K, Kilickesmez O. Clear depiction of inflammatory abdominal aortic aneurysm with diffusion-weighted magnetic resonance imaging. Cardiovasc Intervent Radiol 2009; 33:379–382. [CrossRef]

20. Nakayama T, Yoshimitsu K, Irie H, et al. Usefulness of the calculated apparent diffusion coefficient value in the differential diagnosis of retroperitoneal masses. J Magn Reson Imaging 2004; 20:735–742. [CrossRef]

21. Rosenkrantz AB, Spieler B, Seuss CR, Stifelman MD, Kim S. Utility of MRI features for differentiation of retroperitoneal fibrosis and lymphoma. AJR Am J Roentgenol 2012; 199:118–126. [CrossRef]

22. Vivas I, Nicolás AI, Velázquez P, Elduayen B, Fernández-Villa T, Martínez-Cuesta A. Retroperitoneal fibrosis: typical and atypical manifestations. Br J Radiol 2000; 73:214–222. [CrossRef]

23. Magrey MN, Husni ME, Kushner I, Calabrese LH. Do acute-phase reactants predict response to glucocorticoid therapy in retroperitoneal fibrosis? Arthritis Rheum 2009; 61:674–679. [CrossRef]