

Role of Diffusion-Weighted MR Imaging in Characterization of Retro-Peritoneal Fibrosis and Differentiating it from Malignant Neoplasms

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Abstract

Background: Diffusion-weighted imaging (DWI) is a non-invasive method that is based on the movement of water molecules across tissues. DWI and the apparent diffusion coefficient (ADC) may provide additional information to that obtained from conventional MRI. DWI can contribute to differentiate between active and chronic (inactive) RPF as well as between benign RPF and malignant neoplasms with RPF morphology.

Aim of Study: To evaluate diffusion-weighted imaging (DWI) features and signal intensity values at T2-weighted magnetic resonance (MR) imaging for differential diagnosis of benign retroperitoneal fibrosis (RPF) and plaque-like retroperitoneal malignant neoplasms.

Patients and Methods: Thirty-eight patients (mean age 56.50 ± 11.125 years; range 29-76 years, 24 males and 14 females) with plaque-like confluent retroperitoneal soft-tissue masses were divided into three groups: group I, 16 patients with malignant RPF and retroperitoneal malignant neoplasm; group II, 10 patients with active RPF; and group III, 12 patients with chronic RPF. MRI protocol included T1-weighted (non-enhanced and contrast-enhanced), T2-weighted, and DWI ($b=1000 \text{ sec/mm}^2$) images and apparent diffusion coefficient (ADC) values.

Results: Overall sensitivity, specificity, and positive and negative predictive values as well as diagnostic accuracy when using ADC values were (90%, 91.7%, 90%, 91.7%, and 90.9%, respectively) in differentiating between active and chronic RPF. While, overall sensitivity, specificity, and positive and negative predictive values as well as diagnostic accuracy when using ADC values were (81.8%, 75%, 81.8%, 75%, and 79%, respectively) in differentiating between malignant from benign cases.

Conclusion: DWI can contribute to differential diagnosis of active from chronic RPF and benign RPF from malignant neoplasms with RPF morphology. ADC of chronic RPF was higher than that for active RPF or malignant group. Lesions in the malignant group and active RPF group had similar enhancement patterns, while those in the chronic RPF group demonstrated less enhancement. Signal intensity values on

T2-weighted images were not useful for differentiating these conditions.

Key Words: Retroperitoneum – fibrosis – MRI – DWI – ADC.

Introduction

RPF refers to a range of diseases characterized by the presence of a fibroinflammatory plaque-like confluent tissue that develops in the periaortic retroperitoneum [1-3]. The abdominal aorta, iliac vessels, and, frequently, the IVC and ureters are surrounded by the tissue [1,4]. This process may extend to neighboring structures, frequently entrapping and obstructing the ureters and eventually leading to renal failure [1,5,6]. Most often the disease is idiopathic; however, malignancy, surgery, drugs, or infections can be associated with this condition [1,7].

It has been reported that malignant cells are present in 8% of RPF cases (malignant RPF) [8]. Also, malignant neoplasms in the para-aortic region (e.g., lymphoma or malignant infiltration originating from the stomach, testis, kidney, pancreas, prostate, or endometrium) with plaque-like confluent tissue morphology (without fibrosis) may mimic RPF [9,10]. It is important to differentiate benign RPF from malignant RPF and para-aortic malignant neoplasms to diagnose the underlying pathologic process and to determine the patient's prognosis. While dependent on the underlying cause, the prognosis for patients with benign RPF is generally favorable [7]. On the other hand, the prognosis for malignant para-aortic neoplasm and malignant RPF is poor, with a mean survival of 3-6 months for malignant RPF [11-13].

Imaging findings-including the morphologic parameters of lesions, contrast material enhance-

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ment, and 18F-FDG uptake patterns and SI characteristics on T2-W MR images are used to differentiate benign RPF from malignant RPF [14-16]. However, Cronin et al., reported that the imaging findings were not reliable enough to allow differentiation of benign RPF from malignant RPF [7].

Diffusion-weighted imaging (DWI) is a non-invasive method that is based on the movement of water molecules across tissues. DWI and the apparent diffusion coefficient (ADC) may provide additional information to that obtained from conventional MRI [17]. DWI can contribute to differentiate between active and chronic (inactive) RPF as well as between benign RPF and malignant neoplasms with RPF morphology [18].

While non-invasive imaging modalities can help exclude secondary causes of RPF, biopsy is often required for histologic confirmation, since imaging is ineffective in the differentiation of benign from malignant neoplasms. Biopsy results can yield a false-negative result, however, as metastatic cells may not have a homogeneous distribution in the fibrotic mass [7]. Also, it is important to make the distinction between active and chronic (inactive) RPF for the therapeutic management of benign RPF cases [3,19].

The aim of this study was to evaluate the role of MR imaging including DWI features and ADC value as well as T2-W SI in the differentiation between active and chronic (inactive) RPF as well as between benign RPF and malignant neoplasms with RPF morphology.

Patients and Methods

A prospective cohort observational study included 38 patients with plaque-like confluent retroperitoneal soft tissue masses in the para-aortocaval region diagnosed by CT and/or MRI.

The study was done at the radiology unit at Urology and Nephrology Center, Mansoura University, Egypt. Patients were referred to us from the outpatient clinics between November 20, 2020, and January, 2022.

Inclusion criteria:

Patients with plaque-like confluent retroperitoneal soft tissue masses in the para-aortocaval region diagnosed by CT and/or MRI.

Exclusion criteria:

- Patients who refused the study.
- Contraindications for MRI such as:

- Patients with cardiac pacemaker.
- Patients with metallic cochlear implants.
- Claustrophobic patients.
- Patients with bad general conditions.

Ethical consideration:

- The protocol of this study was submitted for approval and accepted by Medical Research Ethics Committee - Institutional Review Board (IRB) at the faculty of medicine, Mansoura University, Egypt.
- An informed consent of participation and publication was obtained from all the patients who were included in this study after full explanation of the benefits and the risks of the procedure.
- No further apparent risks to the patients who were included in this study.
- Privacy and confidentiality of all data of the patients were guaranteed and there was a code number for every patient's file that included all investigations stored at picture archiving and communication system (PACS).
- There was no funding source.

MRI protocol:

After taking full clinical history and laboratory investigations including serum creatinine (sCr) level estimation, all patients were subjected to multiparametric MRI (mp MRI) of the abdomen and pelvis using 3 Tesla MRI scanner (Philips, Ingenia). Imaging was in the supine position using phased-array body coil.

The MRI study protocol included the following sequences; all sequences were performed in the axial planes:

- T1-weighted turbo spin-echo sequence (T1-W).
- T2-weighted turbo spin-echo sequence (T2-W).
- Multisection single-shot spin-echo echo-planar DWI sequence ($b=800\text{sec}/\text{mm}^2$) without breath holding (fat saturation was used sometimes to avoid chemical-shift artifacts).
- Breath-hold T1-W fat-suppressed spoiled gradient-echo shared prepulse sequences before intravenous contrast administration and during the arterial, venous and delayed phases after intravenous contrast administration in 23 of 38 patients (14 patients in group I, 5 patients in group II, and 4 patients in group III).

Biopsy either US, CT or ureteroscopy-guided that is often required for histopathological confirmation.

Image analysis:

Regions of interest (ROIs) measuring at least 1cm² (size range, 1-3cm²) on the lesions on DWI, ADC map, and post-contrast images were placed by avoiding obvious areas of inhomogeneity.

The ROI was placed within the lesions in the area with the highest SI in DWI and the lowest ADC value in ADC map. On post-contrast images, the ROI was placed in the area with the most enhancement. We used the same sizes and positions of the ROIs in the different sequences. At least three measurements were performed and averaged for each lesion.

Statistical analysis:

Qualitative data were described using number (n) and percentage (%). While quantitative data were described using median (range) [minimum and maximum] for non-parametric data and mean ± standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test.

Significance of the obtained results was judged at the (0.05) level (a critical two-sided *p*-value <0.05 was used for statistically significant differences).

The sensitivity, specificity, positive, negative predictive values, and diagnostic accuracy were calculated with a 95% confidence interval (CI) using ROC curves.

IBM SPSS software, version 25.0 (IBM, Armonk, NY) was used.

Results

This is a prospective study that includes 38 patients (mean age 56.50±11.125 years; range 29-76 years, 24 males and 14 females) with plaque-like confluent retroperitoneal soft tissue masses in the para-aortocaval region diagnosed by CT and/or MRI.

The patients were divided into 3 groups on the basis of the final pathologic diagnosis. Group I included 16 patients with malignant RPF and retroperitoneal malignant neoplasm (mean age 64.44±7.48 years, 10 males and 6 females), group II included 10 patients with active RPF (mean age 49.90±12.75 years, 6 males and 4 females), and group III included 12 patients with chronic RPF (mean age 51.42±6.89 years, 8 males and 4 females).

There was no statistically significant difference in T2-W SI (*p*=0.081) as most of the lesion were

isointense. Unlike, there was statistically significant difference in DWI and ADC SI (*p*<0.001) as Active RPF and malignant neoplasms with RPF morphology usually show restricted diffusion; however, in chronic RPF, there is no restricted diffusion. Also, there was statistically significant difference in post-contrast SI (*p*<0.001) as in active stages and malignant neoplasms with RPF morphology, variable enhancement patterns were seen with intravenous contrast administration, while no enhancement may be seen in the quiescent stages (Table 1).

Table (1): MRI findings in between the studied groups.

	Malignant	Active PRF	Chronic PRF	Test of significance
T2-W SI:	n=16	n=10	n=12	
Hypointense	0	0	3 (25)	χ ² MC=8.31 <i>p</i> =0.081
Isointense	15 (93.8)	10 (100)	9 (75)	
Hyperintense	1 (6.2)	0	0	
DWI SI:	n=16	n=10	n=12	
Hypointense	0	0	12 (100)	χ ² MC=38.95 <i>p</i> <0.001 *
Isointense	1 (6.2)	0	0	
Hyperintense	15 (93.8)	10 (100)	0	
ADC SI:	n=16	n=10	n=12	
Hypointense	15 (93.8)	10 (100)	0	χ ² MC=38.95 <i>p</i> <0.001*
Isointense	1 (6.2)	0	0	
Hyperintense	0	0	12 (100)	
Post-contrast SI:	n=14	n=5	n=4	
Non-enhancing	0	0	4 (100)	χ ² MC=23 <i>p</i> <0.001 *
Enhancing	14 (100)	5 (100)	0	

MC: Monte Carlo test. *Statistically significant.

As regard the quantitative analysis of the MRI findings in comparison between the studied groups, there was statistically significant difference in ADC value (*p*<0.001) in differentiating the malignant and active RPF cases from the chronic RPF cases (Table 2).

Table (2): Mean DWI quotient, ADC value and post-contrast quotient in between the studied groups.

	Malignant	Active PRF	Chronic PRF	Test of significance
ADC ₃ value ₃ (* 10 ⁻³ mm ² /s)				F=38.48
Mean ± SD	0.72±0.22	0.87±0.16	1.44±0.22	<i>p</i> <0.001 *

F: One Way ANOVA test. *Statistically significant.

When the ADC value cut-off point was 1.105, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 90%, 91.7%, 90%, 91.7%, and 90.9%, respectively with AUC=0.983 in differentiating the active RPF cases from the chronic RPF cases (Table 3) (Fig. 1).

Table (3): Validity of DWI quotient, ADC value and post-contrast quotient in differentiating between the active RPF and chronic RPF cases.

	AUC (95% CI)	p- Value	Cut-off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
ADC value	0.983 (0.941-1.000)	<0.001*	1.105	90.0	91.7	90.0	91.7	90.9

AUC: Area under the curve.
CI : Confidence interval.
*Statistically significant.

PPV: Positive predictive value.
NPV: Negative predictive value.

Table (4): Validity of DWI quotient, ADC value and post-contrast quotient in differentiating the malignant cases from the benign (active and chronic RPF) cases.

	AUC (95% CI)	p- Value	Cut-off point	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
ADC value	0.861 (0.747-0.975)	<0.001*	0.860	81.8	75.5	81.82	75.0	79.0

AUC: Area under the curve.
CI : Confidence interval.
*Statistically significant.

PPV: Positive predictive value.
NPV: Negative predictive value.

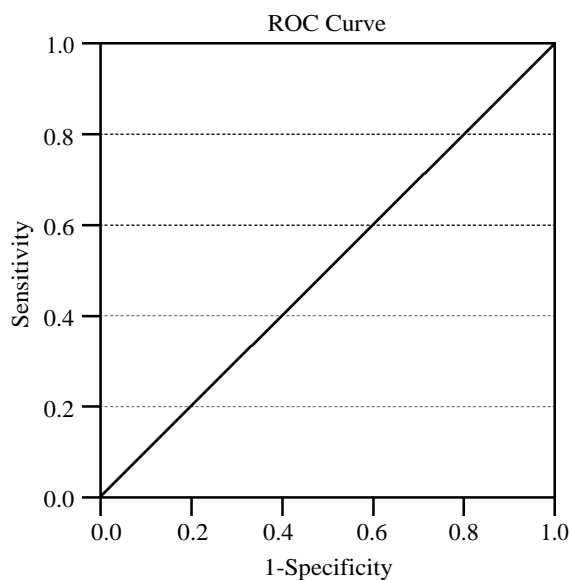


Fig. (1): ROC curve of ADC value in differentiating the active RPF cases from the chronic RPF cases.

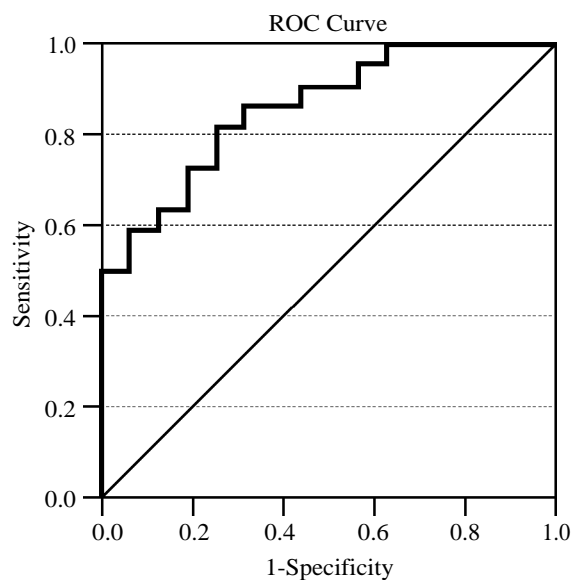


Fig. (2): ROC curve of ADC value in differentiating the malignant cases from the benign (active and chronic RPF) cases.

When the ADC value cut-off point was 0.860, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 81.8%, 75%, 81.8%, 75%, and 79%, respectively with AUC=0.861 in differentiating the malignant cases from the benign (active and chronic RPF) cases (Table 4) (Fig. 2).

This is a case of a 49-year-old female patient presented with acute bilateral loin pain 1 week ago. She was diagnosed with bilateral mild HUN

down to plaque-like confluent retroperitoneal soft tissue mass by NCCT scan. Her sCr level was 2.9mg/dL. She underwent urgent bilateral JJ stents fixation, then US-guided biopsy and was diagnosed histopathologically as active RPF. She received medical treatment in the form of corticosteroids for 6 months with improvement of symptoms and resolution of obstructive complications (her sCr level became 1.9mg/dL) on follow-up visits (Fig. 3).

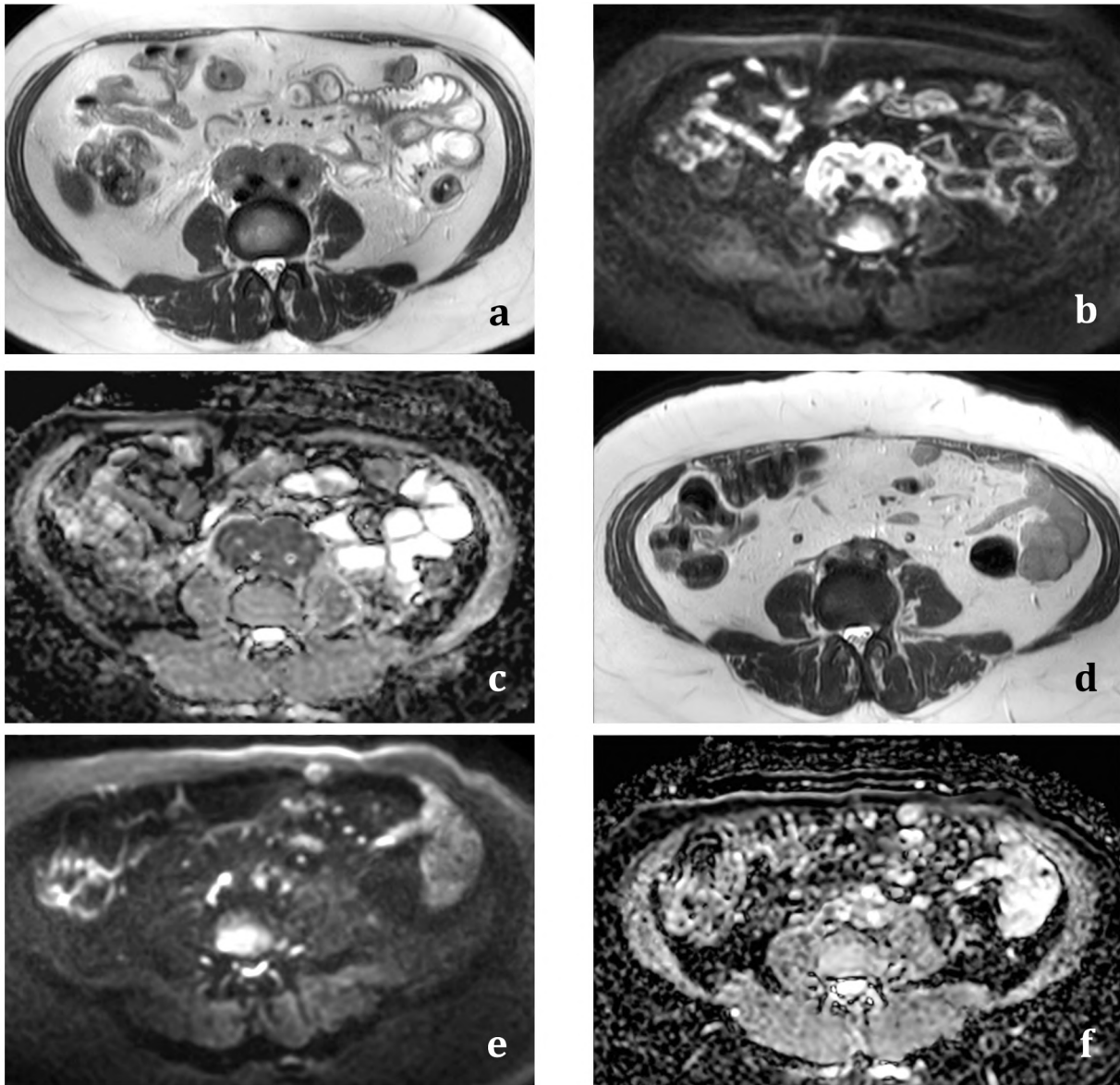


Fig. (3): MR images of active RPF (group II). (A) Axial T2-WI demonstrated a plaque-like lesion at the para-aortocaval region surrounding the aorta and IVC displaying high SI at (B) DWI and low SI at (C) ADC map that correspond with low ADC values. (D) Axial T2-WI after 6 months demonstrated significant reduction of the lesion's size with no residual diffusion restriction at (E) DWI and (F) ADC map.

Discussion

This study is a prospective study that includes 38 patients (mean age 56.50 ± 11.125 years; range 29-76 years, 24 males and 14 females) with plaque-like confluent retroperitoneal soft tissue masses in the para-aortocaval region diagnosed by CT and/or MRI.

However Bakir et al., study was a retrospective study, it showed similar demographics to our study as it included 51 patients (34 males and 17 females) with mean age 57.06 ± 10.85 years and range 26-88 years [18].

Also, these demographics are consistent with what was reported by Kermani et al. that although RPF can occur at any age, the onset of signs and symptoms is typically seen in people aged 40-65 years. It is two to three times more common in men than in women [20].

We divided the patients into 3 groups on the basis of the final pathologic diagnosis. Group I included 16 patients with malignant RPF and retroperitoneal malignant neoplasm (mean age 64.44 ± 7.48 years, 10 males and 6 females), group II included 10 patients with active RPF (mean age 49.90 ± 12.75 years, 6 males and 4 females), and

group III included 12 patients with chronic RPF (mean age 51.42 ± 6.89 years, 8 males and 4 females).

Bakir et al., also divided the patients into 3 groups; group I included 25 patients with malignant RPF and retroperitoneal malignant neoplasm, group II included 16 patients with chronic RPF, and group III included 10 patients with active RPF [18].

For the qualitative analysis of the MRI findings, the SI of the lesion at T2-WI, DWI ($b=800$ sec/mm²) and ADC map was evaluated visually to determine if it was hypointense, isointense or hyperintense. The diffusion was considered restricted if a lesion displayed high SI with a diffusion sequence and low SI on ADC maps. While, the SI of the lesion at pre- & post contrast T1-WI was evaluated visually to determine if it was enhancing or not.

Arrive et al. suggested that instead of using morphologic features and enhancement patterns at MRI, SI characteristics on T2-WI (by using a technique similar to ours with comparison of SI on T2-WI between the lesion and ipsilateral psoas muscle) are more useful in differentiating benign and malignant RPF [11].

Controversy, there was no significant statistically significant difference ($p=0.081$) on T2-WI between benign and malignant RPF in our study as most of the lesion were isointense. The reason for these differing results is not clear, but other studies reported that active idiopathic RPF, malignant RPF, and retroperitoneal malignant neoplasms exhibit similar SI on T2-WI [18,21].

We detected restricted diffusion on DWI in 15 (93.8%) of 16 patients in the malignant group, 10 of 10 in the active RPF group, and 0 of 12 in the chronic RPF group.

Similar results were reported by Bakir et al., that also detected restricted diffusion on DWI images in 23 (92%) of 25 patients in the malignant group, 10 of 10 in the active RPF group, and 0 of 16 in the chronic RPF group [18].

The reason why active RPF demonstrated restricted diffusion while chronic RPF did not, might be related to the different time of onset of the processes. In the early stages of fibrosis, highly vascular tissue and collagen are present in the plaque, in addition to polyclonal B and CD4+ T cell infiltrates, plasma cells, histiocytes, and macrophages. Later, fibrosis replaces inflammatory tissue [22]. In the early stages where the cellular

content of the plaque is high, water diffusion may be restricted, owing to the reduced extracellular space and also to cell membranes acting like a barrier to water movement. In the chronic stage, with the regression of the inflammation and the onset of fibrosis, the less cellular environment and the relative increase in extracellular stage allow free water diffusion. The restricted diffusion in the malignant group, like active RPF, might be due to their highly cellular environment [22].

In addition, the number of examinations with contrast material administration in our study was low (23 of 38 patients), especially in patients with RPF either in active ($n=5$) or chronic ($n=4$) stages and this can be explained as the fibroinflammatory tissue usually entraps the ureters and causes obstructive uropathy and subsequent renal failure [3]. Ureteral involvement is bilateral in most cases. Some patients present with non-functioning kidneys as a result of long-lasting obstructive uropathy [23,24]. But we have observed that the lesions in the malignant group and active RPF group had similar enhancement patterns, while the lesions in the chronic RPF group demonstrated less enhancement compared with the others. These results are in line with other studies [11,18,21].

Other authors have assessed the role of DWI in the differential diagnosis of retroperitoneal masses and RPF. In the study by Rosenkrantz et al., which included 22 patients with RPF and 9 patients with malignant retroperitoneal neoplasm, the ADC was significantly lower in malignant retroperitoneal neoplasm than in RPF (mean, $[0.92 \pm 0.17] * 10^{-3}$ mm²/s vs $[1.40 \pm 0.38] * 10^{-3}$ mm²/s; $p=0.003$) [9]. However, in a study by Spieler et al., which included 11 patients with RPF and 16 patients with malignant retroperitoneal neoplasm, there was no significant difference in mean ADC values between malignant retroperitoneal neoplasm ($1.26 * 10^{-3}$ mm²/s; range, $[0.54-2.03] * 10^{-3}$ mm²/s) and RPF ($1.35 * 10^{-3}$ mm²/s; range, $[0.61-2.45] * 10^{-3}$ mm²/s) ($p=0.57$) [25]. The discrepancies between these two studies may be due to the fact that neither of them had made a distinction between active and chronic RPF. But our study made a distinction between active and chronic RPF demonstrating very high sensitivity, specificity, PPV, NPV, and diagnostic accuracy when using ADC value cut-off point of 1.105 (90%, 91.7%, 90%, 91.7%, and 90.9%, respectively with AUC = 0.983).

Finally, when all of the patients in our study were included in the evaluation of the differential diagnosis of malignant and benign lesions, the sensitivity, specificity, PPV, NPV, and diagnostic

accuracy were 81.8%, 75%, 81.8%, 75%, and 79%, respectively with AUC=0.861 when using the ADC value cut-off point of 0.860. Similar results were reported by Bakir et al. that demonstrated sensitivity (92%) and specificity (62%) [18].

Our study had a few limitations such as our patient population size was limited and this was especially true for the active RPF group, where some statistical analyses could not be performed owing to small sample size. So, additional studies on a larger scale could be better in the diagnosis of disease and treatment of patients using DWI sequences. A further shortcoming of our study was that the number of patients evaluated for contrast enhancement was low in the active RPF (n=5) and chronic RPF (n=4) groups.

Conclusion:

In conclusion, the ADC value of chronic RPF is statistically higher than that for acute RPF or malignant RPF and retroperitoneal malignant neoplasia with an RPF morphology. We observed that if restricted diffusion was detected in a para-aortic plaque-like mass, the differential diagnosis included a malignant neoplasm (including malignant RPF) or active RPF; if there was no restricted diffusion, however, the differential diagnosis included chronic RPF. A biopsy would still be required for differentiation of active from malignant RPF, but DWI might also be useful during biopsy procedures in targeting presumptive tumoral nests in plaque lesions and in the evaluation of treatment in acute RPF cases. Additional studies with larger patient populations could better clarify the contribution of DWI in the diagnosis of disease and treatment of patients.

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دور التصوير بالرنين المغناطيسي بخاصية الانتشار في تمييز التليفات خلف الصفاق وتفرقتها عن الأورام الخبيثة

تعد التليفات في منطقة خلف الصفاق واحدة من أمراض الأنسجة الضامة ذات الطابع المناعي مع معدل حدوث ١/١٠٠٠٠٠ سنوياً في أعمار تتراوح بين ٤٠ إلى ٦٠ عام ومعدل انتشار بين الذكور إلى الإناث بنسبة ١:٢.

وتتميز التليفات في منطقة خلف الصفاق بوجود نسيج ليفي في المنطقة الواقعة حول الشريان الأورطي. ويحيط هذا النسيج عادة بالشريان الأورطي والوريد الأجوف السفلي بالإضافة إلى الحالبين. وقد تتشابه هذه التليفات الحميدة مع العديد من الأورام الخبيثة التي تظهر في منطقة خلف الصفاق.

ولذا فإنه من المهم التفرقة بين هذه التليفات الحميدة وتلك الأورام الخبيثة لمعرفة التشخيص ومال المرض مع تحديد خطة واضحة للعلاج.

ويعد التصوير الطبقي من الطرق الهامة للتفرقة بين التليفات الحميدة والأورام الخبيثة في منطقة خلف الصفاق عن طريق استخدام الصبغات والتصوير المقطعي بالإصدار البوزيتروني. والرنين المغناطيسي باستخدام التصوير الزمني الثاني وخاصية ومعامل الانتشار الخلوي.

وقد هدفت هذه الدراسة إلى تقييم دور التصوير بالرنين المغناطيسي في التفرقة بين التليفات الحميدة والأورام الخبيثة في منطقة خلف الصفاق بالإضافة إلى التفرقة بين التليفات الحميدة النشطة والمزمنة الغير نشطة في تلك المنطقة.