Clinical Benefits of MRF in Brain Tumors

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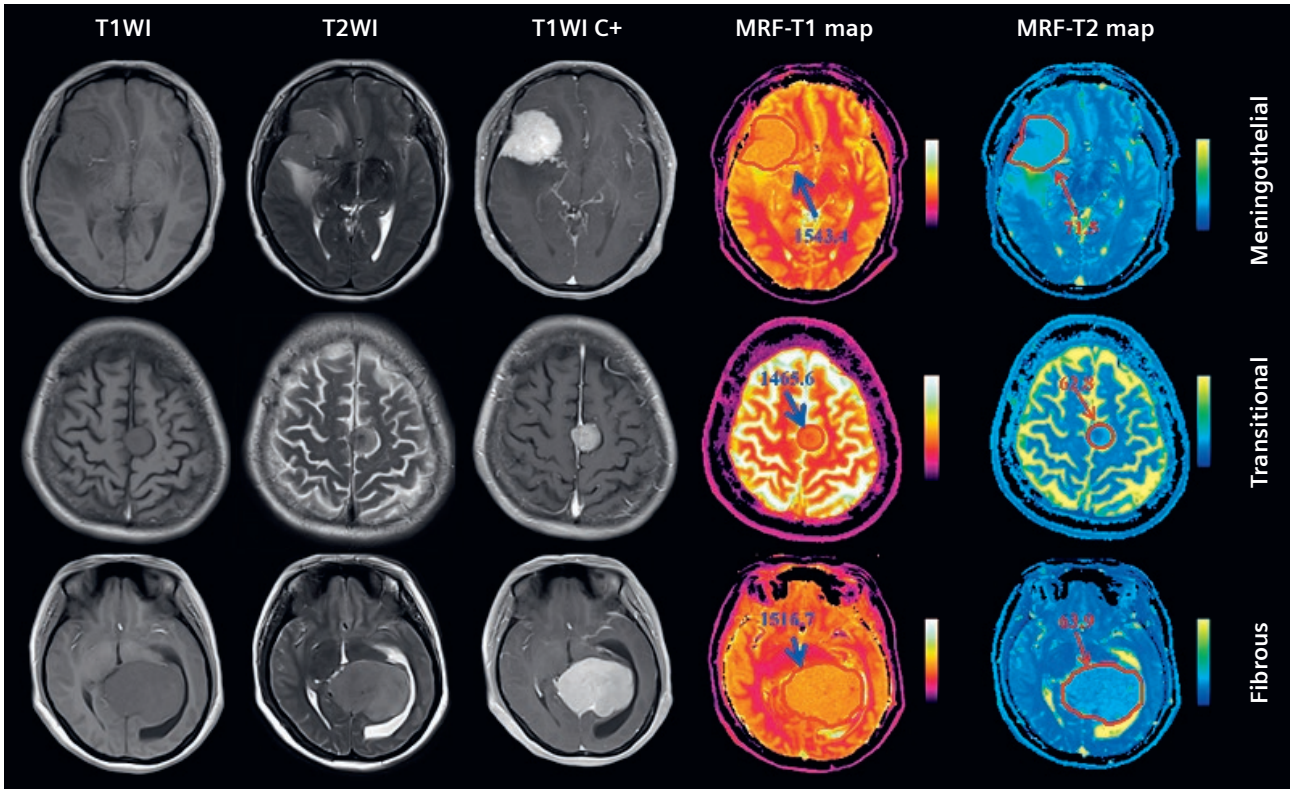
Abstract

Preoperative differentiation between the subtypes of brain tumors could help to guide treatment. Conventional MRI cannot directly quantify the characteristics of brain tumors such as pituitary adenomas and meningiomas. Magnetic Resonance Fingerprinting (MRF) is an imaging technique that allows simultaneous quantification of T1 and T2 values. Quantitative T1 and T2 values yielded from MRF of gonadotroph pituitary macroadenomas were significantly higher than those of the non-gonadotroph pituitary macroadenomas. Moreover, meningothelial meningiomas had significantly higher T1 and T2 values than transitional and fibrous meningiomas. Thus, MRF may help to preoperatively differentiate between gonadotroph and non-gonadotroph pituitary macroadenomas and also to distinguish transitional and fibrous meningiomas from meningothelial meningiomas. MRF shows potential for guiding the treatment of pituitary macroadenomas and meningiomas.



1 Three representative patients with different meningioma subtypes. The T1 and T2 values in the solid tumor area of meningothelial patients appear slightly higher than those of transitional and fibrous patients.

Introduction

Radiology is essential for the initial evaluation of patients with primary brain tumors to characterize tumor types and determine treatment options [1]. The dominant modality is magnetic resonance imaging (MRI) because the multitude of image contrasts of conventional structural MRI allow for good localization of tumor-infiltrated areas. In addition, advanced image-based physiological and molecular biomarkers have been shown to offer comprehensive information about the biological characteristics of tumor types. However, conventional MRI is generally qualitative, providing relative intensity differences between tissues rather than absolute measurements from single tissues as the primary means for characterizing underlying pathology in tumor evaluation. This process may lead to interpretation discrepancies between different radiologists based on these qualitative MRI images and may therefore affect the objective comparison in the patients' follow-up [2].

Quantitative MRI techniques such as T1 and T2 relaxation time mapping could mitigate this problem by directly quantifying the tissue properties, providing a more accurate characterization of underlying changes at the cellular level than standard imaging. Several studies have used MR relaxometry for brain tumor diagnosis. Although most of these studies focus on T2 relaxometry, a recent study showed that T1 mapping might play an essential role in the earlier detection of recurrent tumors in patients on antiangiogenic therapy [2]. Nevertheless, because early conventional approaches for T1 and T2 mapping can only measure one parameter at a time, the reduced time efficiency of such conventional relaxometry techniques is one of the obstacles hindering their application in routine use.

Advanced multiparametric MRI schemes have been proposed to meet the clinical need for fast acquisition of quantitative MR biomarkers, allowing for reproducible and comprehensive measurement of clinically relevant tissue characteristics. Among these techniques, MR Fingerprinting (MRF) is a novel imaging framework that simultaneously estimates multiple quantitative biophysical parameters such as T1, T2, and proton density of different tissues in a clinically practicable acquisition time [3]. These quantitative tissue property measurements allow multiparametric analysis on perfectly co-registered maps, which have shown improved sensitivity and specificity in the characterization of pathological conditions, such as multiple sclerosis [4], epilepsy [5, 6], and brain tumors [7–9]. For example, recent studies found that MRF-derived T1 and T2 maps have shown specificity in identifying the quantitative difference in the solid tumor region and peritumoral regions in different brain tumor types [7]. Also, one study that used radiomic analysis of MRF found that texture analysis of MRF-derived maps can improve our ability to differentiate common adult brain tumors such as low-grade gliomas, glioblastomas, and metastases [9].

Here, we would like to demonstrate our initial experience with the clinical application of MRF in brain tumor diagnosis at our site, mainly focusing on meningiomas [10] and pituitary macroadenomas [11].

MRF sequence and protocol

MR Fingerprinting is a simple, fast, non-invasive quantitative MRI technique that enables measuring multiple physiological parameters simultaneously in a single, efficient acquisition [12, 13]. The MRF framework can be divided into a data acquisition and a pattern matching step. Firstly, MRF uses random excitation flip angles and repetition times (TRs) for data acquisition to obtain incoherent and distinguishable signal evolutions called "fingerprints". Next, in the pattern matching stage, the unique "fingerprints" from each voxel are matched to a set of simulated fingerprints that constitute a dictionary which is generated by Bloch simulations of the same acquisition. Finally, the magnetic resonance parameters (e.g., T1 and T2) that produce the best match are used as definitive quantitative results.

A prototypical 2-dimensional, spiral, fast imaging with steady-state precession based MRF sequence was used to scan patients with brain tumors on a 3T MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The protocol was as follows: transverse orientation, field of view (FOV) 256 × 256 mm^2, matrix 256 × 256, slice thickness 5 mm, flip angle variable 0–74°, TR variable between 12.1 and 15.0 ms, 3,000 measurements, and acquisition time 41 s/slice. Before the MRF acquisition, a B1 map [14] of the whole volume was acquired in 20 seconds and used during the MRF reconstruction.

For the inline MRF data processing, the quantitative T1 and T2 maps were simultaneously generated by matching the measured MRF signal time courses to the dictionary. In particular, the dictionary was calculated for a range of discrete T1, T2, and B_1-field values based on Bloch simulations. The pre-calculated MRF dictionary comprised 691,497 entries of possible signal evolutions covering a wide range of discrete T1 (10 ~ 4500 ms), T2 (2 ~ 3000 ms), and B_1-field values (factors 0.6–1.4 relative to the nominal B_1-field). To improve the reconstruction speed, the dictionary was compressed to 50 main components in the time domain [15]. T1 and T2 maps were output for each section and used for the quantitative analysis.

MR Fingerprinting is not for sale in the U.S. Its future availability cannot be ensured.

In addition to the MRF sequence, the patients received conventional MRI scans, including T1w, T2w, FLAIR, DWI, and contrast-enhanced T1w imaging on meningioma, and T1w, T2w, and contrast-enhanced T1w imaging on pituitary macroadenoma.

MRF in meningioma

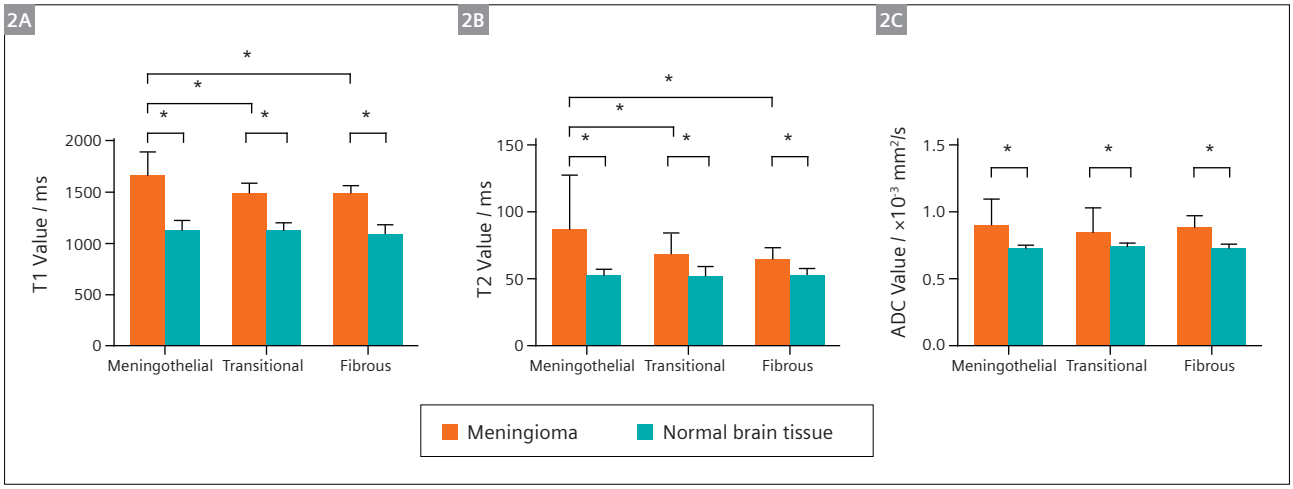
Meningiomas are the second most common central nervous system primary tumor [16]. Most meningiomas are World Health Organization (WHO) grade I, and the most common histological subtypes are meningothelial, transitional, and fibrous meningiomas. Although grade I meningiomas are benign, compared with the meningothelial subtype, transitional and fibrous meningiomas are associated with a higher bleeding risk during surgery and a worse outcome at follow-up [17]. Therefore, an accurate diagnosis of transitional and fibrous meningiomas before surgery is essential for selecting the most appropriate surgical procedure. However, conventional MRI can only reflect the gross morphological changes of tumors. The ability of conventional MRI such as T1w, T2w, and DWI-derived ADC values to differentiate WHO grade I transitional and fibrous meningiomas from meningothelial meningiomas is limited because of the overlap in imaging characteristics and ADC values among these subtypes. Therefore, we tried to use new MRI techniques such as MRF to improve the diagnostic accuracy in differentiating between meningioma subtypes [10].

MRF and conventional MRI data were acquired on 53 patients with suspected meningiomas before surgery. After surgery, 46 patients with pathologically confirmed meningothelial (n = 15), transitional (n = 18), and fibrous meningiomas (n = 13) were included for data analysis.

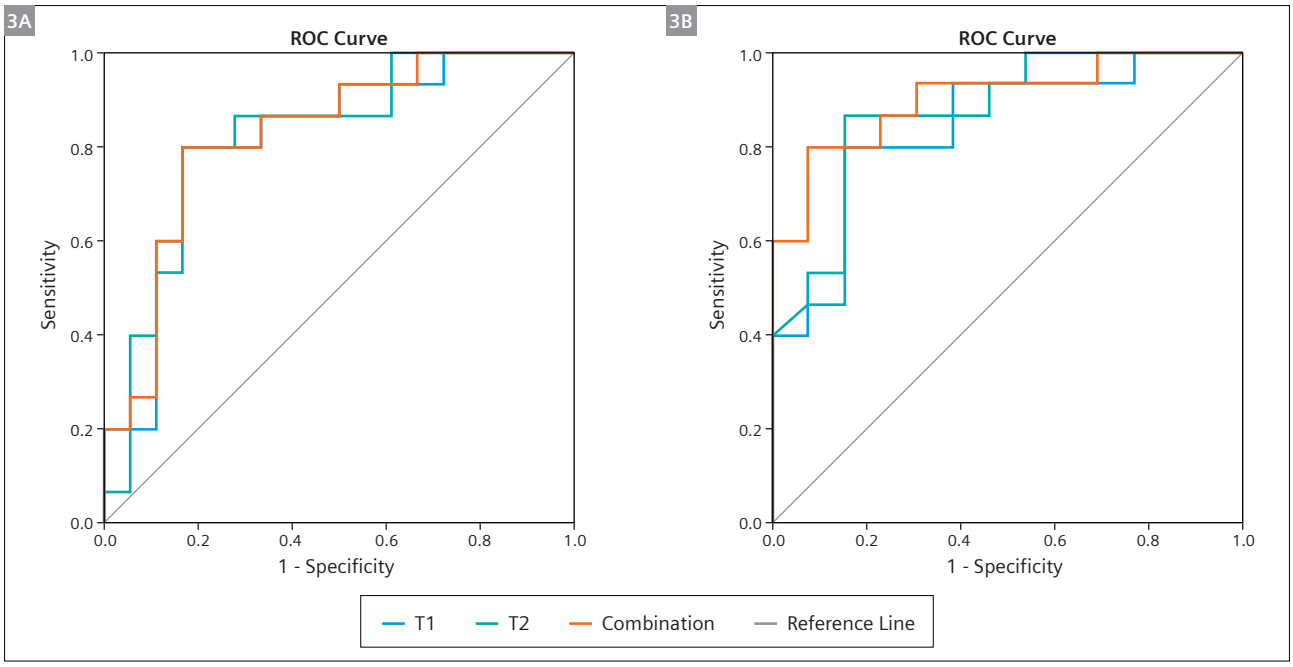
Data from three representative patients with different meningioma subtypes are shown in Figure 1. The T1WI and T2WI signals in the solid tumor areas of these patients were similar, and all showed noticeable enhancement. Therefore, there are still limitations in distinguishing between meningioma subtypes using conventional MRI. In the maps generated with MRF, the T1 and T2 values of the solid tumor areas of the meningothelial patients appeared to be slightly higher than those of the transitional and fibrous patients.

Further statistics found that the meningothelial subtype had significantly higher T1 and T2 values in the solid tumor area than transitional and fibrous meningiomas (Fig. 2A, B). No statistically significant difference was found in the T1 and T2 values between transitional and fibrous meningiomas. The ADC values of meningothelial, transitional, and fibrous meningiomas were not significantly different (Fig. 2C). Furthermore, the T1, T2, and ADC values of normal brain tissue were not significantly different between the three subtypes. The T1, T2, and ADC values of the three tumor subtypes differed significantly between the solid tumor area and the contralateral normal brain tissue. There were no statistically significant differences between the three meningioma groups in T1WI, T2WI, or contrast-enhanced T1WI.

Receiver operating characteristic (ROC) curve analysis was conducted, and the areas under the ROC curves (AUCs) were calculated between groups with statistically significant differences to evaluate the efficacy of T1 and T2 values in differentiating various subtypes of meningiomas. The combination of T1 and T2 values achieved the best diagnostic performance for differentiating transitional from meningothelial meningiomas (AUC = 0.826, sensitivity = 80%, and specificity = 83.33%) and differentiating



2 Quantitative MRI parameter comparison between three meningioma subtypes: **(2A)** MRF-derived T1 maps, **(2B)** MRF-derived T2 maps, and **(2C)** apparent diffusion efficient (ADC) values. T1 and T2 values of meningothelial patients are significantly higher than those of transitional and fibrous meningioma patients. [10]



3 A receiver operating characteristic (ROC) curve of T1 and T2 values and the combination of the T1 and T2 values (combined variable) for the differential diagnosis of **(3A)** meningothelial and transitional meningiomas and **(3B)** meningothelial and fibrous meningiomas. [10]

fibrous from meningothelial meningiomas (AUC = 0.903, sensitivity = 80%, and specificity = 92.31%), as shown in Figure 3.

Our results suggested that transitional and fibrous meningiomas have significantly lower T1 and T2 values than meningothelial meningiomas. However, conventional MRI, including T1WI, T2WI, contrast-enhanced T1WI, and ADC values, indicated no statistically significant differences between transitional/fibrous meningiomas and meningothelial meningiomas. The ROC analyses showed that the T1 and T2 mapping generated by MRF might differentiate transitional and fibrous meningiomas from meningothelial meningiomas. These findings could benefit preoperative treatment plans for meningiomas and provide a more accurate prognosis.

MRF in pituitary macroadenoma

Pituitary adenomas account for 10–20% of all primary brain tumors. Macroadenomas represent about one-half of pituitary adenomas in the clinic [18]. The latest 2017 WHO classification of pituitary adenomas uses immunohistochemistry as the primary ancillary tool for diagnosis. Among them, gonadotroph adenomas are defined as tumors producing luteinizing hormone (β-LH) and follicle-stimulating hormone (β-FSH), which are secreted by the gonadotropic cells of the anterior pituitary gland [19]. In addition, there are several non-gonadotroph adenomas, including somatotroph adenomas, lactotroph adenomas, corticotroph adenomas, and null cell adenomas (18). Somatostatin receptor type 3 (SSTR3) is expressed in 94% of gonadotroph pituitary adenomas, a putative target for drug therapy replacement for commonly used surgical treatment [20]. Therefore, preoperative differentiation between gonadotroph and non-gonadotroph pituitary macroadenomas could help to guide treatment. However, conventional MRI cannot directly quantify the characteristics of pituitary adenomas and therefore has limited capability to identify gonadotroph pituitary adenomas.

Our group aimed to use MRF to differentiate gonadotroph from non-gonadotroph pituitary macroadenomas according to the 2017 WHO classification of pituitary adenomas [11].

MRF and conventional MRI data from 57 patients with pituitary macroadenomas were included for analysis. Among them, 30 (52.6%) were categorized as gonadotroph pituitary macroadenomas; non-gonadotroph pituitary macroadenomas were diagnosed in 27 patients (47.4%).

Conventional MRI and MRF images of representative gonadotroph pituitary macroadenoma and non-functioning corticotroph pituitary macroadenoma are shown in Figure 4. The mean MRF-derived T1 and T2 values in the gonadotroph pituitary macroadenomas (T1 value, 1617 ± 274 ms; T2 value, 85 ± 26 ms) were significantly higher than those in the non-gonadotroph pituitary macroadenomas

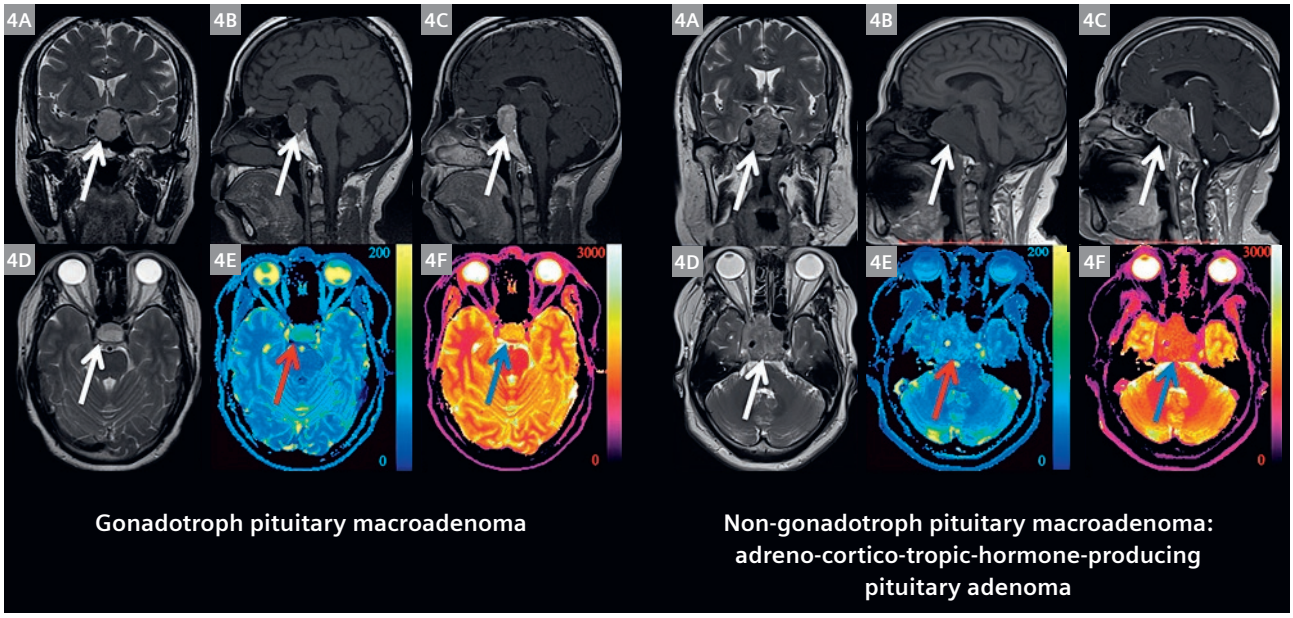
(T1 value, 1412 ± 180 ms; T2 value, 58 ± 13 ms), as shown in Figure 5.

Regarding the differentiation between gonadotroph and non-gonadotroph pituitary macroadenomas, the AUC for MRF-derived T2 values (0.888, 95% CI 0.776–0.956) was significantly greater than that for MRF-derived T1 values (0.742, 95% CI 0.609–0.849) (p = 0.034, Fig. 6).

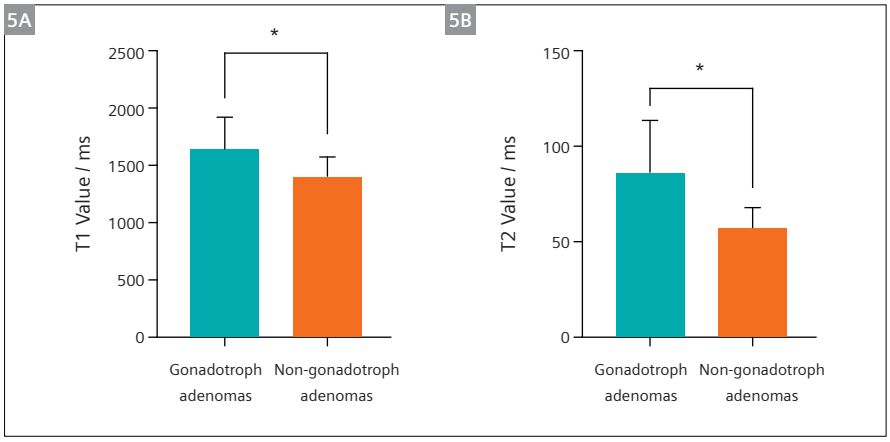
This work showed that the quantitative T1 and T2 values derived from MRF were significantly higher in gonadotroph than in non-gonadotroph pituitary macroadenomas. These findings may be helpful in preoperatively differentiating these macroadenoma types, which will guide their treatment.

Conclusion

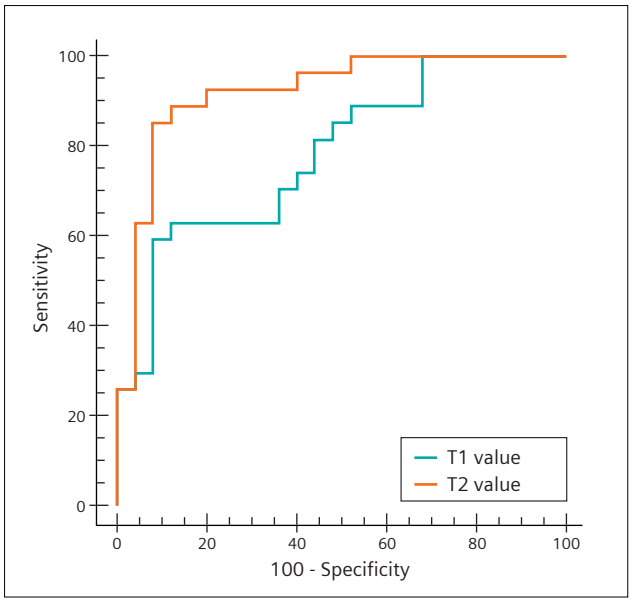
MRF shows greater potential than conventional qualitative MRI for brain tumor differential diagnosis. Quantitative T1 and T2 measurements can also be conducted using conventional MRI relaxometry mapping methods. However, this requires more scan time because the T1 and T2 measurements are acquired separately. MRF can simultaneously acquire T1 and T2 maps, thereby shortening the acquisition time and yielding perfectly aligned images that will benefit the data analysis. In addition to T1 and T2 relaxometry, the MRF framework allows for quantifying further tissue parameters such as diffusion or perfusion information based on its flexible sequence design



4 Representative gonadotroph pituitary macroadenoma and non-gonadotroph pituitary macroadenoma. **(4A)** Coronal T2-weighted image, **(4B)** sagittal T1-weighted image, **(4C)** gadolinium-based contrast-enhanced sagittal T1-weighted image, and **(4D)** transverse T2-weighted image. **(4E)** MRF-derived T2 map shows increased T2 relaxation times in the tumor. **(4F)** MRF-derived T1 map shows increased T1 relaxation times in the tumor.



5 Average comparison of MRF-derived T1 values **(5A)** and T2 values and **(5B)** in ROIs in gonadotroph pituitary macroadenomas compared with non-gonadotroph pituitary macroadenomas. [11]



6 Comparison of receiver operating characteristic (ROC) curve analysis for differentiating gonadotroph and non-gonadotroph pituitary macroadenomas. The area under the ROC curve for MRF-derived T2 values was significantly greater than that for MRF-derived T1 values. [11]

characteristics [13]. This opens the door to a new approach to using imaging biomarkers in many applications of quantitative MRI, which will ultimately help the diagnosis and treatment of brain tumors.

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