Gliomas are the primary tumors that develop in the central nervous system (CNS). Diffuse glioma is defined by indefinite border of tumor mass and is considered as a more aggressive form of gliomas. Diagnosis of glioma was mainly based on the 2007 World Health Organization (WHO) classification, which considered increased cellularity, nuclear atypia, mitotic activity, microvascular proliferation, and necrosis for malignant criteria (histologic grade of gliomas). Histological evaluation for grading is important for the treatment of diffuse gliomas; however, histologic grade is not the only prognostic determinant in diffuse gliomas. The chromosomal aberrations such as deletion and mutation are common in gliomas, and oligodendrogial phenotype gliomas with 1p/19q co-deletion tend to have a better prognosis and respond well to chemotherapy and concurrent chemoradiation therapy. Moreover, gliomas with IDH1 mutation have more favorable prognosis than IDH-wildtype gliomas.

Therefore, at the Haarlem meeting in 2014, multidisciplinary specialists concluded that molecular information should be incorporated into the diagnosis of gliomas to make more integrated diagnosis. The updated 2016 WHO classification of CNS tumors incorporated molecular features such as IDH mutation and chromosome 1p/19q co-deletion into the diagnosis of gliomas. Previous classification published in 2007 was mainly based on the histological and immunohistochemical features of the tumor. The new 2016 WHO CNS tumor classification led to substantial changes in diagnosis of both oligodendrogial and astrocytic entities. We have confirmed that the revised 2016 WHO CNS tumor classification has prognostic significance in Mongolian patients with diffuse gliomas, especially those with grade II tumors.
changes in the diagnosis of diffuse gliomas depending on the presence or absence of IDH1 mutation and 1p/19q co-deletion.5,9 Diffuse glioma with both IDH mutation and 1p/19q co-deletion is referred to as oligodendroglioma-like histology, which has a better prognosis compared with intact glioma tissue.10 Although a glioma shows oligodendroglioma-like histologic feature, it is no longer classified as an oligodendroglioma tumor if neither IDH mutation nor 1p/19q co-deletion is present. Diffuse astrocytic gliomas are classified as an IDH-mutant or IDH-wildtype according to the IDH mutation status. IDH-wildtype gliomas with epidermal growth factor receptor (EGFR) amplification are considered to have more aggressive behavior like glioblastoma.11 Diffuse astrocytoma or oligodendroglioma, which has been diagnosed based on histologic features only without molecular testing, is classified into the “NOS (not otherwise specified)” category.11,12 cIMPACT clarified the use of the term NOS and proposed the use of an additional term “NEC (not elsewhere classified)” as well.13 For an NOS designation, diagnostic information (histological or molecular) necessary to assign more specific WHO diagnosis is not available. For an NEC designation, necessary diagnostic testing has been successfully performed, but the results do not readily allow for a WHO 2016 diagnosis. In some instances, this will be caused by a mismatch between clinical, histological, immunohistological and/or genetic features; in others, the results may support a new or emerging entity that is not yet included in the WHO classification.13

In this study, we aimed to reclassify diffuse brain gliomas according to the revised 2016 WHO classification of CNS tumors in Mongolian patients with brain gliomas and to evaluate the prognostic significance of the revised 2016 WHO classification of CNS tumors.

**MATERIALS AND METHODS**

**Tumor samples**

Data of 124 patients who have been diagnosed with diffuse gliomas according to the WHO 2007 criteria in the National Center for Pathology of Mongolia between January 2006 and December 2017 were obtained in this study. We marked the representative tumor areas on hematoxylin and eosin (H&E)–stained sections. Tumor areas containing viable tumor cell infiltration over 60% without necrosis or hemorrhage were selected. Corresponding areas were identified on the formalin-fixed, paraffin-embedded archival blocks, and we constructed tissue microarray (TMA) blocks using 3-mm cores. Each TMA block was verified by H&E staining to determine whether each core has intact glioma tissue.

**IDH mutation status**

In immunohistochemistry, 4-μm-thick tissue sections were deparaffinized in xylene and hydrated by immersing them in a series of graded ethanol. Antigen retrieval was performed in the microwave by placing the sections in epitope retrieval solution (0.01 M citrate buffer, pH 6.0) for 20 minutes; endogenous peroxidase was inhibited by immersing the sections in 0.3% hydrogen peroxide for 10 minutes. Sections were then incubated with IDH1 (1:100, Dianova, Hamburg, Germany) antibody. Then, an OptiView DAB IHC Detection Kit (Ventana Medical Systems, Tucson, AZ, USA) was used following the manufacturer’s recommendations in conjunction with an automated staining procedure using Benchmark XT (Ventana Medical Systems). Finally, the samples were counterstained with hematoxylin, dehydrated, mounted, and evaluated under a light microscope equipped with an Olympus CX21 camera (Tokyo, Japan) (Fig. 1).

**Fluorescence in situ hybridization**

Fluorescence in situ hybridization (FISH) with Vysis probes was used to assess 1p/19q status. TMA sections were deparaffinized with xylene, incubated with 0.3% pepsin in 10 mM HCl at 37°C for 10 minutes, and then denatured at 85°C for 10 minutes. FISH analyses were performed on deparaffinized sections with a dual-color approach for chromosomes 1 and 19, respectively. Target probes were hybridized to subtelomeric 1p36 and 19q13 in combination with control probes on 1q25 and 19p13, respectively. For evaluation, the signal ratio in 50–100 adjacent, non-overlapping interphase nuclei was assessed, and the results were expressed as percentage (Fig. 2).

**Statistical analysis**

Continuous data were presented as the mean ± standard deviation, while categorical data were presented as frequencies and percentages. Continuous variables that were not normally distributed (as evaluated by Kolmogorov-Smirnov tests) were presented as medians and 25th and 75th percentiles. Differences in baseline characteristics were estimated using the chi-square test. Overall survival (OS) was defined as the time from the date of surgery to death from any cause. The discriminative value of the 2007 and 2016 WHO classifications were estimated using Cox
proportional hazard regression model for all-cause mortality. The Kaplan-Meier method was used to estimate survival distributions.

All statistical tests were two-sided, and a p-value of < .05 was considered significant. All statistical analyses were conducted using SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

**Ethics statement**

All procedures performed in the current study were approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1703/385-302) and Research Ethics Committee of the Mongolian National University of Medical Sciences (MNUMS) (2017/3-201702) in accordance with the 1964 Helsinki declaration and its later amendments. Formal
written informed consent was not required with a waiver by the Institutional Review Board of Seoul National University Bundang Hospital and Research Ethics Committee of the MNUMS.

RESULTS

Patient characteristics

Data of 124 patients diagnosed with diffuse brain glioma between January 2006 and December 2017 were collected (men, 48.4% and women, 51.6%). The median age at diagnosis was 41 years (interquartile range [IQR], 29 to 52), and the median follow-up period was 8 months (IQR, 4 to 15). Grade II, III, and IV tumors developed in 45.2% (n = 56), 26.6% (n = 33), and 28.2% (n = 35) of patients, respectively. Approximately 46.8% (n = 58) of patients underwent complete tumor resection, while 53.2% (n = 66) underwent partial tumor resection. According to the 2007 WHO classification, 23.4% (n = 29) of patients developed diffuse astrocytoma; 21% (n = 26), oligodendroglioma; 0.8% (n = 1), oligoastrocytoma; 13.7% (n = 17), anaplastic astrocytoma; 12.9% (n = 16), anaplastic oligodendroglioma; and 28.2% (n = 35), glioblastoma. Patients’ baseline characteristics are summarized in Table 1.

Molecular data and tumor reclassification according to the 2016 WHO classification

A total of 124 patients underwent FISH test; however, 32 patients, whose tissue samples were archived before 2012, showed no signal on FISH test. Therefore, 92 patients were analyzed for 1p/19q co-deletion by FISH. About 32 patients, with absence of signal on FISH test, were reclassified based on histological pattern and IDH1 mutation status only without 1p/19q co-deletion information. Immunohistochemical staining of IDH1 was performed on all 124 patients. 1p/19q co-deletion was detected in 13 of 92 patients (10.5%) who underwent FISH test, and IDH1 mutation was detected in 70 of 124 IDH1 immunostained patients (56.5%).

The molecular studies performed for reclassification have limitations in this study. The updated 2016 WHO classification of CNS tumors recommends full assessment of IDH mutation status (sequence analysis for IDH1 codon 132 and IDH2 codon 172) in cases of diffuse gliomas that are immunohistochemically negative for IDH1 R132H mutation. In the present study, IDH mutation status has been investigated only by immunohistochemistry, and no further molecular analysis for IDH mutation was performed. Therefore, we reclassified IDH1 immuno-negative diffuse gliomas as diffuse gliomas, IDH-wildtype, NOS. Among 32 cases which showed technical failure for FISH test, neither immunohistochemical expression of IDH1 nor morphological phenotype of oligodendroglioma was detected. Therefore, there was no case of oligodendroglioma/anaplastic oligodendroglioma, IDH-mutant, NOS.

According to the updated 2016 WHO classification, diffuse astrocytomas (n = 29) were reclassified into 18 diffuse astrocytomas IDHmut (IDH-mutant), nine diffuse astrocytomas IDHwt (IDH-wildtype), NOS, and two oligodendrogliomas IDHmut and 1p/19q co-deleted. Anaplastic astrocytomas (n = 17) were reclassified into eight anaplastic astrocytomas IDHmut, eight anaplastic astrocytomas IDHwt, NOS, and one anaplastic oligodendroglioma IDHmut and 1p/19q co-deleted. Glioblastomas (n = 35) were all reclassified into glioblastoma IDHwt, NOS. Oligodendrogliomas (n = 26) were reclassified into 16 diffuse astrocytomas IDHmut, eight oligodendrogliomas IDHmut and 1p/19q co-deleted, and two diffuse astrocytomas IDHwt, NOS. Anaplastic oligodendrogliomas (n = 16) were reclassified into 14 anaplastic astrocytomas IDHmut and two anaplastic oligodendrogli-
omas IDHmut and 1p/19q co-deleted. One case of mixed oligoastrocytoma was reclassified as diffuse astrocytoma IDHmut. The summary of integrated diagnosis is shown in Table 2 and Fig. 3.

Table 2. Summary of subgroups of diffuse gliomas according to updated 2016 WHO classification

| Histological diagnosis (WHO 2007) | Integrated diagnoses (WHO 2016) | No. |
|-----------------------------------|---------------------------------|-----|
| Diffuse astrocytoma (n = 29)      | Diffuse astrocytoma IDHmut      | 18  |
|                                   | Diffuse astrocytoma IDHwt, NOS  | 9   |
|                                   | Oligodendroglioma IDHmut, 1p/19q co-deleted | 2   |
| Anaplastic astrocytoma (n = 17)   | Anaplastic astrocytoma IDHmut   | 8   |
|                                   | Anaplastic astrocytoma IDHwt, NOS | 8   |
|                                   | Anaplastic oligodendroglioma IDHmut, 1p/19q co-deleted | 1   |
| Glioblastoma (n = 35)             | Glioblastoma IDHwt, NOS         | 35  |
| Oligodendroglioma (n = 26)        | Diffuse astrocytoma IDHmut      | 16  |
|                                   | Oligodendroglioma IDHmut, 1p/19q co-deleted | 8   |
|                                   | Diffuse astrocytoma IDHwt, NOS  | 2   |
| Anaplastic oligodendroglioma (n = 16) | Anaplastic astrocytoma IDHmut | 14  |
|                                   | Anaplastic oligodendroglioma IDHmut, 1p/19q co-deleted | 2   |
| Mixed oligoastrocytoma (n = 1)    | Diffuse astrocytoma IDHmut      | 1   |
| Total                             |                                 | 124 |

WHO, World Health Organization; IDHmut, isocitrate dehydrogenase mutant; IDHwt, NOS, isocitrate dehydrogenase wildtype, not otherwise specified.

Fig. 3. Change in diagnosis after applying molecular genetics integrated diagnostic criteria according to the updated 2016 WHO classification. WHO, World Health Organization; IDHmut, isocitrate dehydrogenase mutant; IDHwt, NOS, isocitrate dehydrogenase wildtype, not otherwise specified; 1p/19q codel, 1p/19q co-deleted.

There was a significant change in frequency of both oligodendrogial (34.7% to 10.5%) and astrocytic (37.1% to 60.7%) entities after reclassification according to the new 2016 WHO classification. The frequencies of 1p/19q co-deletion and IDH1 mutation were significantly higher in patients with low-grade tumors (grade II) than in patients with high-grade tumors (grades III and IV) (17.9% vs 4.4%, p < .05 for 1p/19q co-deletion and 80.4% vs 36.8%, p < .001 for IDH1 mutation). Notably, neither 1p/19q co-deletion nor IDH1 mutation was observed in patients with grade IV glioblastoma (Table 3).
The new 2016 WHO classification showed a statistically significant survival advantage for grade II tumors compared with the 2007 WHO classification (Fig. 4C, D). Based on the 2007 WHO classification, no survival difference was found between patients with grade II tumors including those with oligodendroglioma, diffuse astrocytoma, and oligoastrocytoma (p = .437). However, the new 2016 WHO classification showed that oligodendroglioma IDHmut and 1p/19q co-deleted had better survival compared with diffuse astrocytoma IDHwt, NOS in grade II tumors (p < .01). Both 2007 and 2016 WHO classifications did not show any survival difference in patients with grade III and grade IV tumors (p = .777 and p = .936, respectively) (Fig. 4E, F).

**DISCUSSION**

Our study results were summarized as follows: (1) the new 2016 WHO classification led to substantial changes in the diagnosis of diffuse gliomas, and (2) the new integrated histomolecular classification, based on molecular data, provided more valuable prognostic information.

Studies over the last two decades clearly demonstrated that the genetic basis of oncogenesis is important for the development of brain tumor entities and clarified their role in patients’ prognosis. Boulay et al.14 and Hata et al.15 reported chromosomal changes in human gliomas. Notably, Mizoguchi et al.16 investigated the role of 1p/19q co-deletion in patients with glioblastoma and its prognostic relation. Furthermore, several studies revealed the frequency of IDH1 mutation and its prognostic value in human gliomas.17-20 Based on these results, new integrated WHO CNS tumor classification was introduced to clinical practice in 2016; conceptual and practical advances were made over previous version.1 First, 2016 WHO classification is based on not only histological features but also genetic alterations of gliomas, such as 1p/19q co-deletion and IDH mutation, for diffuse brain glioma classification. Second, molecular pathologic tests are essen-

### Table 3. Comparison between 2007 and 2016 WHO classification of diffuse gliomas

| Original histological diagnosis according to WHO 2007 | WHO grade | No. (%) |
|----------------------------------------------------|-----------|---------|
| Astrocytic tumors                                  |           |         |
| Diffuse astrocytoma                                | II        | 29 (23.4)|
| Anaplastic astrocytoma                             | III       | 17 (13.7)|
| Glioblastoma                                       | IV        | 35 (28.2)|
| Oligodendrogliian tumors                           |           |         |
| Oligodendroglioma                                  | II        | 26 (21.0)|
| Anaplastic oligodendroglioma                       | III       | 16 (12.9)|
| Mixed oligoastrocytoma                            | II        | 1 (0.8) |
| Integrated diagnosis according to updated WHO 2016  |           |         |
| Diffuse astrocytoma IDHmut                         | II        | 35 (28.2)|
| Diffuse astrocytoma IDHwt+, NOS                    | II        | 11 (8.9) |
| Anaplastic astrocytoma IDHmut                       | III       | 22 (17.7)|
| Anaplastic astrocytoma IDHwt+, NOS                  | III       | 8 (6.5)  |
| Oligodendroglioma IDHmut+, 1p/19q co-deleted        | II        | 10 (8.1) |
| Anaplastic oligoastrocytoma IDHmut+, 1p/19q co-deleted| III       | 3 (2.4)  |
| Glioblastoma                                       | IV        | 35 (28.2)|

WHO, World Health Organization; IDHmut, isocitrate dehydrogenase mutant; IDHwt, NOS, isocitrate dehydrogenase wildtype, not otherwise specified.

### Table 4. Discriminative value of 2007 and 2016 WHO classification based on Cox proportional hazard regression for all-cause mortality

| WHO grade | HR 95% CI | p-value |
|-----------|-----------|---------|
| 2007 WHO classification | | |
| Oligodendroglioma | RF | |
| Diffuse astrocytoma | 0.60 | 0.27–1.37 | .227 |
| Mixed oligoastrocytoma | 1.30 | 0.17–9.96 | .802 |
| Anaplastic astrocytoma | 2.16 | 1.01–4.65 | .048 |
| Anaplastic oligodendroglioma | 2.42 | 1.12–6.22 | .025 |
| Glioblastoma | 2.67 | 1.36–5.24 | .004 |
| 2016 WHO classification | | |
| Oligodendroglioma IDHmut+, 1p/19q co-deleted | RF | |
| Diffuse astrocytoma IDHmut | 1.07 | 0.31–3.72 | .913 |
| Anaplastic astrocytoma IDHmut+, 1p/19q co-deleted | 2.94 | 0.49–17.6 | .239 |
| Anaplastic astrocytoma IDHwt, NOS | 3.70 | 0.87–15.6 | .075 |
| Diffuse astrocytoma IDHmut, NOS | 4.13 | 1.02–16.8 | .047 |
| Anaplastic astrocytoma IDHmut | 3.95 | 1.16–13.4 | .028 |
| Glioblastoma IDHwt, NOS | 4.50 | 1.34–15.0 | .015 |

WHO, World Health Organization; HR, hazard ratio; CI, confidence interval; IDHmut, isocitrate dehydrogenase mutant; IDHwt, NOS, isocitrate dehydrogenase wildtype, not otherwise specified.
tial for the diagnosis of diffuse gliomas. The 2016 WHO classification of CNS tumors requires at least IDH1 immunohistochemistry and 1p/19q co-deletion status for the diagnosis of diffuse gliomas in addition to histologic evaluation. With regard to IDH mutation, mutation analyses of both IDH-1 and IDH-2 are recommended more than immunohistochemistry for the detection of IDH1 hotspot mutation (p.R132H).

Mellai et al. reported that IDH1 mutations consisted 98.5%

Fig. 4. Kaplan-Meier curves for overall survival according to the 2007 WHO classification (A, C, E) and 2016 WHO classification (B, D, F), respectively. (A, B) For all tumors. (C, D) For grade II tumors. (E, F) For grades III and IV tumors. WHO, World Health Organization.
of all IDH mutations in gliomas. Among IDH1 mutations, 93.7% were c.395G > A (p.R132H) which can be detected by mIDH1R132H antibody immunostaining. There was a statistically significant correlation between mIDH1R132H antibody immunostaining and the relevant mutation c.395G > A (p.R132H) (p = .0001). Different types of IDH1 gene mutations at codon R132 have been identified, of which c.395G > A (p.R132H) mutation accounts for about 93%, c.394C > T (p.R132C) for 4%, and c.394C > A (p.R132S) for 1.5% in the different types of gliomas.17,22

The 2016 WHO classification of CNS tumors is a global standard, and it has better prognostic significance than traditional histological classification. To perform the molecular diagnosis of gliomas according to the 2016 WHO classification of CNS tumors, full assessment of IDH mutation status and 1p/19q analyses are mandatory. Operating a well-equipped molecular laboratory is a challenging situation in the developing countries including Mongolia. Expansion of facilities for molecular pathology is required to avoid the diagnosis of diffuse glioma, NOS. Nowadays pathology laboratories in developing countries struggle to provide specialized molecular tests, and it requires increase of medical costs.

In this study, we could reclassify Mongolian diffuse gliomas according to the new 2016 WHO classification. Reclassification revealed substantial changes in diagnosis of both oligodendroglial and astrocytic entities. For example, histologically astrocytic entities, which had both IDH mutation and 1p/19q co-deletion, were reclassified into oligodendroglial entities (30 of 42 patients). Furthermore, molecular subgroups, such as IDHmut and IDHwt, NOS, were added to the diagnosis of diffuse glioma based on the results of immunohistochemical staining of IDH1. Similar results were observed in the French POLA cohort study by Tabouret et al.3

The previous studies suggest that 1p/19q co-deletion or IDH mutation is a relatively early event during the development of glioma.23,24 As a result, the frequency of 1p/19q co-deletion or IDH mutation could be higher in low-grade gliomas. In our study, the frequency of 1p/19q co-deletion and IDH1 mutation were significantly higher in patients with low-grade gliomas than in those with high-grade gliomas (17.9% vs 4.4%, p < .05 and 80.4% vs 36.8% p < .001, respectively).

Reclassification of diffuse gliomas not only categorizes molecular subgroups of diffuse gliomas but it also has important prognostic value. Yan et al.25 revealed that tumors with IDH mutation are distinctive genetically and clinically, and had better outcomes than those with wildtype IDH gene. Akagi et al.10 and Taburet et al.3 demonstrated that the new 2016 WHO classification has better prognostic value in terms of OS. In particular, IDHmut is a strong prognostic marker and is associated with better survival compared with IDHwt.5,10 However, the prognostic advantage of IDH1mut was only evident for low-grade gliomas in this study.

In our study, the 2016 WHO classification showed higher hazard ratio for OS than the 2007 WHO classification and reinforced the prognostic value of integrated histomolecular classification. The 2007 WHO classification did not show survival difference in grade II tumors, whereas 2016 WHO classification showed that oligodendroglioma, IDHmut and 1p/19q co-deleted and diffuse astrocytoma IDHmut had better survival compared with diffuse astrocytoma IDHwt, NOS in grade II tumors.

Finally, our study has several limitations. First, the total study population was relatively small compared with those in other similar studies. Therefore, further studies with a large sample size are required to confirm these findings. Second, there were some technical difficulties associated with FISH testing. In our study, 32 patients who were diagnosed before 2012 had no signal on FISH test. It could be caused by laboratory suboptimal conditions such as poor fixation of tissue and storage duration of tissue blocks. Therefore, we reclassified those cases based on histological pattern and IDH1 mutation status only without 1p/19q co-deletion information. Third, IDH mutation status has been investigated only by immunohistochemistry, and no further molecular analysis for IDH mutation was performed in cases of diffuse gliomas that are immunohistochemically negative for IDH1 R132H mutation. Therefore, we could not avoid the diagnosis of diffuse gliomas, IDH-wildtype, NOS.

This is the first study to report the reclassification of Mongolian diffuse gliomas according to the revised 2016 WHO CNS tumor classification. There has been no study regarding pathological classification of brain gliomas according to the 2007 WHO classification as well as survival analysis of gliomas in Mongolia. In spite of several technical limitations, our results were still similar to those of previous publications. Additionally, we have confirmed that the revised 2016 WHO CNS tumor classification is also feasible for Mongolian diffuse gliomas and that it has prognostic significance in Mongolian patients with diffuse gliomas.

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Conflicts of Interest
The authors declare that they have no potential conflicts of interest.

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