Original paper

Can oligodendrocyte transcriptional factor-2 (Olig2) be used as an alternative for 1p/19q co-deletions to distinguish oligodendrogliomas from other glial neoplasms?

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Abstract

Aim of the study: *Oligodendrocyte transcriptional factor-2 (Olig2) is an essential marker for oligodendrocytes expression. We aimed to explore the expression of Olig2 in different glial neoplasms and to investigate if diffuse Olig2 expression can replace 1p19q co-deletion for the diagnosis of oligodendroglioma.*
Material and methods: *Olig2 was performed on 53 samples of different glial neoplasms using immunohistochemistry (IHC). 1p/19q deletions were investigated using fluorescence in situ hybridization (FISH).*
Results: *Olig2 labelling of different glial neoplasms revealed various expressions, in which 26 tumours showed diffuse expression (≥ 60%) and 23 tumours showed partial focal expression (< 50%). Four tumours showed no expression. Of the 26 tumours, 6 oligodendrogliomas had 1p19q co-deletion and the remaining 3 oligodendrogliomas showed no co-deletion. Three non-oligodendroglial tumours were found to have 19q deletion. The FISH of the remaining tumours (14/26) showed no aberrations. There was no significant difference in the final diagnosis by using 1p19q co-deletion test among glial neoplasms with diffuse Olig2 expression (p = 0.248).*
Conclusions: *Olig2 marker cannot be used as an alternative diagnostic method for 1p19q co-deletion to distinguish oligodendrogliomas from other glial neoplasms. Although some glial tumours showed diffuse Olig2 expression, 1p19q co-deletion testing is the best diagnostic method.*

Key words: gliomas, oligodendroglioma, Olig2, FISH, 1p19q co-deletion.

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Introduction

The most common primary brain tumours are those with a glial cell origin, which cannot be fully classified by cellular morphology only [12]. The molecular analysis became crucial for glioma differentiation, grading and prognosis. Loss of heterozygosity (*LOH*) at specific chromosomes is critical for tumorigenesis and possible transformation of low-grade gliomas to higher grade gliomas [10]. One of these common genetic biomarkers is 1p19q co-deletion. This genetic alteration results from the combined deletion of entire 1p19q after unbalanced translocation between chromosomes 1 and 19 [t(1:19)(q10;p10)] [8]. Although there are currently no available molecular markers that reliably distinguish oligodendroglial tumours from astrocytomas, 1p19 co-deletion has been considered as one of the hallmark criteria for the diagnosis of oligodendroglioma, based on the 2016 World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) [1,8,10]. Hence, recent clinical trials have approved the associations between 1p19q co-deletion and prolonged overall survival of patients treated with radiation with or without chemotherapy [3,4]. One of the limitations of FISH technique is that it can detect deletions at a particular locus but cannot assess the extent of these deletions (partial or full arm). This alteration recently was found in association with Isocitrate dehydrogenase-1 (*IDH1*) mutation; a common criterion to diagnose oligodendroglioma. However, *IDH1* mutation can be seen in other subsets of astrocytomas [17].

Although partial loss of one or other chromosomes have been described in astrocytomas, such as *LOH* on 19q for anaplastic astrocytoma and secondary glioblastoma, the co-deletion has also been reported in some cases of astrocytoma [14,15]. Around 4-12% of primary glioblastomas were also proven to have 1p19q co-deletion [17]. Kaneshiro *et al.* found that 3% of 337 glioblastomas demonstrated evidence for 1p19q co-deletion [9]. This finding has never been discussed further in the literature. These tumours were astrocytic in nature and have shown features of classical glioblastoma [9]. It was unclear if those cases were primary glioblastoma or secondary glioblastoma upgraded from anaplastic oligodendroglioma. Another study done by Sim *et al.*, who evaluated 80 glioblastomas, has explored 1p/19q co-deletion in only two tumours [16]. Despite these findings, FISH for 1p/19q co-deletions remains a widely employed methodology to evaluate gliomas with oligodendroglial components.

The association of brain gliomas with 1p19q co-deletion and Olig2 expression has never been explored. Olig2, a member of the group of basic helix-loop-helix transcription factors, is essential for the development of neural progenitors and oligodendrocytes [12]. Several studies have detected prominent Olig2 expression in oligodendrogliomas and oligoastrocytomas [2,5-7,11,13]. Many neuropathologists use Olig2 marker as a diagnostic tool to diagnose oligodendroglial neoplasms (oligodendroglioma and oligoastrocytoma) when Olig2 is diffusely expressed in the tumours. However, this association is not proven yet and requires further investigations.

Lu *et al.* found that Olig2 was expressed in oligodendroglial tumours more than in astrocytic tumours [11]. Nevertheless, Olig2 cannot be used as a distinguishing marker between oligodendroglioma and astrocytic neoplasms. The expression of Olig2 was proven to be weak in many glioblastomas except glioblastoma cases with oligodendroglial component (GBMO), which have shown prominent Olig2 expression in only oligodendroglial foci [7]. This also has been found in pilocytic astrocytoma cases where oligo nodules are seen [5]. Moreover, Olig2 expression is not merely restricted to oligodendroglial areas as it was typically expressed in some grade II astrocytomas.

In this study, we aim to explore the relationship between Olig2 expression and 1p19q deletion in different glial neoplasms and also to investigate if diffuse Olig2 expression can replace 1p19q co-deletion for the diagnosis of oligodendroglioma.

Material and methods
Patients selection

This study included 53 patients with different types of glial neoplasms from one medical institution in Saudi Arabia. The cases were diagnosed after complete surgical resection or tumour biopsy. The study was ethically approved by the National Biomedical Ethics Committee at King Abdulaziz University (HA-02-J-008) under general ethical approval. The clinical data retrieved from the hospital records included age, gender, tumour type and location, and recurrence interval (Table I). The histological diagnosis was made based on classification of the 2016 WHO [10].

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Table I. Demographic data of the 53 patients enrolled in this study. 26 cases were identified to have diffuse Olig2 expression through immunohistochemistry IHC

Demographic data	Total cases (N = 53)	Cases with 1p19q (n = 26)
Age		
Mean (SD)	28.8 (22.9)	36.1 (20.8)
Gender, n (%)		
Female	21 (39.6)	12 (46.2)
Male	32 (60.4)	14 (53.8)
Tumour location, n (%)		
Frontal	13 (24.5)	12 (46.2)
Parietal	10 (18.9)	6 (23.1)
Temporal	10 (18.9)	6 (23.1)
Occipital	2 (3.8)	1 (3.8)
Lateral ventricle	1 (1.9)	0 (0.0)
Posterior fossa	15 (28.3)	3 (11.5)
Brainstem	1 (1.9)	0 (0.0)
Thalamic	1 (1.9)	0 (0.0)
Histopathological diagnosis, n (%)		
Pilocytic astrocytoma	3 (5.7)	2 (7.7)
Pleomorphic xanthoastrocytoma	2 (3.8)	2 (7.7)
Diffuse astrocytoma	5 (9.4)	1 (3.8)
Oligodendroglioma	9 (17.0)	9 (34.6)
Oligoastrocytoma	1 (1.9)	1 (3.8)
Anaplastic astrocytoma	5 (9.4)	5 (19.2)
Glioblastoma	11 (18.9)	6 (23.1)
Ependymoma	17 (32.1)	0 (0.0)
Olig2 Labelling Index, n (%)		
Diffuse expression	26 (49.1)	26 (100)
Partial expression	12 (22.6)	
Focal expression	11 (20.8)	
No expression	4 (7.5)	

The staining pattern was categorized as (i) diffusely expressed, (ii) partially expressed, (iii) focally expressed, and (iv) not expressed (Fig. 1A-C, 2A-D) based on the following scoring system:

Expression	Labelling index (%)*
No expression	0
Focal expression	> 0-19
Partial expression	> 19-59
Diffuse expression	≥ 60

*For statistical analysis, the scores were divided by 100.

Tumour samples

Archival formalin-fixed and paraffin-embedded (FFPE) tissue blocks of 53 tumours, diagnosed with different types of glial neoplasms, were utilized in this study. Haematoxylin and Eosin (H&E)-stained sections were re-examined by a certified neuropathologist (MK) to assure that the histopathological diagnosis has been made based on 2016 WHO classification of CNS tumours.

Methodology

Immunohistochemistry (IHC) for Olig2 and IDH1 antibodies

Protocol

4-μm FFPE tissue sections were used in the IHC process. The IHC assay was performed on two types of antibodies (a) anti-$IDH1^{R132H}$ (clone: H09, rabbit monoclonal antibody, Dianova) and (b) anti-Olig2 (EPR2673, rabbit monoclonal antibody, Cat#ab109186, Abcam). The procedure was performed with the ultraView DAB detection Kit on a BenchMark XT automated stainer from Ventana (Tucson, AZ, USA). A protocol was established so that the entire assay procedure consisted of deparaffinization with EZ Prep at 75°C, heat pre-treatment in Cell Conditioning medium (Ag unmasking) (CC1; Ventana) for 60 min and then primary incubation for 16 min at 37°C. The antibodies were optimized using different dilutions, range of 1 : 100-1 : 300. The slides were counterstained with Haematoxylin II for 16 minutes and bluing reagent was used for 16 min. After that, the slides were removed from the slide stainer and then immersed into successive alcohol buffers at different concentrations for 3 min.

Assessment

For Olig2, nuclear and perinuclear staining of tumour cells was considered a positive expression. After immunostaining, a single focal area of positive expression per patient sample was evaluated under light microscopy using high-power (40×) magnification. The positively stained cells and total cells, including positively and negatively stained cells, were counted manually using labelling index based on the following equation:

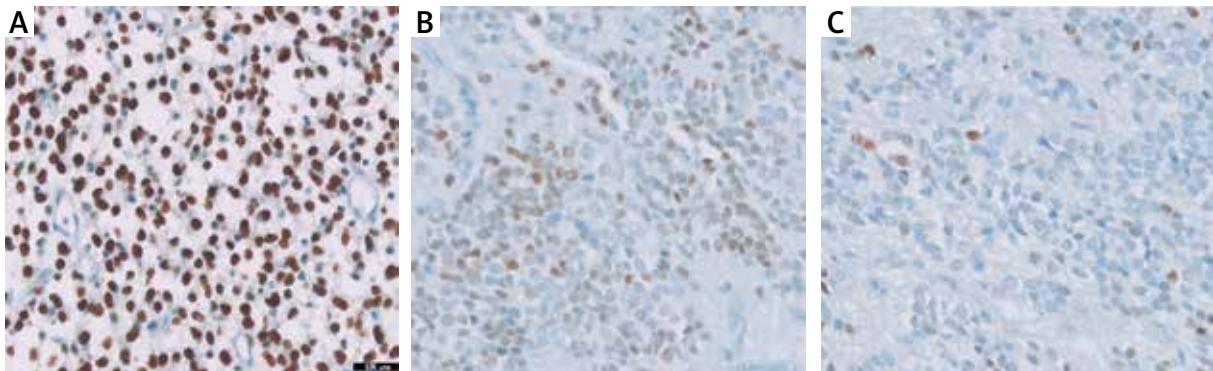Labelling index (%) = [(Olig2$^+$ stained tumour cells)/(total cells) × 100].

Fig. 1. Olig2 expression using immunohistochemistry (IHC). **A**) Diffuse expression, **B**) partial expression, **C**) focal expression. Magnification 40×.
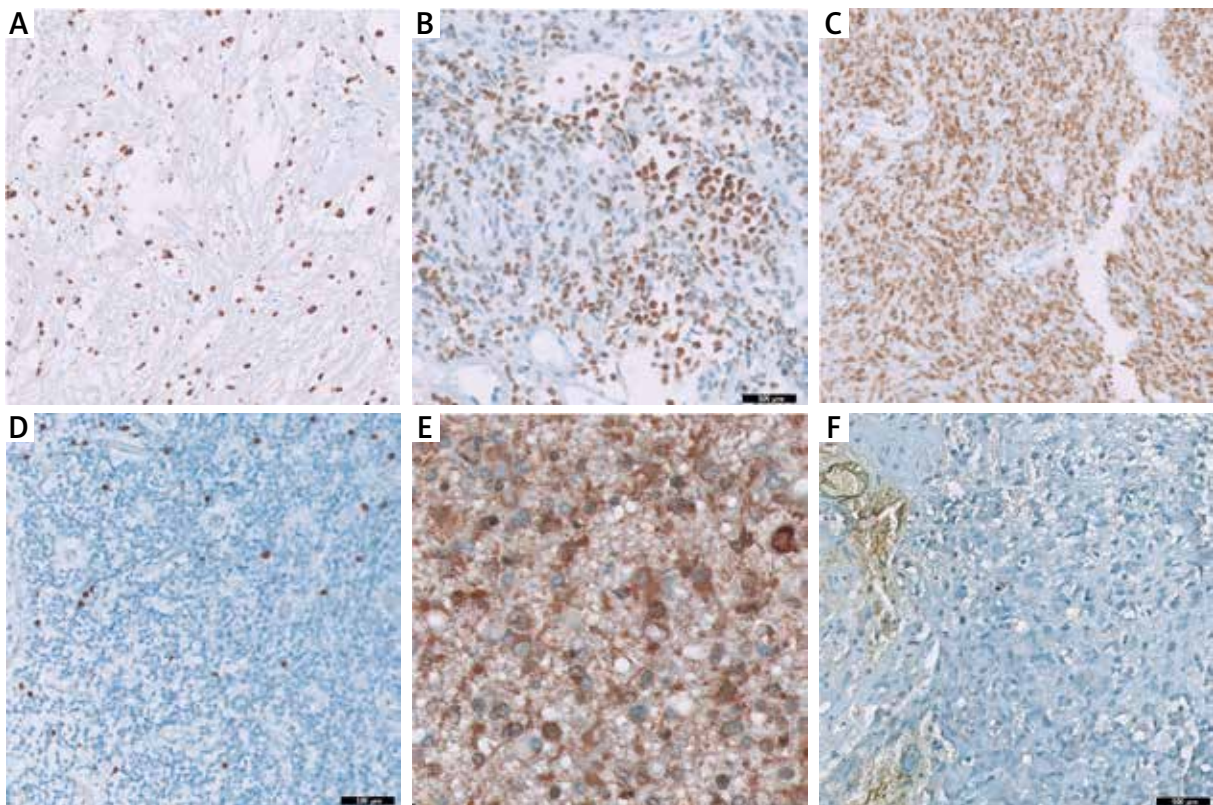

Fig. 2. Olig2 expression and *IDH1* mutation in different types of gliomas. **A**) Partial Olig2 expression in pilocytic astrocytoma, **B**) diffuse Olig2 expression in glioblastoma, **C**) diffuse Olig2 expression in pleomorphic xanthoastrocytoma, **D**) focal Olig2 expression in glioblastoma, **E**) $IDH1^{mutant}$ glioblastoma, **F**) $IDH1^{wildtype}$ glioblastoma. Magnification 40×.

Tumour cases ($n = 26$) with diffuse Olig2 expression have been tested for $IDH1^{R132H}$ mutation. Sections in which > 10% of glial tumour cells positively stained were defined as $IDH1^{mutant}$ (Fig. 2E, F).

Fluorescent *in situ* hybridization (FISH) technique

Fluorescent *in situ* hybridization (FISH) was used for the detection of deletions involving the human chromosomal region 1p36 as well as chromosomal

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region 19q13 on FFPE tissue slides of the 26 tumour cases that showed diffuse expression by Olig2.

Protocol

A 5-µm-thick FFPE tissue on positive charge slides was deparaffinised according to the instructions of the ZytoLight FISH-Tissue Implementation Kit (Zyto-Vision, Bremerhaven, Germany). This process was followed with digestion by pepsin to allow for probe hybridization. Then DNA was denatured by heating and the hybridization was performed using 10 µl of the probe onto each pretreated specimen. The used probe (ZytoLight SPEC 19q13/19p13 Dual Color Probe) appears with orange signals at 1p36 loci and the control locus 1q25 appears with red signals, the other probe target 19q13 locus with orange signals and the control locus 19p133 appears green. Target DNA and probes were codenatured at 74°C for 5 minutes and incubated at 37°C overnight in a humidified hybridization chamber (ThermoBrite, Abbott Molecu-

lar Inc.). Post-hybridization washing was performed to remove excess unbound probes. At the end, the slides were counterstained with DAPI (4',6-diamidi-no-2-phenylindole) for cellular visualization.

Assessment

Enumeration of 1p/19q signals was conducted by two technologists independently. Scoring of 100 non-overlapping nuclei within the target areas (100 total tumour cell nuclei) for each probe set was performed using a Metasystem station (Zeiss MetaSystems, Thornwood, NY, USA) equipped with an appropriate excitation emission filter. Results were reported as the ratio of the total number of orange signals to green signals for each probe set (1p36:1q25 and 19q13.3:19p13 signals) (Fig. 3).

Statistical methods

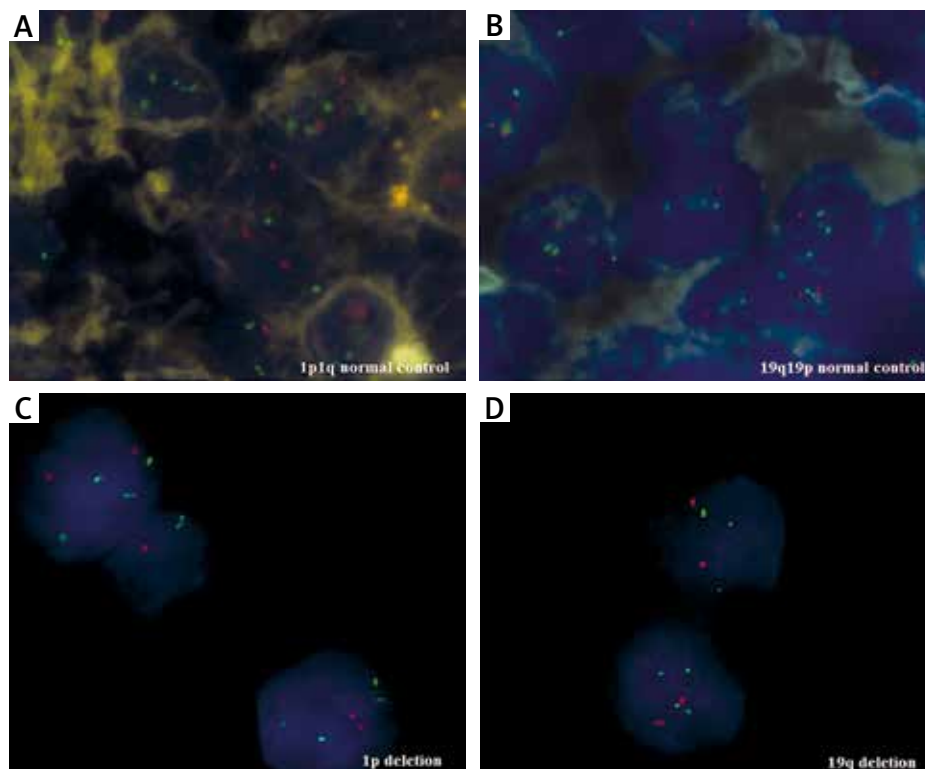Data are described as frequencies and percentages. Chi-square and Fisher's exact were used to

Fig. 3. FISH for 1p and 19q deletion using two probes in two different slides and normal control. The used probe (ZytoLight SPEC 19q13/19p13 Dual Color Probe) appears with orange signals at 1p36 loci and the control locus 1q25 appears with red signals, the other probe target 19q13 locus with orange signals and the control locus 19p133 appears green. "Green" signal is normal and "Red" signal is abnormal. **A)** 1p1q normal control, **B)** 19q19p normal control, **C)** 1p deletion, **D)** 19q deletion.

Table II. Demographic information of the 26 patients who showed diffuse Olig2 expression ≥ 60%. The differentiation includes histogenesis, IDH1 mutation, and 1p19q fluorescence *in situ* hybridization (FISH) testing

Histopathological diagnosis	Grading	Olig2 LI (%)	IDH1 status	FISH
Oligoastrocytoma	Grade III	99	IDH-wildtype	19q deletion
Pleomorphic xanthoastrocytoma	Grade II	97	IDH-wildtype	Intact
Glioblastoma	Grade IV	96	IDH-mutant	Intact
Anaplastic astrocytoma	Grade III	94	IDH-wildtype	19q deletion
Oligodendroglioma	Grade III	94	IDH-mutant	1p19q co-deletion
Oligodendroglioma	Grade III	93	IDH-mutant	1p19q co-deletion
Glioblastoma	Grade IV	93	IDH-mutant	Intact
Glioblastoma	Grade IV	92	IDH-wildtype	Intact
Glioblastoma	Grade IV	92	IDH-wildtype	Intact
Oligodendroglioma	Grade III	91	IDH-mutant	1p19q co-deletion
Oligodendroglioma	Grade III	90	IDH-mutant	Intact
Oligodendroglioma	Grade III	90	IDH-mutant	1p19q co-deletion
Diffuse astrocytoma	Grade II	87	IDH-mutant	Intact
Anaplastic astrocytoma	Grade III	86	IDH-wildtype	Intact
Pilocytic astrocytoma	Grade I	85	IDH-wildtype	Intact
Anaplastic astrocytoma	Grade II	83	IDH-mutant	19q deletion
Oligodendroglioma	Grade III	83	IDH-mutant	Intact
Anaplastic astrocytoma	Grade III	81	IDH-mutant	Intact
Pleomorphic Xanthoastrocytoma	Grade III	80	IDH-wildtype	Intact
Anaplastic astrocytoma	Grade III	80	IDH-wildtype	Intact
Glioblastoma	Grade IV	79	IDH-wildtype	Intact
Pilocytic astrocytoma	Grade I	77	IDH-wildtype	Intact
Oligodendroglioma	Grade I	65	IDH-mutant	1p19q co-deletion
Glioblastoma	Grade IV	63	IDH-mutant	Intact
Oligodendroglioma	Grade III	63	IDH-mutant	1p19q co-deletion
Oligodendroglioma	Grade III	60	IDH-mutant	Intact

LI – labelling index, FISH – fluorescence in situ hybridization

explore the association of between *IDH1* mutation and the type of glial neoplasms. The McNemar χ^2 test was used to explore the diagnostic accuracy between oligodendroglial and non-oligodendroglial neoplasms using FISH technique or IHC. All statistical analyses were performed using the IBM SPSS1 ver. 24 statistical software programs (SPSS Inc., Chicago, IL, USA).

Results

This study included 53 patients diagnosed with different types of glial neoplasms (oligodendroglial and non-oligodendroglial tumours). The mean age was 28 years; 32 males (60.4%) and 21 females (39.6%). Patients aged less than 18 years were 19 cases. The type of glial neoplasms and their locations are summarized in Table I. Olig2 immuno-

Table III. Fluorescence *in situ* hybridization (FISH) testing for the 26 tumour cases that showed diffuse Olig2 expression

	1p19q cases (*n* = 26)
FISH result	
No deletion	17 (65.4%)
19q deletion	3 (11.5%)
1p19q co-deletion	6 (23.1%)
1p19q Co-deletion	
No	20 (76.9%)
Yes	6 (23.1%)

labelling of different glial neoplasms have revealed various staining expressions, in which 26 tumours have shown diffuse Olig2 expression (≥ 60%) while 23 tumours have shown partial or focal expression (< 50%). Four tumours have shown no Olig2 expres-

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Table IV. Relationship between glial neoplasms and 1p19q co-deletion in tumours with diffuse Olig2 expression (≥ 60%)

FISH result	Tumour with diffuse Olig2 expression ≥ 60%		Total	p-value
	Oligodendroglioma	Non-oligodendroglioma		
1p19q codeletion	6	0	6	0.248*
No 1p19q codeletion	3	17	20	
Total	9	17	26	

McNemar χ² test with continuity correction

Table V. IDH1 mutation in glial neoplasm with diffuse Olig2 expression (≥ 60%)

IDH status	Oligodendroglioma	Non-oligodendroglioma	Total	p-value[a]
IDH1mutant	6 (100.0)	9 (45.0)	15 (57.7)	0.065
IDH1wildtype	0 (0.0)	11 (55.0)	11 (42.3)	

[a] Fisher's exact test

Table VI. The diagnostic accuracy of FISH 1p19q co-deletion superior to diffuse Olig2 expression (≥ 60%) in the diagnosis of oligodendroglioma

Diagnostic decision	95% Confidence interval		
	Estimate (%)	Lower (%)	Upper (%)
True prevalence	23.1	9.0	43.6
Test sensitivity	100.0	54.1	100.0
Test specificity	85.0	62.1	96.8
Diagnostic accuracy	88.5	69.8	97.6
Positive predictive value	66.7	29.9	92.5
Negative predictive value	100.0	80.5	100
Proportion of false positives	15.0	3.2	37.9
Proportion of false negative	0.0	0.0	45.9

sion (Table I). Tumours that showed diffuse Olig2 expression of ≥ 60% were tested for *IDH1* mutation and 1p19q co-deletion using FISH (Tables II, III).

Of the 26 tumours, 6 oligodendrogliomas had 1p19q co-deletion and the remaining three oligodendrogliomas showed unremarkable FISH results (Table II). However, all the 9 cases of oligodendrogliomas were IDH1^mutant. Additionally, 3 tumours were found to have 19q deletion: 2 anaplastic astrocytomas and 1 oligoastrocytoma. The FISH of the remaining tumours (14/26) did not detect any chromosomal deletion or gain (Tables II, III). There was no significant difference in the final diagnosis among glial neoplasms with diffuse Olig2 expression by using FISH 1p19q co-deletion test (*p* = 0.248) (Table IV). It clarifies that diffuse expression of Olig2 cannot be solely used to distinguish oligodendroglioma from other glial neoplasms. Furthermore, *IDH1* mutation cannot be also used as an additional marker to Olig2 expression to diagnose oligodendroglial neoplasms without 1p19q co-de-

letion (Table V). FISH for 1p19q co-deletion has revealed 100% diagnostic sensitivity, 85% specificity and 88.5% accuracy (Table VI).

Discussion

Since Olig2 is an essential marker for the development of neuronal progenitor, it is used to express oligodendrocytes in CNS. It has also been used for a long time as a marker to distinguish oligodendroglioma from astrocytoma. This diagnostic method is currently proven wrong. Several studies found that Olig2 is highly expressed in different types of glial neoplasms such as glioblastomas and astrocytomas [6]. Around 4-12% of glioblastomas were also proven to have 1p19q co-deletion [17]. A study done by Mizoguchi *et al*. detected rare cases of glioblastoma with 1p19q co-deletion and high Olig2 expression [13]. Although 1p19q co-deletion is the most common genetic alteration found in oligodendrogliomas, its association with *IDH1* mutation was commonly

explored. This association has never been correlated with Olig2 expression in different glial neoplasms.

Less than 50% of Olig2 expression in glial neoplasms are considered normal as the oligodendrocytes distribute normally in the neuropil and they may infiltrate into the tumours. Glial tumours with ≥ 60% Olig2 expression warrant what type of cellular lineage the tumour may have. Currently, some neuropathologists use Olig2 as a biomarker to distinguish oligodendroglioma from other glial tumours. In our study, we have proven this diagnostic manner was wrong. We found that there was no significant difference in the final diagnosis among all glial neoplasms with diffuse Olig2 expression (≥ 60%) by using FISH test. This clarifies that diffuse Olig2 expression is not an optimum and standard method to distinguish oligodendroglioma from other tumours. However, FISH for 1p19q co-deletion remains the best diagnostic test for oligodendroglioma, regardless of Olig2 expression as it has shown 88.5% diagnostic accuracy. Although FISH can detect other chromosomal deletions at a particular locus it cannot assess the extent of these deletions (partial or full arm). In contrast, FISH can detect partial 1p and/or 19q LOH that are commonly found in astrocytic tumours.

Some glioblastomas have also demonstrated evidence for 1p19q co-deletion [9,16]. It was unclear if those cases were primary glioblastomas or secondary glioblastomas upgraded from anaplastic oligodendrogliomas. The expression of Olig2 was proven to be weak in these cases except glioblastomas with oligodendroglial component (GBMO), which showed prominent Olig2 expression in only oligodendroglial foci [5,7]. Despite these findings, FISH for 1p19q co-deletions remains a widely employed methodology in evaluating gliomas with oligodendroglial components. In our study, in 26 out of 34 tumours that showed diffuse Olig2 expression, the 1p19q co-deletion was only found in oligodendrogliomas. The remaining cases were not distinguished by using Olig2 expression.

Conclusions

Olig2 marker cannot be used as an alternative diagnostic method for 1p19q co-deletion to distinguish oligodendrogliomas from other glial neoplasms. Although some glial tumours have shown diffuse Olig2 expression, 1p19q co-deletion testing is crucial. Furthermore, *IDH1* mutation is considered as an additional marker of 1p19q co-deletion to support the diagnosis of oligodendroglioma.

Funding

Ethics approval

The study was ethically approved by the National Biomedical Ethics Committee at King Abdulaziz University (HA-02-J-008) under general ethical approval.

Availability of data and material

The data that support the findings of this study are available from the corresponding author (MK) upon request.

Disclosure

The authors report no conflict of interest.

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