Original Investigation

The Diagnostic Value of Conventional MRI and CT Features in the Identification of the IDH1-Mutant and 1p/19q Co-Deletion in WHO Grade II Gliomas

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Rationale and Objectives: The classification of patients based on pathology and molecular features is important for improving WHO grade II glioma patient prognosis, especially for the initially diagnosed patients. Less invasive and more convenient methods for the prediction of the pathological type and gene status are desired.

Materials and Methods: This study investigates the ability to use conventional magnetic resonance imaging (MRI) and computed tomography (CT) features for determining the Isocitrate Dehydrogenase (IDH)-mutant and 1p/19q-codeletion status, through a retrospective review of information obtained from 189 WHO grade II glioma patients. Diffuse astrocytoma (IDH-mutant), Diffuse astrocytoma (IDH- wildtype) and Oligodendroglioma (IDH-mutant and 1p/19q co-deletion) were included in this cohort. All patients were divided into IDH-mutant group and IDH-wildtype group according to the IDH R132H mutation status. Moreover, all patients were divided into 1p/19q co-deletion group and 1p/19q non-codeletion group according to the 1p and 19q chromosome status. Patients underwent pre-operative CT and MRI scans, followed by operation and histopathological analyses, including immunohistochemistry and polymerase chain reaction analysis for IDH mutants, and fluorescence capillary electrophoresis analysis for the 1p/19q co-deletion. The χ^2 test, logistical regression and receiver operating characteristic curve analysis were conducted for statistical analysis.

Results: IDH-mutant group patients exhibited a higher calcification frequency (25.2% vs 2.4%, $p = 0.006$) and lower frequency of T1 enhancement (20.4% vs 38.1%, $p = 0.028$) comparing patients in IDH-wildtype group, while 1p/19q co-deletion group patients exhibited a higher calcification frequency (46.67% vs 2.6%, $p < 0.001$) and lower homogenous signal frequency in T2WI (12.0% vs 31.6%, $p = 0.014$), sharp lesion margins (14.7% vs 43.0%, $p = 0.010$), T2/fluid attenuated inversion recovery mismatch signs (22.7% vs 50.9%, $p = 0.001$), and subventricular zone involvement (64.0% vs 15.8%, $p = 0.021$) comparing patients in 1p/19q non-codeletion group. According to the results of receiver operating characteristic analysis, these features were observed to have certain diagnostic abilities, especially with regard to combination parameters, which had a high diagnostic capability, with an area under the curve of 0.848.

Conclusion: Conventional MRI and CT features, which still represent the most convenient and widely used predictive method, might be a promising noninvasive predictor for differentiating between varied WHO grade II gliomas. Patients with calcification and T1 nonenhancement are more likely to be IDH-mutant. Moreover, patients with noncalcification, homogenous signal, sharp lesion margins, subventricular zone involvement on T2 and T2/fluid attenuated inversion recovery mismatch signs are more likely to be 1p/19q non-codeletion.

Key Words: Gliomas; Conventional MRI features; Molecular pathology; Noninvasive predictor.

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INTRODUCTION

WHO grade II gliomas are intracranial tumors with infiltrative and invasive properties that have a very low cure rate. The average overall survival (OS) for patients with WHO grade II gliomas from the time of diagnosis is approximately 5 to 6 years, with a range of 3−10 years (1). The tumor growth rate, treatment sensitivity, and overall patient survival are highly dependent on the dominant cell lineage and its mutational status (2,3). The majority

(65%−90%) of WHO grade II gliomas have mutations in IDH (4−10). Meanwhile approximate 32%−45% of WHO grade II gliomas harbor 1p/19q co-deletion (7−10). The molecular features to be considered during classification have been integrated into the 2016 WHO guidelines for the classification for gliomas, together with the traditional morphological and pathological features (11). Pathologists usually differentiate between gliomas, particularly low-grade gliomas (LGGs), by classifying them into subgroups, based on the status of IDH mutations and 1p/19q co-deletions. These deletions are crucial factors for the diagnosis and prognosis of gliomas (8,12−15). According to the previous studies, WHO grade II gliomas can be subclassified into three main molecular groups: (1) LGGs with IDH-wildtype, (2) LGGs with IDH-mutant and 1p/19q non-codeletion, (3) LGGs with IDH-mutant and 1p/19q co-deletion. Studies have demonstrated that the incidence of IDH mutations,1p/19q co-deletions, and Telomerase reverse transcriptase (TERT) promoter mutations in gliomas were better predictors for outcome, regardless of histological analysis results (14,16,17). Patients with IDH-mutant and 1p/19q co-deletion presented the most favorable prognosis independent of therapy and better chemosensitivity, while patients with IDH-wildtype showed the worst prognosis (7,10,14,15). Taking the clinical practice into consideration, patients with specific gene status are better suited the specific medicine just like the procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) for 1p/19q co-deletion patients in phase III trial RTOG 9402. Procarbazine, lomustine, and vincristine plus RT doubled the OS of 1p/19q co-deletion patients to 14.7 years but didn't help the OS of 1p/19q non-codeletion patients (14). Hence, a noninvasive method that is more capable of distinguishing oligodendrogliomas, IDH-mutants, and 1p/19q-co-deletions from WHO grade II gliomas could assist pathologists, physicians, and surgeons in selecting appropriate treatment strategies, especially among initially diagnosed patients and patients who do not prefer surgery as a treatment option.

Despite the biopsies and surgical resection can get the determined diagnosis of IDH1-mutant and 1p/19q co-deletion status, a method using conventional MRI and computed tomography (CT) to predict IDH1 and 1p/19q status, which are associated with outcome, chemosensitivity, and radiosensitivity of glioma patients, is a cheaper, safer and more acceptable alternative. Every part of brain is functional and minimal damage, even biopsies which is relative low risk, affects neurological integrity. Since several IDH targeting medicines are undergoing preclinical studies even early-phase trials, noninvasive approach to identify IDH and 1p19q status may provide guidance and reference for surgical decision, RT and chemotherapy especially for the patients who cannot suffer safe gross total resection. The results of several studies using amino acid positron emission tomography (PET), magnetic resonance imaging (MRI)-based texture analysis, and advanced MRI technologies, such as perfusion and diffusion magnetic resonance (MR), have shown the ability of these methods to predict the gene mutational status (18−21). However, the convenient and widely used conventional MRI and CT method still efficiently offers diagnostic value for genotype classification (22). The present study aims to analyze images and define conventional features of MRI and CT exams, to determine their ability to distinguish between IDH-mutation and IDH-wildtype as well as 1p/19qco-deletion and 1p/19q non-codeletion. The results of our study would extend the scope of conventional MRI and CT exams and be valuable for determining treatment strategies, outcomes, and chemosensitivity.

METHODS

Patients

We retrospectively analyzed 189 patients who were newly diagnosed with WHO II gliomas, at the neuroscience department of a medical facility, between January 2016 and December 2018. Diagnosis of each patient was pathologically confirmed. Sequences from presurgical MRI and CT scans were used for assessment. All patients included only if they met all the following inclusion criteria: (1) The ages of patients were between 18 and 70, (2) Newly diagnosed WHO grade II gliomas confirmed by histopathology, (3) patients who underwent preoperative MRI and CT scans. Exclusion criteria: (1) Patients who received craniotomy before, (2) Test of IDH mutation or 1p/19q codeletion status were not available. This study was approved by the ethics committee.

Imaging Protocol

ALL patients underwent CT and MRI scans within 7 days before the operation. A 512*512 matrix with 1.5-mm slices was used for CT scans which were performed on a 64-multidetector CT scanner (Philips Healthcare, Cleveland, OH). All MRI scans were performed on a 3.0-T MR system (Signa HDx, GE Healthcare, Milwaukee, WI). Patients were imaged in the supine position using a 16-channel neurovascular head and neck array coil. An axial T1-weighted spin-echo sequence (TR/TE, 428/11.6 ms), T2-weighted spin-echo sequence (TR/TE, 3000/59.5 ms) without contrast enhancement, T2-fluid attenuated inversion recovery (FLAIR) sequence (TR/TE, 9000/119ms) and the contrast-enhanced T1-weighted axial images (TR/TE, 410/11ms) were performed. The contrast-enhanced T1-weighted axial images were obtained after the Gd-DTPA (0.1 mmol/kg, Bayer AG) administration. The parameters of MRI would be as follows: a section thickness of 3mm with an intersection gap of 1 mm.

Imaging Features

CT and MRI scans were independently reviewed by two neuroradiologists with more than 7 years of MR and CT neuroimaging, who were blinded to clinical information,

pathology diagnosis, and molecular classification. The features of the conventional MRIs and CTs were determined using a binary scoring method, and a consensus was reached. Issues such as discordant findings between the two radiologists were resolved through an adjudication by a third senior neuroradiologist independently, after independent data collection.

The following nine imaging features were taken into consideration during analysis: (1) calcification (presence or absence on CT scans); (2) a homogeneous signal on T2WI (presence or absence); (3) sharp lesion margins on T2WI (sharp or indistinct); (4) peritumoral edema (presence or absence); (5) T2/FLAIR mismatch (presence or absence); (6) cortex invasion on T2WI (presence or absence); (7) subventricular zone (SVZ) involvement on T2WI (presence or absence); (8) insular involvement on T2WI (presence or absence); and (9) T1 enhancement (presence or absence).

Genotyping and Immunohistochemistry

The combined loss of genetic material from chromosomal arms 1p and 19q has long been recognized as a molecular signature for oligodendroglia tumors. Such tumors result from an unbalanced translocation, which leads to the loss of a hybrid chromosome, and subsequently, the loss of heterozygosity. The deletion of the 1p and 19q promoter in our patient cohort was detected using fluorescence capillary electrophoresis (23).

The IDH status was determined via immunohistochemistry, and genotyping on tumor DNA was performed after a polymerase chain reaction (PCR) of the exon 4 (including codon 132) of the IDH1 gene was performed, followed by direct sequencing.

Statistical Analysis

The χ^2 test and logistical regression analysis were performed to determine the relationship between the imaging features and IDH-mutant and 1p/19q-codeletion statuses. Receiver operating characteristic (ROC) curve analysis was performed using the MEDCALC statistical software (MedCalc Software bvba, Ostend, Belgium, V. 19), to determine the diagnostic value of the IDH1 mutation and 1p/19q co-deletion status, for predicting oligodendrogliomas, IDH-mutants, and 1p/19q co-deletions. All statistical analyses were performed using the IBM SPSS 20.0 statistical software (IBM Corp.). A p value of <0.05 was considered statistically significant.

RESULTS

All 189 enrolled patients were newly diagnosed with WHO II gliomas. We chose newly diagnosed WHO grade II gliomas confirmed by histopathology between 18 and 70 years old. Preoperative MRI and CT scans of these patients were enough for analysis. No patient was excluded after we checked whether the patients received craniotomy before and performed the IDH mutation or 1p/19q co-deletion status testing. Eligible patients included 106 males and 83 females, with an average age of 40.98 ± 11.84. The patient characteristics are shown in Table 1. Post-surgical histological examinations demonstrated that 72 patients exhibited diffuse astrocytoma and IDH-mutations; 42 exhibited diffuse astrocytoma and the IDH wild type; 75 exhibited oligodendrogliomas, IDH-mutations, and 1p/19q co-deletions. In this cohort, 147 patients had IDH1 mutations, while 75 had 1p/19q co-deletions.

First, we divided all the patients into IDH-mutant group and IDH-wildtype group according to the IDH R132H mutation status to further analysis. The selected conventional MRI and CT features for the different subgroups are shown in Table 2, Table 3, and Table 4. Statistical differences in calcification and T1 enhancement were observed for patients with different IDH1 mutational statuses. Patients with IDH1 mutations exhibited a higher rate of calcification (25.2% vs 2.4%) and lower rate of T1 enhancement (20.4% vs 38.1%) (Table 3), as compared to patients with wild-type IDH1. Multivariate analysis demonstrated that calcification and T1 enhancement were independently associated with the IDH mutation status. Though this suggests that the ROC analysis of these two features were diagnostically important, the diagnostic value was not powerful; values for area under the curve

TABLE 1. Characteristics of WHO Grade II Gliomas

	IDH1-Mutant		1p/19q Co-Deletion		Total
	+	−	+	−	
Gender					
Male	81 (42.86%)	25 (13.23%)	37 (19.58%)	69 (36.51%)	106 (56.08%)
Female	66 (34.92%)	17 (8.99%)	38 (20.11%)	45 (23.80%)	83 (43.92%)
Age	41.09 ± 10.75	40.57 ± 15.10	42.45 ± 10.10	39.96 ± 12.79	40.98 ± 11.84
Pathology					
Diffuse astrocytoma, IDH-mutant	72 (38.10%)	0	0	72 (38.10%)	72 (38.10%)
Diffuse astrocytoma, IDH-wildtype	0	42 (22.22%)	0	42 (22.22%)	42 (22.22%)
Oligodendroglioma, IDH-mutant and 1p/19q co-deletion	75 (39.68%)	0	75 (39.68%)	0	75 (39.68%)
Total	147 (77.78%)	42 (22.22%)	75 (39.68%)	114 (60.30%)	

TABLE 2. CT (Calcification) MRI Characteristics of WHO Grade II Gliomas

Imaging Biomarkers	Number	Percentage (%)
Calcification (+/-)	38/151	20.1/79.9
Homogenous signal on T2WI (+/-)	45/144	23.8/76.2
Sharp lesion margins on T2WI (+/-)	60/129	31.7/68.3
Peritumoral Edema (+/-)	156/33	82.5/17.5
T2/FLAIR Mismatch (+/-)	75/114	39.7/60.3
Cortex invaded sign (+/-)	127/62	67.2/32.8
Subventricular zone involvement (+/-)	128/61	67.7/32.3
Insular involvement (+/-)	28/161	14.8/85.2
T1 enhancement (+/-)	46/143	24.3/75.7

CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

(AUC) were 0.614 and 0.588. In addition, a combination of these two parameters (AUC = 0.687) still had a higher diagnostic value (Fig 1).

On the other hand, all patients were divided into 1p/19q co-deletion group and 1p/19q non-codeletion group according to the 1p and 19q chromosome status to explore the relationship between the image parameters and 1p/19q co-deletion status. Since all the 1p/19q co-deletion gliomas are IDH1 mutated, the groups can be considered as Oligodendroglioma (IDH-mutant and 1p/19q co-deletion) group and Diffuse astrocytoma (IDH-wildtype or IDH-mutant) groups. Univariate and multivariate analyses demonstrated that calcification ($p < 0.001$), homogenous signals on T2WI ($p = 0.014$), sharp lesion margins ($p = 0.010$), T2/FLAIR mismatch signs ($p = 0.001$), and SVZ involvement ($p = 0.021$) were independently associated with the 1p/19q co-deletion status (Table 4, Fig 2). Despite all the tumors with calcification exhibiting an IDH1 mutation (IDHI-mut), only 3 tumors displaying an IDHI-mut did not harbor the 1p/19q co-deletion. Patients with the 1p/19q co-deletion had a higher calcification frequency (46.67% vs 2.6%) and lower frequency of homogenous signal in T2WI (12.0% vs 31.6%), sharp lesion margins (14.7% vs 43.0%), T2/FLAIR mismatch signs (22.7% vs 50.9%), and SVZ involvement (64.0% vs 15.8%). Because all the 1p/19q co-deletion gliomas had an IDH1-mut in this cohort, ROC analysis was then performed to assess diagnostic performance. Except for SVZ involvement (AUC = 0.531), all other features, such as calcification (AUC = 0.720), homogenous signals on T2WI (AUC = 0.598), sharp lesion margins (AUC = 0.642), and T2/FLAIR mismatch signs (AUC = 0.641) demonstrated the diagnostic value of detecting LGG IDH mutants and 1p/19q-co-deletions (Fig.2). The combination of the 4 parameters mentioned previously had the highest diagnostic efficiency, and the AUC was 0.848 (Fig 2).

DISCUSSION

Here, we investigate the role of conventional MRI features for the detection and assessment of the mutational status of

TABLE 3. CT (Calcification) and MRI Characteristics of IDH1-Mutant and IDH1-Wild WHO Grade II Gliomas

	IDH1-mutant		*p* value
	+	–	
Gender (male/female)	81 (42.86%)/66 (34.92%)	25 (13.23%)/17 (8.99%)	
Age	41.09 ± 10.75	40.57 ± 15.10	
Calcification			0.006
Yes	37 (19.58%)	1 (0.53%)	
No	110 (58.20%)	41 (21.69%)	
Homogeneous signal on T2WI			0.911
Yes	35 (18.52%)	10 (5.29%)	
No	112 (59.26%)	32 (16.93%)	
Sharp lesion margins on T2WI			0.356
Yes	47 (24.87%)	13 (6.88%)	
No	100 (52.91%)	29 (15.34%)	
Peritumoral Edema			.0116
Yes	125 (66.14%)	31 (16.40%)	
No	22 (11.64%)	11 (5.82%)	
T2/FLAIR Mismatch			0.168
Yes	53 (28.04%)	22 (11.64%)	
No	94 (49.74%)	20 (10.58%)	
Cortex invaded sign			0.183
Yes	103 (54.50%)	24 (12.70%)	
No	44 (23.28%)	18 (9.52%)	
Subventricular zone involvement			0.829
Yes	99 (52.38%)	29 (15.34%)	
No	48 (25.40%)	13 (6.88%)	
Insular involvement			0.234
Yes	20 (10.58%)	8 (4.23%)	
No	127 (67.20%)	34 (17.99%)	
T1 enhancement			0.028
Yes	30 (15.87%)	16 (8.47%)	
No	117 (61.90%)	26 (13.76%)	

CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

WHO grade II gliomas. Our results demonstrate that conventional MRI and CT features are associated with IDH1 mutations and the 1p/19q co-deletion status. Glioma patients with IDH-1 mutations have a higher probability of exhibiting calcification and non-enhancement, while patients with the 1p/19q non-codeletion have a higher probability of exhibiting non-calcification, homogenous signals on T2WI, sharp lesion margins, T2/FLAIR mismatch signs, and SVZ involvement. These results would help us determine non-invasive treatment and surgical strategies. Although several previous studies have associated clinical and MRI characteristics with gene mutational status, most of them were based on a sample of patients with WHO grade II and III gliomas (22,24–26). In this study, we focused exclusively on patients with WHO grade II gliomas, as the distinct histopathological and radiological features of high- and LGGs might interfere with their gene mutational status.

TABLE 4. CT (Calcification) and MRI Characteristics of Patients with WHO Grade II Gliomas Exhibiting 1p/19q Co-Deletions and Non-codeletions

	1p/19q Co-Deletion (and IDH1-Mutant)		*p* Value
	+	−	
Gender (male/female)	37 (19.58%)/38 (20.11%)	69 (36.51%)/45 (23.80%)	
Age	42.45 ± 10.10	39.96 ± 12.79	
Calcification			<0.001
Yes	35 (18.52%)	3 (1.59%)	
No	40 (21.16%)	111 (58.73%)	
Homogeneous signal on T2WI			0.014
Yes	9 (4.76%)	36 (19.05%)	
No	66 (34.92%)	78 (41.27%)	
Sharp lesion margins on T2WI			0.010
Yes	11 (5.82%)	49 (25.93%)	
No	64 (33.86%)	65 (34.39%)	
Peritumoral Edema			0.832
Yes	10 (5.29%)	91 (48.15%)	
No	65 (34.39%)	23 (12.17%)	
T2/FLAIR Mismatch			0.001
Yes	17 (8.99%)	58 (30.69%)	
No	58 (30.69%)	56 (29.63%)	
Cortex invaded sign			0.257
Yes	55 (29.10%)	72 (38.10%)	
No	20 (10.58%)	42 (22.22%)	
Subventricular zone involvement			0.021
Yes	48 (25.40%)	80 (42.33%)	
No	27 (14.29%)	34 (17.99%)	
Insular involvement			0.135
Yes	10 (5.29%)	18 (9.52%)	
No	56 (29.63%)	96 (50.79%)	
T1 enhancement			0.758
Yes	19 (10.05%)	27 (14.29%)	
No	56 (29.63%)	87 (46.03%)	

CT, computed tomography; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

We found that calcification and T1 enhancement were independently associated with the IDH mutational status, while calcification, homogenous signals on T2WI, sharp lesion margins, T2/FLAIR mismatch signs, and SVZ involvement were independently associated with the 1p/19q co-deletion status. All the features mentioned previously have great diagnostic value for the detection of oligodendrogliomas, IDH mutants and 1p/19q-codeletions.

Currently, neuro-oncologists and neurosurgeons rely on the molecular features of gliomas to determine appropriate clinical treatment strategies. The clinical value of the methods for molecular pathology analysis has been widely acknowledged. The 2016 WHO classification guidelines for brain tumors are based on both morphological and molecular criteria. Hence, an increasing number of neurosurgeons have used the mutational and methylation status as a reference for selecting comprehensive treatment strategies, especially for patients with LGGs. A complete diagnostic evaluation of LGGs requires the molecular assessment of the IDH1 and 1p/19q co-deletion mutational status (8,15,27). Additionally, the primary classification should be based on the mutational status instead of the grade (28). Based on the 2018 NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology for Central Nervous System Cancers, histologically similar Central nervous system (CNS) neoplasms can be differentiated more accurately for prognosis and, in some instances, for predicting responses to different therapies, using genetic testing methods (15,29). A recent retrospective, multicenter study demonstrated the reduced benefit of maximal surgery among patients with 1p/19q co-deletions (14).

The genetic landscape in gliomas define their biological behavior. The different biological behaviors of these tumor cells result in histological heterogeneity, which lead to neuroimaging heterogeneity. Although no imaging methodology can truly determine the genetic status of tumor cells as accurately as a histological and molecular assessment, neuroimaging techniques, such as CT, MRI, and PET-CT/MRI are effective in providing information regarding the histological grade, tumor cell proliferation, and microvascular state. The non-invasiveness and convenience of imaging technologies renders them critical and accessible pre-surgical tools for the assessment of patients diagnosed with gliomas. In addition, studies have shown that advanced MRI techniques, such as PWI, DWI, and MRS have the ability to predict gene status (2,30,31). Here, we provide evidence for the fact that conventional MRI features also have predictive potential.

Previous studies using CT scans of patients with WHO grade II and III gliomas have demonstrated that calcification was significantly associated with oligodendroglia and 1p/19q co-deletions in an independent manner (32−34). Here, only 1 IDH1-wild tumor displayed calcification. Only 3 of the 114 (2.6%) patients (excluding patients with oligodendrogliomas, (IDH-mutant, and 1p/19q co-deletions) exhibited calcification, while 35 of 75 (46.7%) oligodendroglioma patients exhibited calcification. This might be the reason why patients exhibiting calcification have longer survival rates, as reported previously (35). Based on our study, calcification was significantly associated with both IDH1 mutations and the 1p/19q co-deletion status, and is therefore a valuable predictor of these mutations.

T1 enhancement has been associated with IDH1 mutational status. Previous studies have suggested that WHO grade II gliomas are not typically T1 enhanced tumors. With the advent of gene sequencing, their association with T1 enhancement has been reported in 10%−50% of WHO grade II gliomas (36−38). T1 enhancement reflects the areas exhibiting neoangiogenesis in most patients, but its prognostic value remains contested. Daumas-Duport et al suggested that enhancement was associated with prognosis, while Pallud et al believed that only certain specific patterns of enhancement, such as "nodular-like" enhancements were associated with

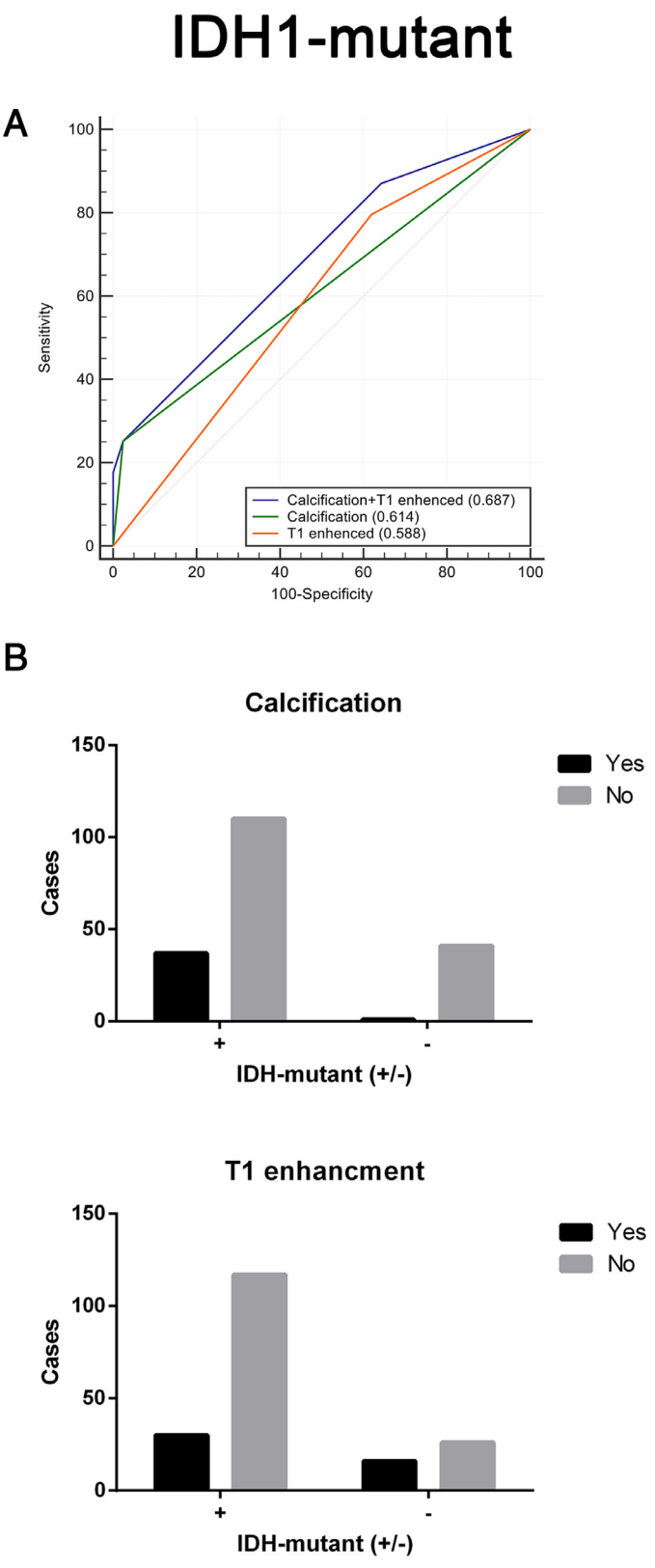

Figure 1. Calcification and T1 enhancement were associated with the IDH1 mutation status. (a) ROC analysis indicated that calcification had occurred, and a combination of these two parameters showed the diagnostic value for IDH1-mutant WHO grade II gliomas. (b) Bar graphs showed that calcification ($p = 0.006$) and T1 enhancement ($p = 0.028$) displayed significant differences. Patients with IDH1 mutations exhibited a higher rate of calcification (25.2% vs 2.4%) and lower rate of T1 enhancement (20.4% vs 38.1%), as compared to patients with IDH1-wild. ROC, receiver operating characteristic.

poor prognosis (39,40). In our study, 46 of 189 WHO grade II glioma patients (24.3%) exhibited a T1 enhancement, which was associated with lower IDH1 mutation rates. Although T1 enhancement did not have a suitable diagnostic value (AUC below 0.6), the diagnostic value of MRI features was reinforced, in combination with the calcification feature.

Homogeneous signals, sharp lesion margins on T2WI, and T2/FLAIR mismatches were associated with the 1p/19q

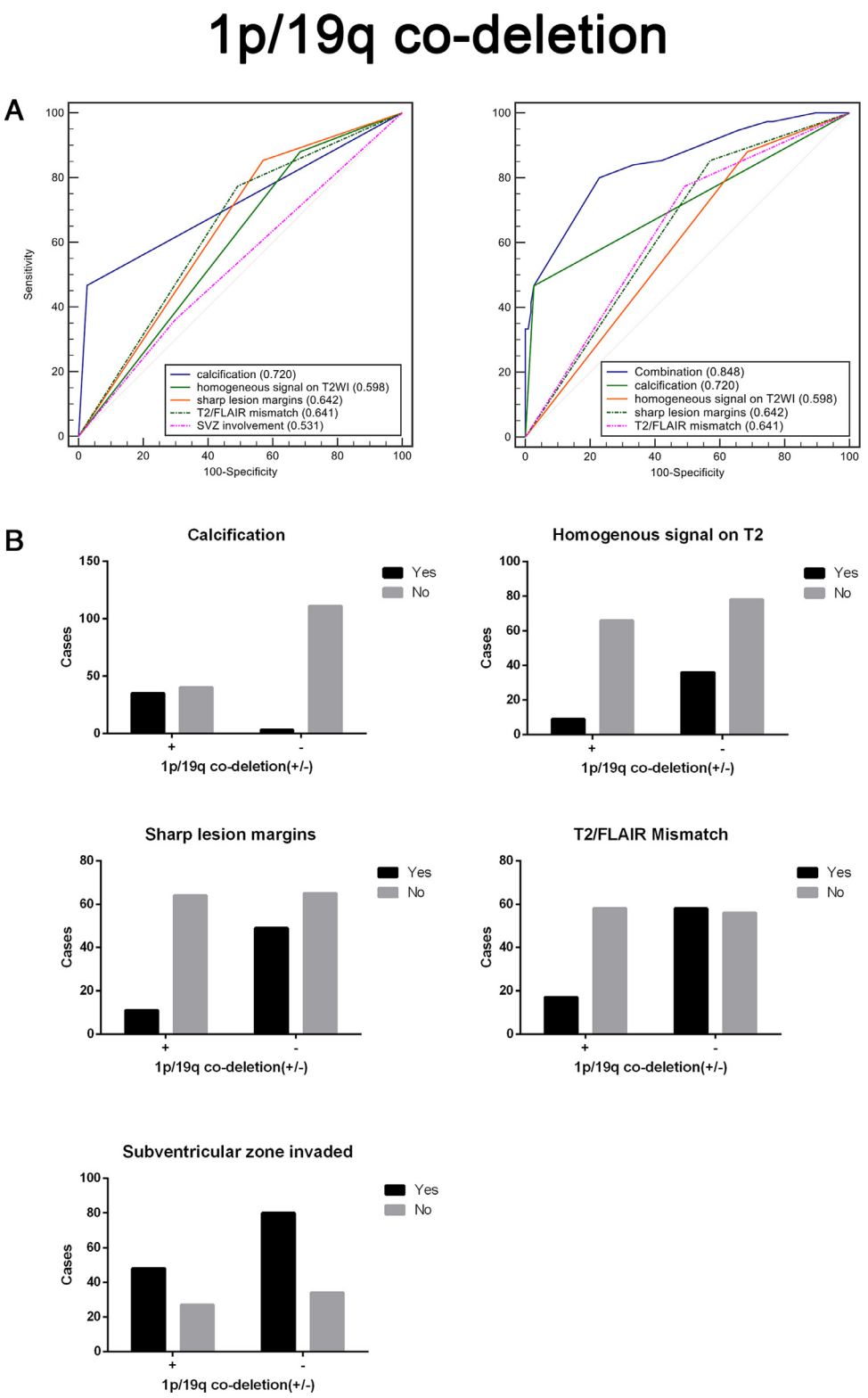

Figure 2. Calcification, sharp lesion margins, T2/FLAIR mismatches, homogenous signals on T2WI, and SVZ involvement were associated with the 1p/19q co-deletion status. (a) ROC analysis indicated that 4 features showed diagnostic value with regard to the 1p/19q co-deletion in WHO grade II gliomas. The highest diagnostic efficiency was observed with combination parameters, including calcification, sharp lesion margins, T2/FLAIR mismatches, and homogenous signals on T2WI. (b) Bar graphs showed that calcification ($p < 0.001$), sharp lesion margins ($p = 0.010$), T2/FLAIR mismatches ($p = 0.001$), homogenous signal on T2WI ($p = 0.014$), and SVZ involvement ($p = 0.021$) displayed significant differences. Patients with a 1p/19q co-deletion had a higher calcification frequency (46.67% vs 2.6%) and lower homogenous signal frequency in T2WI (12.0% vs 31.6%), sharp lesion margins (14.7% vs 43.0%), T2/FLAIR mismatch signs (22.7% vs 50.9%), and subventricular zone involvement (64.0% vs 15.8%). FLAIR, fluid attenuated inversion recovery; ROC, receiver operating characteristic; SVZ, subventricular zone.

co-deletion status, based on our results, and had the ability to distinguish between oligodendrogliomas, IDH1-mutations, and 1p/19q co-deletions. The presence of these features suggests a higher possibility of development of 1p/19q non-codeletion gliomas. In previous studies, the characteristics of tumor borders were assessed using T1WI and T2WI. These studies showed that sharp borders could be observed only on T1WI, but not on T2WI (24,26); such findings were inconsistent with our results. Patients with 1p/19q non-codeletion tumors had significantly higher frequencies of homogeneous signals (31.6% vs 12.0%), sharp lesion margins on T2WI (43.0% vs 14.7%), and T2/FLAIR mismatches (50.9% vs 22.7%), as compared to patients with 1p/19q co-deletion tumors. Signs of a T2/FLAIR mismatch indicated that 1p/19q non-codeletion tumors had higher levels of free water in the tumor mass. Previous histopathological studies reported that astrocytoma cells appeared as hypercellular areas of neoplastic cells with irregular, elongated hyperchromatic nuclei and a high degree of fibrillary, while oligodendroglioma cells exhibited a swollen cytoplasm, indicating that the level of intracellular water retention was higher (41–43). A greater amount of free water in the intracellular spaces of tumor tissues might result in a higher T2 signal, and hence obscure signals from tumor cells, leading to a homogeneous signal. This would make tumors appear bulky and indicate peritumoral tissue compression. The sharp lesion margins on T2WI might present as a potential boundary between free water in the tumor area and surrounding tissues, and are less likely to infiltrate tumor cells.

There are few reports regarding the involvement of SVZ in WHO II grade gliomas. Several studies have discussed the relationship between SVZ involvement and LGGs; however, these studies had small sample cohorts, and were therefore, hardly representative (44,45). However, studies on the relationship between SVZ involvement and survival, which included patients with high grade gliomas, demonstrated that SVZ involvement resulted in predictions of poorer clinical outcomes and prognosis (46,47). In this study, SVZ involvement had no significant diagnostic value; however, it was still associated with the 1p/19q co-deletion status in univariate and multivariate analysis. The 1p/19q non-codeletion tumors had a slightly higher SVZ involvement frequency (70.2% vs 64.0%). This might be one of the reasons why tumors exhibiting SVZ involvement result in worse prognosis.

The classification of patients with WHO grade II gliomas based on pathology and molecular features is important for improving prognosis. It can predict the survival rate and level of sensitivity toward treatment, thus impacting strategies selected for surgery and RT. Although the guidelines for CNS tumor recommend maximal safe resection of LGG, some recent studies, especially after The 2016 WHO classification of tumors of the central nervous system published, reported results worth discussing. The reliable evidences suggest that the benefit of maximal resection may be attenuated in patients with chemosensitive tumor, such as primary CNS lymphoma. Unlike the astrocytoma and glioblastoma patients, oligodendroglioma (IDH1 mutations, and 1p/19q co-deletions) patients didn't achieve the improved OS with subtotal resection, compared to biopsy-only watchful-waiting (48). The postoperative residual tumor volume of oligodendroglioma patients would affect OS when it exceeded 8 cm^3, while only 1 cm^3 residuals would impact OS in astrocytomas (49). Despite some studies showed even the gross-total resection was not associated with improved OS in oligodendroglioma patients (50), maximal safe resection of low grade glioma is still the most recommended (51). Since the surgical strategy in oligodendroglioma remains controversial, individualized surgery may prolong the OS with appropriate resection range, which would maintain corresponding neurological function. Gross-total resection is a better option when maximal safe resection is feasible. But we should perform subtotal resection surgery for oligodendrogliomas who cannot suffer safe gross total resection carefully. The predictive methods of present study give us more choices when facing LGG patients.

Nowadays, it is difficult to implement the classification method for patients undergoing a preliminary surgery, because of the delay in obtaining genetic test results. Because the initial surgery performed on patients with WHO II gliomas plays a vital role throughout the entire treatment process, presurgical molecular features are more favored during decision making. The analysis of presurgical images is the most effective method used by neurosurgeons to determine glioma treatment strategies. Despite the advancement in MRI and PET-CT/MR research, the conventional MRI is still the most convenient and widely used analysis method in most medical institutions. In the present study, we demonstrated that the conventional MRI, the equipment for which is available in almost every hospital, could be used as an effective technique for predicting the gene mutational status, and assist neurosurgeons in the formulation of the most appropriate surgical plan, especially when the advanced methods are unavailable because of expensive or technic reasons.

This study has two major limitations. First, patient survival was not assessed, because patients with low grade gliomas have a longer OS timespan, and our follow-up period was limited in this study. Second, our patient cohort was small. Third, this was a single center study, which might be affected by an inherent selection bias. Future studies should involve larger patient cohorts from multicenters and longer follow-up periods.

ETHICAL APPROVAL

All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all the individuals who participated in the study.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.acra.2020.03.008.