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ROLE OF 3D DOUBLE INVERSION RECOVERY IN DETECTING MULTIPLE SCLEROSIS USING 3 TESLA MRI SYSTEM IN SAUDI ARABIA

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Background*:* Magnetic Resonance Imaging (MRI) is one of the diagnostic imaging modalities employing in lesion detection in neurological disorders such as Multiple Sclerosis (MS). Advances in MRI techniques such as Double Inversion Recovery (DIR), Fluid Attenuated Inversion Recovery (FLAIR) and T2 Weighted Imaging (T2WI) sequences made it more sensitive to distinguish and investigate the lesion load on different anatomical regions of the brain .MRI is used as a strong tool to record the history of the disease and evaluate the response to treatment.

Methodology: A total of 97 MS patients were included in our retrospective study, confirmed by neurologist. The patients were randomly selected from the major hospital in Saudi Arabia. All images were obtained using 3T Scanner (Siemens Skyra). The images from the DIR, FLAIR, and T2WI sequences were compared on axial planes with identical anatomic position and the number of lesions were assigned to their anatomical region.

Statistical analysis was done using IBM SPSS statistics software version 25.0. To determine association and linear relationship, nonparametric method for comparison such as Friedman's analysis of variance by rank and Wilcoxon-test and Spearman correlation were used

Results: Majority of our patients suffered from the duration of the disease between 2 to 3 years (44.3%). The frequency analysis for types of the MS among patients represented that the majority (n=87) of the patients were at Relapsing Remitting MS.

Comparing the lesion load measurement at various brain anatomical regions showed a significant difference among those three methods ($P<0.05$). The highest number of lesions in all anatomical regions belonged to DIR with a mean number ($M=37.67$) which was significantly higher than other sequences followed by FLAIR ($M=29.57$) which was significantly higher than T2WI ($M=27.47$). DIR was highly sensitive in detection of intracortical lesions ($M=2.35$) with a better delineation between grey matter/white matter margins in different anatomical areas.

The highest contrast ratio in all anatomical regions belonged to DIR which was significantly higher than other sequences followed by T2WI which was significantly higher than FLAIR, except for Lesion/CSF which FLAIR showed the highest ratio.

The correlation between the number of lesions and EDSS in DIR in infratentorial region ($r= 0.584$, $p<0.001$) was strong, positive and significant and the highest sensitivity of the DIR sequence (92.9% at the cut-off points of "4.5") with an accuracy of 0.883 ($p<0.001$) and specificity of 73.5% was observed in infratentorial region.

Conclusion: DIR is a valuable MRI sequence for better delineation, greater contrast measurements and the increasing total number of MS lesions in MRI, compared with FLAIR and T2WI and DIR revealed more intracortical lesions as well, therefore, in MS patients it is recommended to add DIR sequence in daily routine imaging sequences.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERANAN PEMULIHAN PENYONSANGAN BERKEMBAR 3D BAGI MENGESAN *MULTIPLE SCLEROSIS* MENGGUNAKAN SISTEM 3TESLA MRI DI ARAB SAUDI

Oleh

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Latar belakang kajian: Pengimejan Magnetik Resonans (*MRI*) adalah salah satu modaliti pengimejan yang digunakan untuk mengesan anatomi struktur kawasan yang tekesan bagi pesakit neurologi seperti *Multiple Sclerosis (MS).* Kemajuan di dalam aplikasi teknik *MRI* seperti *Double Inversion Recovery (DIR)* membuatkan modliti ini lebih berkesan untuk membezakan komposisi struktur anantomi di dalam otak. Bagi mengkaji perbezaan struktur anatomi di dalam otak untuk pesakit *MS* menggunakan *DIR*, sekuen *Fluid Attenuated Inversion Recovery (FLAIR)* dan *T2-Weighted Imaging (T2WI)* telah digunakan.

Metode: Sejumlah 97 orang pesakit *MS* telah di pilih untuk kajian retrospektif dimana mereka telah disahkan oleh pakar neurologi sebagai penghidap *MS*. Pesakit telah dipilih secara rawak dari beberapa buah hospital besar di Arab Saudi. Kesemua imej imbasan otak mereka telah diambil meggunakan pengimbas 3 Tesla (*Siemens Skyra*). Imej-imej dari sekuen *DIR, FLAIR* dan *T2WI* telah dibandingkan menggunakan standard plan aksial dengan struktur spesifik bagi setiap komposisi struktur otak telah ditetapkan bagi setiap pesakit supaya ianya selaras antara satu sama lain. Analisis statistik telah dilakukan menggunakan peranti lembut *IBM SPSS* versi 25.0. Bagi menentukan perhubungan linear antara pembolehubah, metod perbandingan non-parametrik seperti Variasi Analisis bagi ranking *Friedman's*, ujian *Wilcoxon* dan korelasi *Spearman* telah digunakan.

Keputusan: Majoriti pesakit ini telah menghidap *MS* dalam tempoh sekitar 2 hingga 3 tahun (4.3%). Kebanyakkan pesakit *MS* ini (n=87) menghidap *MS* jenis *relapsing remitting*..Perbandingan muatan analisis struktur di beberapa bahagian otak menunjukkan perbezaan ketara diantara ketiga-tiga metod yang digunakan ($p<0.05$).

DIR (M=37.67) mempunyai bilangan struktur terkesan yang tertinggi, diikuti dengan *FLAIR* (M=29.57) yang merekodkan signal yang jauh lebih tinggi berbanding *T2WI* (M=27.47). *DIR* terbukti lebih sensitif dalam mengesan struktur intrakortikal (M=2.35), dimana perbezaan sempadan antara *grey matter/white matter* lebih jelas di setiap kedudukan struktur otak yag berlainan.

Ratio kontras tertinggi bagi semua struktur anatomi di dalam otak diperolehi melalui *DIR*, diikuti sekuen *T2WI* dan *FLAIR*, melainkan bagi ratio struktur/*CSF* dimana *FLAIR* menunjukkan ratio kontras tertinggi.

Nilai kolerasi yang kukuh, positif dan ketara ditemui diantara bilangan bendasing dan *EDSS* untuk *DIR* di bahagian *infratentorial* ($r=0.584$, $p<0.001$) dan nilai sensitivity tertinggi untuk sekuen *DIR* (92.9% pada poin pemutus bernilai "4.5") disertakan dengan ketepatan bernilai 0.883 ($p<0.001$) dan kekhususan bernilai 73.7% ditemui di bahagian *infratentorial*.

Kesimpulan: *DIR* sangat berguna bagi sekuen *MRI* di atas kemampuannya untuk membezakan struktur anatomi berdekatan, perbezaan besar pengiraan kontras bagi mengesan struktur *MS* menggunakan *MRI*, jika dibandingkan dengan *FLAIR* dan *T2WI* dan *DIR* juga mengesan lebih banyak struktur intrakortikal, jadi pesakit *MS* amat digalakkan untuk diimbas menggunakan sekuen *DIR* di dalam setiap rutin imbasan mereka

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LIST OF ABBREVIATIONS

2D	2 Dimensional
3D	3 Dimensional
3T	3 Tesla
CGM	Cortical grey matter
CIS	Clinically Isolated Syndrome
CNR	Contrast to Noise Ratio
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DIR	Double Inversion Recovery
DIS	Dissemination in Space
DIT	Dissemination in Time
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
FSE	Fast Spine echo
FLAIR	Fluid attenuated inversion recovery
FOV	Field of view
GAD	Gadolinium containing MRI contrast agents
GE	Gradient echo
GM	Grey Matter
IC	Intracortical
IR	Inversion recovery
JC	Juxtacortical
MZ	Magnetization

MRI	Magnetic resonance Imaging
MS	Multiple sclerosis
NAGM	Normal appearing grey matter
NAWM	Normal appearing white matter
PRMS	Progressive Relapsing Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
RF	Radiofrequency
RRMS	Relapsing Remitting Multiple Sclerosis
SE	Spin echo
SNR	Signal to Noise Ratio
SPMS	Secondary Progressive Multiple Sclerosis
T	Tesla
TI	Inversion Time
T1w	T1 weighted
T2w	T2 weighted
TE	Echo time
TR	Repetition time
WM	White Matter

CHAPTER 1

INTRODUCTION

1.1 Background

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS). It has the highest rate of acquired disability among young people worldwide and accounts for approximately 1.14% of reported neurological diseases (Kumar et al., 2013; Elnekeidy et al., 2014). MS is characterized by a cellular response in some regions, demyelination, axonal loss, and gliosis within the CNS which usually involves the optic nerves, brainstem and cerebellum (Pérez-Cerdá et al., 2016). In patients with MS, the inflammatory process and the degenerative functions lead to demyelination. This eventually disrupts the transmission of action potential and permanent axonal loss, resulting in the clinical manifestation of symptoms in MS patients (Choi et al., 2012; Filippi et al., 2018).

The prevalence of MS varies from place to place due to the differences in the predisposing factors. Previous studies have shown the prevalence of MS in North America and Europe to be approximately 100 per 100,000 individuals. In Eastern Asia and Africa, the rate is far lower, at only 2 cases per 100,000 individuals. (Gökçe et al., 2019).

The majority of Saudi Arabia's population is young, with only 3% being over 65 and 54% under 18 (Alsaqa'aby et al., 2017). It has recently been reported that the prevalence of MS in this country is moderate to high, at approximately 40 to 60 cases per 100,000 individuals. The average age of onset of the disease is 25 years, the age at which individuals plan for their life's career (Alsaqa'aby et al., 2017).

White matter (WM) in the periventricular regions and the calloso-septal interface, including the cerebellum, brainstem, and basal ganglia, are the areas most affected by MS (Sarbu et al., 2016). Nowadays, special attention is paid to grey matter (GM) functioning in MS. Clinical autopsy studies on patients have revealed changes within the cerebral cortex or at the grey/white matter (GM/WM) interface (Vural et al., 2013; Abidi et al., 2017; Filippi et al., 2012; Absinta et al., 2016).

MS is a very costly disease with a significant economic burden on the healthcare system. Due to the high prevalence of MS in Saudi Arabia, MS ranks second to congestive heart failure (Rosengren et al., 2019), with early diagnosis and treatment being important to overcome the rapidly exacerbating costs of MS in relation to disease management (Alsaqa'aby et al., 2017).

Lesions in WM and GM are highly related to cognitive function. The number of lesions detected by magnetic resonance imaging (MRI) is widely used as an indicator of disease activity assessment (Elnekeidy et al., 2014; Filippi et al., 2012).

The discovery of even one cortical lesion on a clinical isolated syndrome (CIS) onset, could be used to identify patients at risk of having a definitive diagnosis of MS. Such a diagnosis has recently been proposed to be included in the diagnostic criteria for MS (Elnekeidy et al., 2014; Abidi et al., 2017). MS symptoms range from loss of sensation, dysfunction, balance changes, esophageal and visual disorders to cognitive impairment (Atula et al., 2016).

Given the important role of cortical lesions in MS, there is great deal of interest in improving the imaging techniques to identify them. The load of cortical lesions in addition to WM lesion evaluation, improves predictions for the conversion of relapsing-remitting MS (RRMS) to secondary-progressive MS (SPMS). It has been found that the number of cortical lesions can be used to predict the progression of clinical disability (Wiggermann et al., 2016). Although MRI is considered as the gold standard in MS diagnosis, treatment monitoring and response assessment (Kaunzner & Gauthier, 2017; Vural et al., 2013), the relatively small size of the cortical lesions produces poor contrast compared with the surrounding normal appearing grey matter (NAGM). In addition, the partial volume effects of cerebrospinal fluid (CSF) may obscure these lesions and they may not be accurately estimated when using conventional MRI (Salminen et al., 2016).

The ability of advanced MRI sequences to evaluate anatomical structures three-dimensionally (in the axial, coronal and sagittal planes) established them as especially appropriate to recognize the progress of MS (Filippi et al., 2016).

In computed tomography (CT) scans, brain atrophy may be evident in chronic MS and some plaques may show increased contrast in post-contrast CT scans in the active phase. With the development of MRI, MS plaques are not only definitively diagnosed in most patients, but follow-up scans can evaluate the response to treatment and help to determine the pattern of the disease. Double dose, post-contrast CT scans also provide information regarding the disease process activities in MS (Loizou et al., 1982). MRI has become a powerful tool to keep a continuous record of the disease treatment or assessing the therapeutic response and progression of the disease. Treatment reduces the progression of T1 black holes, prevents or delays the whole brain atrophy and also, development of the disability and gadolinium enhancement in active lesions will be decreased swiftly. Previous studies have shown a significant effect of treatment on the entire brain parenchyma and prevention of progressive brain atrophy in MRI finding (Kaunzner UW et al., 2017; Zivadinov R et al., 2001).

Due to the development made in the use of MRI and its ability to detect MS plaques in different areas of the brain, almost no studies on the advantages of CT scans in MS have been conducted since 1985.

1.2 Problem Statement

The increasing rate of MS in developing countries is alarming, despite the fact that accurate methods and modalities can be used to diagnose lesions in patients with MS. The diagnostic accuracy of a double inversion recovery (DIR) MRI sequence in the detection of lesions among patients with MS is not considered, with center staff stating that the DIR sequence is too time consuming (Elnekeidy et al., 2014; Abidi et al., 2017). The time interval between the onset of symptoms and the diagnosis of MS has declined in recent decades due to the developments in diagnostic imaging techniques and modalities that have led to the detection of more MS lesions and, consequently, the appropriate treatment of patients (Cerqueira et al., 2018; Abidi et al., 2017). Although imaging modalities such as the fluid-attenuated inversion recovery (FLAIR) sequence are widely used in many imaging centers, they suffer from great limitations in depicting plaques within the brainstem and cerebellum, resulting in the underestimation of lesions in MS patients (Filippi et al., 2019).

The 2D-FLAIR sequence was considered to be less sensitive than the T2WI sequence in this area, possibly a result of artifacts from the CSF and blood inflow in this area. The difference in the intrinsic composition of brain hemisphere lesions on the one hand and posterior fossa lesions on the other, in other words, the rigidity or adaptability difference of neural tissue in and adjacent to lesions in the posterior fossa, can lead to less accumulation of extracellular water compared with hemispheric lesions and a shorter T2 relaxation time. The apparent T2 values of some regions, such as the periventricular area, have been found to be far higher than in the posterior fossa. This may be the reason that some of the lesions in the rapid FLAIR and very long echo sequences in the posterior fossa region are not detectable and are missing (Fechner et al., 2019; Stevenson et al., 1997).

Furthermore, reports from previous studies have recommended improving the detection of MS lesions using 2D and 3D FLAIR MR imaging techniques (Chagla et al., 2008; Saranathan et al., 2014). Challenges still remain in determining the exact anatomical boundaries between WM cortical and subcortical regions when FLAIR MR imaging modality is employed, meaning that it is difficult to depict intracortical lesions.

MRI is performed with multi-sequence protocols which are known to be important tools for recognizing and monitoring MS (Vural et al., 2013; Filippi et al., 2019). Although MRI-derived metrics are well accepted as the most important diagnostic tools for characterizing MS, the association between the extent of the lesions shown on MRI and the clinical appearance of MS is weak. This supports the opinion of Tillema and Pirko (2013) that conventional MRI techniques, alone, are not sufficient to explain the full spectrum of the disease.

The identification of the exact location of the lesions on MS patients is challenging in MS research. One of the best ways is to use advanced MRI techniques such as DIR, which are not usually used in clinical practice, to identify the role of GM lesions in MS

patients (Kolber et al., 2015). Recently, the DIR sequence has eliminated the challenge of detecting cortical GM lesions by using two different pulses which attenuate the CSF in addition to all the WM, thus creating a remarkable delineation between WM and GM. This improves the detection of MS lesions in GM, especially cortical lesions, given its sensitivity of 92.5% and specificity of 94% (Hamed et al., 2019).

Several clinical diagnostic mismatches in the detection and differentiation of neurological lesions, which could be specific to several pathological types of MS, point to disadvantages of using conventional MRI. It is known that there is a lack of information on the correlation between the expanded disability status scale (EDSS) and MRI measures, with EDSS being one of the ordinal variables useful in matching clinical findings with anatomical structural damage to the brain (Sbardella et al., 2013).

To identify more MS lesions in different anatomical areas, recent attempts have been made to increase MRI sensitivity by using different pulse sequences. FLAIR imaging, despite being highly sensitive near the CSF (for example, at the juxtacortical and the periventricular WM regions), is less sensitive to the display of lesions in the posterior fossa. T2W spin echo or turbo spin echo sequences (T2W SE/TSE), although more sensitive in displaying infratentorial lesions than the FLAIR sequence, are not sufficiently capable of displaying plaque in the juxtacortical region (Elnekeidy et al., 2014; Abidi et al., 2017). As shown in Table 1.1

Table 1.1 : Optimal imaging sequence suggested for each lesion type

Lesion category	Optimal imaging sequence	Alternative Confirmatory sequence(s)
Periventricular	FLAIR	T2-weighted, PD-weighted, 3D T1-weighted MPRAGE
Juxtacortical	FLAIR	3D T1-weighted MPRAGE, T2, DIR, PSIR
Cortical	DIR	3D T1-weighted MPRAGE, PSIR; T2-FLAIR less optimal
Infratentorial	T2	FLAIR, PD, 3D T1-weighted MPRAGE

(Adopted from the works of Filippi et al. 2019)

Unfortunately, in patients with MS, no highly sensitive pulse sequences are available that can detect brain lesions in both the supratentorial and infratentorial areas (Filippi et al., 2019). Although MRI sequences such as T2W SE/TSE and FLAIR have higher sensitivity in the diagnosis of WM lesions, their sensitivity in the detection of cortical grey matter (CGM) lesions is low. The detection of CGM lesions, however, remains limited by using conventional MRI sequences (Al-Iedani et al., 2017; Vural et al., 2013; Abidi et al, 2017) (see Table 1.2).

Table 1.2 : Conventional MRI limitation in detection of MS lesions

Study	Relevant findings
Kidd et al. (1999)	Conventional MRI sequences are considered nonoptimal in diagnosing cortical lesions in MS
Van Horssen et al. (2007)	Detection of cortical lesions is limited by their location and size as well as intrinsic properties of the lesions (minimal inflammation, lack of a blood brain barrier disruption)
Geurts et al. (2008)	Detection of cortical grey matter lesions has been limited when using conventional MRI sequences
Schmierer et al. (2010)	The proximity of the MS lesions to CSF causes susceptibility artifacts.

Further limitations of this method are: the difficulty in determining/the inability to determine the amount of damage when observing lesions in normal appearing white matter (NAWM); the inability to identify and calculate the extent of GM variations; and insufficient assessment of compensatory mechanisms in MS (Calabrese et al., 2013; Crespy et al., 2011; Klaver et al., 2013; Vural et al., 2013). Detection of cortical lesions in MS is challenging, because of technical problems and their pathological appearance. Technical deficiencies in conventional, routine MRI techniques cannot reveal intracortical lesions (ICL) due to their small size and poor contrast with respect to NAGM, as well as the effects of partial volume of CSF on T2WI or even in FLAIR techniques. The conventional MR techniques are poor at detecting GM lesions (Calabrese et al., 2013; Abidi et al, 2017).

1.3 Research Questions

Given the aforementioned problems, this study sought to answer the following questions:

1. Will the DIR sequence reveal a greater number of MS lesions in the different anatomical brain region compared with the FLAIR and T2WI sequences?
2. Are there any significant differences in image contrast measurement among MS lesions and surrounding tissue in DIR compared with FLAIR and T2WI sequences?
3. Is there any significant relationship between the lesion load measurement and EDSS in DIR, FLAIR and T2?
4. Is the DIR technique more accurate in the detection of MS lesions than FLAIR and T2WI sequences?
5. Is there any significant difference in the socio-demographic characteristics (gender, age) among MS patients with the number of MS lesions detected with DIR, FLAIR and T2W sequences?
6. Is there any significant relationship between the MS symptoms and the number of lesions among MS patients in different anatomical regions in the three MRI sequences?
7. Is there a significant difference in signal intensity between NAGM and NAWM in DIR, FLAIR and T2WI sequences among the patients and healthy groups?

1.4 Research Objectives

1.4.1 General objective

To identify the diagnostic accuracy of MRI sequences in detecting MS lesions in MS patients in Saudi Arabia.

1.4.2 Specific objectives

1. To compare the total number of brain MS lesions as well as various anatomical regions, specifically, the infratentorial, juxtacortical, subcortical, periventricular and cortical regions when using DIR compared with the FLAIR and T2WI sequences.
2. To compare the image contrast measurements between MS lesions and surrounding tissues for the T2, FLAIR and DIR sequences.
3. To investigate the correlation between lesion load measurement in the DIR, FLAIR and T2W imaging sequences and the Expanded Disability Status Scale (EDSS).
4. To compare the diagnostic accuracy of the DIR, FLAIR and T2W sequences in the detection of MS lesions.
5. To describe the demographic data of MS patients and compare them with the number of lesions detected by the three MRI sequences.
6. To determine the relationship between MS symptoms and the number of lesions among MS patients in different anatomical regions for the three sequences.
7. To evaluate the signal intensity difference between NAWM and NAGM for the patients and healthy group to determine the sensitivity of DIR in healthy groups.

1.5 Hypothesis

1. The lesion load measurements in different anatomical brain region in MS differ significantly among DIR, FLAIR and T2 sequences.
2. The image contrast of MS lesions among DIR, FLAIR and T2 differs significantly in different anatomical regions
3. The lesion load measurement of the DIR, FLAIR and T2WI sequences is correlated with EDSS.
4. The diagnostic accuracy of the DIR, FLAIR and T2W sequences in the detection of MS lesions differ significantly among patients.
5. There is a relationship between socio-demographic characteristics and the number of lesions in MS patients for the three sequences.
6. There is relationship between MS symptoms and the number of lesions in different anatomical regions in MS patients for the three sequences.

7. The signal intensity and sensitivity of DIR between NAWM and NAGM of the patients and healthy group differ significantly.

1.6 Significance of the study

This study will help to differentiate between the detection and characterization of MS disease when using DIR, FLAIR and T2WI sequences with MS patients. It will also broaden our understanding of the MS patients' patterns in each MRI sequence and the relationship between regional lesions and their clinical presentation.

Once a precise technique is recognized and the obvious differences among those techniques are known, it would be useful to apply the correct technique with higher accuracy at the appropriate time with a view to achieving savings in medical costs. Furthermore, neurologists will have sufficient time to start treatment before the dangerous stage of the disease is reached.

In many cases, young people who suffered from the disease were severely disabled, but the clinicians were not able to make earlier diagnoses as the lesions were not detected. Performing more accurate diagnosis with the correct technique will diminish the degree of disability in MS patients. Furthermore, it will be a great achievement in medical sciences, especially in developing countries, where the cost of treatment for patients who are suffering from MS is high.

1.7 Justification of the Study

There is a need to use more sensitive and specific sequences in MRI for better diagnosis of the MS lesions which could differentiate it from other neurological and pathological conditions. Therefore, it is necessary to conduct a study to compare MRI sequences and to determine which is the most sensitive to characterize patients with MS.

Due to the challenges in detecting cortical lesions, various techniques aimed at global GM assessment have been used (Amiri et al., 2018). DIR sequences have been developed and used to improve the sensitivity of magnetic resonance imaging in detecting such lesions. The DIR sequence has demonstrated a higher number of intracortical lesions compared with conventional MRI methods (Youssef et al., 2018). DIR with two different inversion pulses suppresses the CSF as well as the entire WM, thus, a superior boundary between GM and WM will be achieved (Wattjes et al., 2007).

The DIR sequence has the potential to enhance the sensitivity of MRI in the diagnosis of more MS lesions to overcome the technical limitations of conventional MRI sequences. However, the importance of GM damage in patients and the importance of the DIR technique in identifying cortical lesions prompted us to conduct this study to

emphasize the prominent role of this sequence in the hope of introducing and operating the DIR technique in many imaging centers in Saudi Arabia.

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