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The Overview of Practical Guidelines for Gliomas by KSNO, NCCN, and EANO

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Gliomas have been histologically diagnosed as the third most common primary tumor of the central nervous system (CNS) in a relatively small portion of Korea. Despite the rarity of gliomas, the disease entity is very dynamic due to its various molecular characteristics, compared with other CNS tumors. The practice of managing glioma patients is not globally established as a precise standard guideline because of the different socio-medical environments of individual countries. The Korean Society for Neuro-Oncology (KSNO) published guidelines for managing adult glioma in 2019, and the National Comprehensive Cancer Network and European Association of Neuro-Oncology published guidelines in September 2021 and March 2021, respectively. However, these guidelines have several different recommendations in practice, including tissue management, adjuvant treatment after surgical resection, and salvage treatment for recurrent/progressive gliomas. Currently, the KSNO guideline working group is preparing an updated version of the guideline for managing adult gliomas. In this review, common features have been verified and different points are analyzed. Consequently, this review is expected to be informative and helpful to provide high quality evidence and a strong recommendation level for the establishment of new KSNO guidelines for managing gliomas.

Keywords Guideline; Gliomas; KSNO; Practice.

INTRODUCTION

Gliomas are the most common primary parenchymal brain tumors in the United States [1]. They have been histologically diagnosed as the third most common primary tumor of the central nervous system (CNS) in a relatively small portion of Korea [2]. According to the new World Health Organization (WHO) classification of CNS tumors in 2021 [3], grade 1 gliomas include 1) diffuse astrocytoma (MYB- or MYBL1-altered) and 2) polymorphous low-grade neuroepithelial tumors in young individuals. Grade 2 and 3 gliomas include 1) astrocytoma (isocitrate dehydrogenase [*IDH*]-mutant), 2) oligodendroglioma (*IDH*-mutant and 1p/19q-codeleted), and 3) pleomorphic xanthoastrocytoma. Grade 4 gliomas include 1) astrocytoma (*IDH*-mutant), 2) glioblastoma (*IDH*-wild-type), and 3) diffuse hemispheric glioma (H3G34-mutant). Despite the rarity of gliomas among primary CNS tumors, the disease entity is very dynamic due to its various molecular characteristics, compared with other CNS tumors. The classification of gliomas has been frequently modified due to further advancement of molecular genetic information. The recent WHO classification of CNS tumors was officially published in 2016 as a revised version of the 4th edition of the WHO classification of CNS tumors without full establishment of a concrete diagnostic process because of the rapid advancement of molecular and genetic approaches to diagnose gliomas. Consecutively, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was established to enhance the understanding of the molecular pathogenesis of brain tumors, warranting more rapid integration of this information into clinical practice before the offi-

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cial WHO update. The goal of cIMPACT-NOW was to facilitate input and consensus review of novel diagnostically relevant data and determine how advanced molecular and genetic information could be practically incorporated into future CNS tumor classifications [4]. Although these efforts are ongoing, the practice of managing glioma patients is not globally established as a precise standard protocol because of the different socio-medical environments in individual countries.

In Korea, a working group was appointed by the Korean Society for Neuro-Oncology (KSNO) in February 2018 to establish guidelines for the management of patients with brain tumors. The working group published the KSNO guidelines for adult glioblastoma patients in April 2019 and for grades 2 and 3 glioma patients in October 2019. These guidelines were optimized under unique medical circumstances in Korea. Although the KSNO guidelines were mainly based on the National Comprehensive Cancer Network (NCCN) and European Association of Neuro-Oncology (EANO) guidelines with modifications and changes according to the unique background of Korea, there are several points with discrepancies. In this review, the individual guidelines for glioma by KSNO, NCCN, and EANO will be analyzed and compared with each other. Consequently, this review is expected to be helpful and informative to update KSNO guidelines for glioma patients.

DIAGNOSIS

KSNO guidelines recommend a multidisciplinary approach for treatment planning, if feasible, when the radiological features suggest a glioma. Magnetic resonance imaging (MRI) with contrast enhancement is considered an essential imaging tool for the diagnosis of gliomas. To obtain sufficient tissue for histopathological diagnosis, neurosurgical intervention is mandatory, even if it is for stereotactic biopsy. To achieve maximal safe resection, neuronavigation systems, intraoperative computed tomography (CT) or MRI, intraoperative ultrasonography, intraoperative mapping techniques, and fluorescence-guidance with 5-aminolevulinic acid (ALA) are recommended. Histopathological diagnosis should be officially based on the 2016 WHO classification of CNS tumors [5]. For the workup of gliomas, codeletion of 1p/19q testing and *IDH1* and *IDH2* mutation tests are essential for molecular diagnosis of gliomas, as well as histopathological features [6-8]. The O^6-methylguanine-DNA-methyltrasferase (*MGMT*) promoter methylation test is required to predict the response to treatment for all grades of gliomas, especially glioblastoma [6]. An ATP-dependent helicase (*ATRX*) mutation test is also required for the workup of grade 2 gliomas. If the tumor has *IDH*-wildtype, the following molecular tests are strongly recommended: 1) epidermal growth factor receptor (*EGFR*) amplification, 2) combined whole chromosome 7 gain and whole chromosome 10 loss, and 3) telomerase reverse transcriptase (*TERT*) promoter mutation. If the histopathological diagnosis is WHO grade 2 gliomas, patients with the aforementioned molecular features of glioblastoma should be treated on the basis of the guidelines for WHO grade 4 glioblastoma [8].

The NCCN guidelines are similar to those of KSNO in terms of the diagnostic process. The principles of surgical resection include gross total resection with minimal surgical morbidity using an intraoperative microscope, frameless stereotactic image guidance, preoperative functional MRI and/or diffusion tensor image fiber tracking, awake craniotomy, motor and/or speech mapping, intraoperative MRI, and intraoperative fluorescence-guided surgery with 5-ALA [9]. For standard histological examination and classification, histological subgrouping of CNS neoplasms is recommended to follow the WHO classification of CNS tumors, and it should be considered an inherently subjective nature of certain aspects of histological interpretation. In addition, the NCCN guidelines state that molecular/genetic characterization does not replace standard histological assessment, but serves as a complementary approach to providing additional diagnostic and prognostic information that often enhances treatment selection. In terms of analytic methods, genome-wide profiling of CpG methylation patterns can be a powerful way to classify brain tumors, including those with equivocal histological features. In accordance with the KSNO guidelines, the molecular features of glioblastoma in lower grade gliomas are also emphasized to have similar clinical outcomes as those of the typical WHO grade 4 glioblastoma and to be treated with standard therapy for grade 4 glioblastoma [9]. In addition, NCCN panels encourage molecular testing of glioblastomas if a driver mutation, such as *BRAF* 600E-activating mutations or neurotrophic tyrosine receptor kinase (*NTRK*) fusion, is detected, because it may be reasonable to treat with a target therapy in clinical trials and/or because of its intractable status against conventional treatment. The following molecular markers are recommended for use by neuropathologists to facilitate characterization of gliomas, and/or neuro-oncologists to guide treatment decisions: *IDH1* and *IDH2* mutations, codeletion of 1p and 19q, *MGMT* promoter methylation, *ATRX* mutation, *TERT* promoter mutation, H3F2A mutation, and *BRAF* mutation [9].

The EANO guidelines recommend that treatment decisions in patients with glioma should be made on the basis of tissue diagnosis, including the assessment of molecular markers relevant for diagnosis; therefore, upfront surgery is commonly performed with both diagnostic and therapeutic intent [10]. To avoid surgical morbidity and adverse outcomes from inadequate biopsy sampling, the EANO guidelines state that the surgical management of patients with glioma should take place

in high-volume specialist centers where large numbers of patients are referred to specialist neurosurgeons rather than individual neurosurgeons' surgical practice [11]. The EANO guidelines state the importance of tissue diagnosis more concretely than those by KSNO and NCCN; if possible, some tumor tissue should be cryopreserved for molecular assessments that require high-quality DNA and RNA samples. In the same way as the KSNO and NCCN guidelines, the diagnostic process should follow the 2016 WHO classification and subsequent recommendations from cIMPACT-NOW, as the following molecular biomarkers are central to categorizing gliomas in adults: *IDH* mutation, 1p/19q codeletion, histone H3K27M mutation, histone H3.3 G34R/V mutation, *TERT* promoter mutation, *EGFR* amplification, chromosome 7 gain combined with chromosome 10 loss (the +7/−10 signature), and homozygous deletions on 9p21 involving the CDKN2A and CDKN2B gene loci (CDKN2A/B homozygous deletion). Accordingly, glioma classification integrates histological tumor typing and grading, and analyses of molecular markers. Additional recommendations by EANO are as follows: 1) immunohistochemistry for mutant *IDH1* R132H protein and nuclear expression of *ATRX* should be performed routinely in the diagnostic assessment of diffuse gliomas; 2) if immunohistochemistry for *IDH1* R132H is negative, sequencing of *IDH1* codon 132 and *IDH2* codon 172 should be conducted in all WHO grade 2 and 3 diffuse astrocytic and oligodendroglial gliomas and in all glioblastomas of patients aged <55 years, to enable integrated diagnoses according to the WHO classification and to guide treatment decisions; 3) 1p/19q codeletion status should be determined in all *IDH*-mutant gliomas with retained nuclear expression of *ATRX*; 4) *MGMT* promoter methylation status should be determined in glioblastomas, notably in elderly or frail patients, to aid in decision-making for the use of temozolomide; 5) CDKN2A/B homozygous deletions should be explored in *IDH*-mutant astrocytomas; 6) combined chromosome 7 gain and chromosome 10 loss (+7/−10 signature), *EGFR* amplification, and *TERT* promoter mutation should be tested in *IDH*-wildtype diffuse gliomas lacking microvascular proliferation and necrosis as histological features of WHO grade 4 glioblastoma to allow for a diagnosis of *IDH*-wild-type glioblastoma; 7) assessment of H3K27M status should be done in diffuse gliomas involving the midline; and 8) *BRAF* V600 mutations might be assessed in *IDH*-wild-type diffuse gliomas.

The KSNO and NCCN guidelines commonly recommend the following histological and molecular genetic studies as essential steps for diagnosis and grading of gliomas: 1) codeletion of 1p/19 test, 2) *IDH* mutation test, 3) *ATRX* mutation test, and 4) *MGMT* promoter methylation status (Table 1). For the determination of therapeutic strategies, the following molecular genetic analyses are also recommended: 1) *TERT* promoter mutation, 2) *EGFR* amplification, and 3) chromosome 7 gain and 10 loss. NCCN considers the following molecular genetic studies for further target therapy in clinical trials: 1) *NTRK* gene fusion, 2) *BRAF* V600E, 3) mammalian target of rapamycin mutation, and 4) methyl ethyl ketone mutation. EANO recommends a detailed molecular genetic analysis for glioma diagnosis and grading, such as *IDH* mutation test, *ATRX* mutation test, codeletion of 1p/19 test, *TERT* promoter mutation, *EGFR* amplification, chromosome 7 gain and 10 loss, and H3.3 G34R/V (Table 1).

ADJUVANT TREATMENT FOR GLIOBLASTOMA

The KSNO guidelines classified glioblastoma patients according to age (≤70 years vs. >70 years) and the Karnofsky Performance Scale (KPS, <60 vs. ≥60) for the application of the protocol. Among glioblastoma patients aged ≤70 years, if

Table 1. Histological diagnosis for glioma grading in KSNO, NCCN, and EANO guideline

KSNO	NCCN	EANO
Essential	Essential	Essential
- Codeletion of 1p/19 test	- Codeletion of 1p/19 test	- *IDH* mutation test
- *IDH* mutation test	- *IDH* mutation test	- *ATRX* mutation test
- *ATRX* mutation test	- *ATRX* mutation test	- Codeletion of 1p/19 test
- *MGMT* promoter methylation	- *MGMT* promoter methylation	- *TERT* promoter mutation
Consider glioblastoma features	Additional	- *EGFR* amplification
- *TERT* promoter mutation	- *NTRK* gene fusion	- Chromosome 7 gain and 10 loss
- *EGFR* amplification	- *BRAF* V600E	- H3.3 G34R/V
- Chromosome 7 gain and 10 loss	- *mTOR* mutation	Additional
	- *MEK* mutation	- CDKN2A/B
		- H3K27M mutation

ATRX, ATP-dependent helicase; BRAF, V-Raf murine sarcoma viral oncogene homolog B1; CDKN2A, cyclin dependent kinase inhibitor 2A; EGFR, epidermal growth factor receptor; IDH, isocitrate dehydrogenase; MEK, methyl ethyl ketone; mTOR, mammalian target of rapamycin; NTRK, neurotrophic tyrosine receptor kinase; TERT, telomerase reverse transcriptase

the patient has a good performance status (KPS ≥60 or Eastern Cooperative Oncology Group [ECOG] performance score ≤2), concurrent chemoradiotherapy with temozolomide followed by adjuvant temozolomide chemotherapy (Stupp's protocol) [12], or standard brain radiotherapy alone should be considered. However, if the patient has a poor performance status (KPS <60 or ECOG performance score ≥3), hypofractionated brain radiotherapy (preferred) ± concurrent or adjuvant temozolomide, temozolomide alone (Level III), or supportive treatment can be considered. In contrast, for glioblastoma patients aged >70 years, if the patient has a good performance status (KPS ≥60 or ECOG performance score ≤2), the following therapeutic options should be considered: hypofractionated brain radiotherapy + concurrent and adjuvant temozolomide, concurrent chemoradiotherapy with temozolomide followed by adjuvant temozolomide chemotherapy, or hypofractionated brain radiotherapy alone. If the patient has a poor performance status (KPS <60 or ECOG performance score ≥3), the following therapeutic options should be considered: hypofractionated brain radiotherapy alone, temozolomide chemotherapy if methylated *MGMT* promoter (Level III) is present, or supportive treatment. In poorly performing patients or the elderly, a hypofractionated accelerated course is reasonable with the goal of completing the treatment within 2−3 weeks [6].

Similarly, the NCCN guidelines classified glioblastoma patients according to age (≤70 years vs. >70 years) and KPS (<60 vs. ≥60) for the application of the protocol, and also considered the methylation status of the *MGMT* promoter in patients aged ≤70 years with a good performance scale. The NCCN guidelines preferentially recommend that all glioblastoma patients participate in clinical trials for eligible conditions. Among glioblastoma patients aged ≤70 years with a good performance status (KPS ≥60) and methylated *MGMT* promoter, concurrent chemoradiotherapy with temozolomide followed by adjuvant temozolomide chemotherapy ± alternating electrical field therapy or standard brain radiotherapy + concurrent temozolomide and adjuvant lomustine, and temozolomide chemotherapy should be considered. Among them, if the patient has a good performance status (KPS ≥60) with an unmethylated *MGMT* promoter, concurrent chemoradiotherapy with temozolomide followed by adjuvant temozolomide chemotherapy ± alternating electrical field therapy, or standard brain radiotherapy alone should be considered. In addition, if the patient has a poor performance status (KPS <60), hypofractionated RT ± concurrent or adjuvant temozolomide should be preferentially considered [9].

The EANO guidelines recommend Stupp's regimen as the standard of care for patients with *IDH*-wildtype glioblastoma, aged <70 years and with a KPS >70. They also recommend considering the methylation status of the *MGMT* promoter when determining the therapeutic option in elderly patients (aged >65−70 years) who are not considered candidates for Stupp's regimen as follows: 1) radiotherapy (40 Gy in 2.67 Gy fractions) for patients with *MGMT* promoter-unmethylated tumors and 2) temozolomide chemoradiotherapy or temozolomide for patients with *MGMT* promoter-methylated tumors. The EANO guidelines suggest that temozolomide might only be active in patients with *MGMT* promoter-methylated tumors, whereas its activity in patients with *MGMT* promoter-unmethylated tumors is probably marginal [10]. Distinctively, the EANO guidelines recommend temozolomide chemoradiotherapy (54−60 Gy in 1.8−2.0 Gy fractions) without concomitant temozolomide for the potential treatment regimens for WHO grade 4 astrocytoma, *IDH*-mutant (cIMPACT-NOW, previously glioblastoma, *IDH*-mutant, WHO grade 4) [10].

The criterion of elderly patients being at least 70 years old was the same in the KSNO and NCCN guidelines. However, the EANO guidelines included ages 65−70 years in their classification of elderly patients. Therefore, there is no concrete definition of old age. Many investigators have reported their data based on old age of >70 years. Although there is uniform consensus for old age (>70 years) among the KSNO working group, a worldwide retrospective multi-institute study can help establish a meaningful age with a prognostic turning point. In principle, the NCCN and EANO guidelines recommend different strategies based on the *MGMT* promoter methylation status [9,10]. However, the KSNO guidelines were the same as the standard treatment with Stupp's regimen, regardless of the methylation status of the *MGMT* promoter in patients with good performance status (Table 2). One of the reasons is that the Korean government's health insurance does not cover alternating electric field therapy. Another difference in the KSNO guidelines from that of NCCN and EANO is the strength of consideration for clinical trials; enrollment for clinical trials is preferentially considered in Western countries. The medical circumstances and environment in Korea are not activated as much as in Western countries because of several cultural and commercial reasons. To overcome these limitations in Korea, co-operation is necessary in neuro-oncology societies.

ADJUVANT TREATMENT FOR GRADE 3 GLIOMAS

WHO grade 3 anaplastic astrocytoma, *IDH*-mutant (Table 3)

The KSNO guidelines recommend the following modalities for patients with anaplastic astrocytoma, *IDH*-mutant: standard brain radiotherapy and adjuvant temozolomide

Table 2. Adjuvant treatment for glioblastoma patients by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) For patients age >70 & KPS ≥60: CCRT (hypofractionated or standard) & adjuvant temozolomide
	2) For patients age >70 & KPS <60: RT alone (hypofraction) or temozolomide (*MGMT* methylated patient)
	3) For patients age ≤70 & KPS ≥60: CCRT (standard) & adjuvant temozolomide
	4) For patients age ≤70 & KPS <60: RT (hypofraction) ± concurrent or adjuvant temozolomide
NCCN	1) For patients of age ≤70 & KPS ≥60, without consideration of the methylation status of *MGMT* promoter: CCRT & adjuvant temozolomide ± TTF
	2) For patients of age ≤70 & KPS <60, without consideration of the methylation status of *MGMT* promoter: hypofractionated RT ± concurrent or adjuvant temozolomide
	3) For patients of age >70, KPS ≥60 & methylated *MGMT* promoter: hypofractionated RT + concurrent or adjuvant temozolomide
	4) For patients of age >70, KPS ≥60 & unmethylated *MGMT* promoter: CCRT & adjuvant temozolomide ± TTF
	5) For patients of age >70 & KPS <60: hypofractionated RT alone
EANO	1) Temozolomide CCRT (54−60 Gy in 1.8−2.0 Gy fractions)
	2) For patients aged >65−70 years and *MGMT* unmethylated tumors: RT (40 Gy in 2.67 Gy fractions)
	3) For patients aged >65−70 years and *MGMT* methylated tumors: temozolomide CCRT or temozolomide

CCRT, concurrent chemoradiotherapy; EANO, European Association of Neuro-Oncology; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; MGMT, O^6-methylguanine-DNA-methyltrasferase; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; TTF, tumor treating fields

Table 3. Adjuvant treatment for patients with WHO grade 3 anaplastic astrocytoma, *IDH*-mutant by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) Standard RT & followed adjuvant temozolomide chemotherapy
	2) Standard RT with concurrent and adjuvant temozolomide chemotherapy
	3) Standard RT with neoadjuvant or adjuvant PCV chemotherapy
	4) Standard RT alone
NCCN	- For patients with KPS ≥60
	1) Standard RT & followed adjuvant temozolomide chemotherapy
	2) Standard RT with concurrent & adjuvant temozolomide chemotherapy
	- For patients with KPS <60
	1) RT (hypofractionated)
	2) Temozolomide (category 2B)
	3) Palliative/best supportive care
EANO	RT (54−60 Gy in 1.8−2.0 Gy fractions) followed by temozolomide (or wait-and-see)

EANO, European Association of Neuro-Oncology; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; NCCN, National Comprehensive Cancer Network; PCV, procarbazine, CCNU, and vincristine; RT, radiotherapy; WHO, World Health Organization

chemotherapy, standard brain radiotherapy with concurrent and adjuvant temozolomide chemotherapy, standard brain radiotherapy with neoadjuvant or adjuvant PCV (procarbazine + lomustine + vincristine) combination chemotherapy, or standard brain radiotherapy alone [7].

The NCCN guidelines do not differentiate the therapeutic strategies according to *IDH* mutation but recommend different strategies according to performance status. For patients with KPS ≥60, the following treatments were recommended as preferred regimens: 1) standard radiotherapy followed by adjuvant temozolomide chemotherapy and 2) standard radiotherapy with concurrent and adjuvant temozolomide chemotherapy (12 cycles). However, there are no preferred regimens for patients with KPS <60; therefore, temozolomide chemotherapy alone can be considered [9].

The EANO guidelines recommend standard radiotherapy (54−60 Gy in 1.8−2.0 Gy fractions) followed by temozolomide chemotherapy or PCV chemotherapy for patients with WHO grade 3 anaplastic astrocytoma, *IDH*-mutant, because the role of concomitant temozolomide chemoradiotherapy remains uncertain [10].

WHO grade 3 anaplastic astrocytoma, *IDH*-wildtype

(Table 4)

The KSNO guidelines recommend the same guideline for WHO grade 4 glioblastoma for the treatment of WHO grade

3 anaplastic astrocytoma, *IDH*-wild type, because most anaplastic astrocytomas (except genetic features of *IDH*-mutant) usually have similar clinical and pathological behaviors [7].

The NCCN guidelines recommend the same protocol for all WHO grade anaplastic astrocytomas, regardless of the status of *IDH* mutation [9].

The EANO guidelines recommend standard radiotherapy (54−60 Gy in 1.8−2.0 Gy fractions) or concomitant chemoradiotherapy with temozolomide according to the methylation status of the *MGMT* promoter [10].

WHO grade 3 anaplastic astrocytoma, *NOS* (Table 5)

The KSNO guidelines provide the same recommendation for WHO grade 4 glioblastoma as for the treatment of WHO grade 3 anaplastic astrocytoma, *NOS*, because most anaplastic astrocytomas (except genetic features of *IDH*-mutant) usually have similar clinical and pathological behaviors [7].

The NCCN guidelines recommend the same protocol for all WHO grade anaplastic astrocytomas, regardless of the status of *IDH* mutation [9]. Unlike the KSNO guidelines, the EANO guidelines for WHO grade 3 anaplastic astrocytoma, *NOS*, were the same as those of WHO grade 3 anaplastic astrocytoma, *IDH*-mutant: standard radiotherapy (54−60 Gy in 1.8−2.0 Gy fractions) followed by temozolomide chemotherapy or PCV chemotherapy [10]. This discrepancy may have originated from the differences in the usage of molecular genetic analysis between Europe and Korea.

Table 4. Adjuvant treatment for patients with WHO grade 3 anaplastic astrocytoma, *IDH*-wildtype by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) For patients age >70 & KPS ≥60: CCRT (hypofractionated or standard) & adjuvant temozolomide
	2) For patients age >70 & KPS <60: RT alone (hypofraction) or temozolomide (*MGMT* methylated patient)
	3) For patients age ≤70 & KPS ≥60: CCRT (standard) & adjuvant temozolomide
	4) For patients age ≤70 & KPS <60: RT (hypofraction) ± concurrent or adjuvant temozolomide
NCCN*	- For patients with KPS ≥60
	1) Standard RT & followed adjuvant temozolomide chemotherapy
	2) Standard RT with concurrent & adjuvant temozolomide chemotherapy
	- For patients with KPS <60
	1) RT (hypofractionated)
	2) Temozolomide (category 2B)
	3) Palliative/best supportive care
EANO	1) RT (54−60 Gy in 1.8−2.0 Gy fractions)
	2) Temozolomide CCRT according to *MGMT* promoter methylation status

*Same guideline for patients with WHO grade 3 anaplastic astrocytoma, *IDH*-mutant. CCRT, concurrent chemoradiotherapy; EANO, European Association of Neuro-Oncology; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; MGMT, O^6-methylguanine-DNA-methyltrasferase; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; WHO, World Health Organization

Table 5. Adjuvant treatment for patients with WHO grade 3 anaplastic astrocytoma, *NOS* by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) For patients age >70 & KPS ≥60: CCRT (hypofractionated or standard) & adjuvant temozolomide
	2) For patients age >70 & KPS <60: RT alone (hypofraction) or temozolomide (*MGMT* methylated patient)
	3) For patients age ≤70 & KPS ≥60: CCRT (standard) & adjuvant temozolomide
	4) For patients age ≤70 & KPS <60: RT (hypofraction) ± concurrent or adjuvant temozolomide
NCCN*	- For patients with KPS ≥60
	1) Standard RT & followed adjuvant temozolomide chemotherapy
	2) Standard RT with concurrent & adjuvant temozolomide chemotherapy
	- For patients with KPS <60
	1) RT (hypofractionated)
	2) Temozolomide (category 2B)
	3) Palliative/best supportive care
EANO*	RT (54−60 Gy in 1.8−2.0 Gy fractions) followed by temozolomide (or wait-and-see)

*Same guideline for patients with WHO grade 3 anaplastic astrocytoma, IDH-mutant. CCRT, concurrent chemoradiotherapy; EANO, European Association of Neuro-Oncology; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; MGMT, O^6-methylguanine-DNA-methyltrasferase; NCCN, National Comprehensive Cancer Network; RT, radiotherapy; WHO, World Health Organization

WHO Grade 3 anaplastic oligodendroglioma, *IDH*-mutant, 1p19q codel, and anaplastic oligodendroglioma, *NOS* (Table 6)

The KSNO guidelines recommend the following treatment regimens for anaplastic oligodendrogliomas, including those with *IDH*-mutant and 1p19q-codeletion and those without results of molecular testing: 1) standard brain radiotherapy and neoadjuvant or adjuvant PCV chemotherapy, 2) standard brain radiotherapy with concurrent and adjuvant temozolomide chemotherapy, or 3) standard brain radiotherapy alone. Despite low evidence, the KSNO working group has a consensus (although not uniform) that standard brain radiotherapy without adjuvant chemotherapy for any WHO grade 3 glioma should be considered for patients with poor performance status (KPS ≤60) [7].

The NCCN guidelines recommend standard radiotherapy and adjuvant or neoadjuvant PCV chemotherapy as preferred regimens, and the following treatment can also be considered: 1) standard radiotherapy with concurrent and adjuvant temozolomide chemotherapy, and 2) standard radiotherapy and adjuvant temozolomide chemotherapy. Similar to the KSNO guidelines, the NCCN guidelines also recommend that standard brain radiotherapy (hypofractionated [preferred] or standard) without adjuvant chemotherapy for any WHO grade 3 glioma should be considered for patients with a poor performance status (KPS ≤60) [9].

The EANO guidelines consider watch-and-wait strategies after complete resection for younger patients (<40 years of age), specifically for those without homozygous CDKN2A/B deletion, although only after gross total resection and in the absence of neurological deficits. Alternatively, radiotherapy (54−60 Gy in 1.8−2.0 Gy fractions) followed by PCV chemotherapy is recommended [10]. The EANO guidelines do not recommend temozolomide chemotherapy as a therapeutic option for WHO grade 3 anaplastic oligodendroglioma, *IDH*-mutant, 1p19q codel, but consider age and residual tumor as more important factors in determining the therapeutic strategies (Table 6).

ADJUVANT TREATMENT FOR GRADE 2 GLIOMAS

WHO Grade 2 diffuse astrocytoma, *IDH*-wildtype (Table 7)

The KSNO guidelines recommend to patients with diffuse astrocytoma, *IDH*-wildtype, the following treatment modalities: 1) standard brain radiotherapy and adjuvant temozolomide chemotherapy (Level III), 2) standard brain radiotherapy alone, or 3) observation. However, if patients with diffuse astrocytoma, *IDH*-wildtype, have one more molecular feature of glioblastomas, they should be treated following the protocol for glioblastomas. As aforementioned, the molecular features of glioblastoma are *EGFR* amplification, combined whole chromosome 7 gain and whole chromosome 10 loss, and *TERT* promoter mutation [8].

The NCCN guidelines consider the WHO grade 2 diffuse astrocytoma, *IDH*-wildtype, same as the WHO grade 3 anaplastic astrocytoma in clinical settings. Therefore, the same guideline was applied for WHO grade 2 diffuse astrocytoma, *IDH*-wildtype. For patients with KPS ≥60, the following treatments were recommended as preferred regimens: 1) standard radiotherapy followed by adjuvant temozolomide chemotherapy, and 2) standard radiotherapy with concurrent and adjuvant temozolomide chemotherapy (12 cycles). However, there are no preferred regimens for patients with KPS <60, and temozolomide chemotherapy alone can be considered [9].

The EANO guidelines consider the following treatment strategies for diffuse astrocytomas, *IDH*-wildtype: 1) wait-and-see, 2) radiotherapy (50−54 Gy in 1.8−2.0 Gy fractions), and 3) radiotherapy followed by PCV chemotherapy or concomitant chemoradiotherapy with temozolomide (determined by *MGMT* promoter methylation status). However, this guideline states that

Table 6. Adjuvant treatment for patients with WHO grade 3 anaplastic oligodendroglioma, *IDH*-mutant, 1p19q codel, and anaplastic oligodendroglioma, *NOS* by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) Standard RT & neoadjuvant or adjuvant PCV chemotherapy 2) Standard RT with concurrent & adjuvant temozolomide chemotherapy 3) Standard RT alone (Level III)
NCCN	1) Standard RT & adjuvant or neoadjuvant PCV chemotherapy 2) Standard RT with concurrent & adjuvant temozolomide chemotherapy 3) Standard RT & adjuvant temozolomide chemotherapy
EANO	RT (54−60 Gy in 1.8−2.0 Gy fractions) followed by PCV chemotherapy (or wait-and-see for patients of young age and no residual tumor)

EANO, European Association of Neuro-Oncology; IDH, isocitrate dehydrogenase; KSNO, Korean Society for Neuro-Oncology; NCCN, National Comprehensive Cancer Network; PCV, procarbazine, CCNU, and vincristine; RT, radiotherapy; WHO, world health organization

diffuse astrocytomas, *IDH*-wildtype, are a heterogeneous tumor group that should be further molecularly characterized to differentiate malignant tumors with molecular features of *IDH*-wildtype glioblastoma from indolent tumors (e.g., corresponding to pediatric-type diffuse gliomas) [10].

WHO Grade 2 diffuse astrocytoma (*IDH*-mutant) and oligodendroglioma (*IDH*-mutant, 1p/19q codeletion) (Table 8)

The KSNO and NCCN guidelines classified patients older than 40 years and those who had not undergone gross total resection of tumors as the high-risk group, and those younger than 40 years and those who had undergone gross total resection of tumors as the low-risk group. According to the KSNO guidelines, adjuvant treatment should be considered primarily for patients in the high-risk group: 1) standard radiotherapy and adjuvant PCV chemotherapy, or 2) concurrent chemoradiotherapy with temozolomide and adjuvant temozolomide chemotherapy, or 3) standard radiotherapy with adjuvant temozolomide chemotherapy [8]. According to the KSNO guidelines, the following adjuvant treatment should be considered for patients in the low-risk group: 1) observation and regular follow-up, or 2) standard radiotherapy alone, or 3) adjuvant PCV chemotherapy alone [8].

The NCCN guidelines recommend the following treatments for the high-risk group: 1) standard radiotherapy with adjuvant PCV chemotherapy, 2) standard radiotherapy with adjuvant temozolomide chemotherapy, and 3) standard radiotherapy with concurrent and adjuvant temozolomide chemotherapy. In addition, the NCCN guidelines recommend the following strategies for the low-risk group: enrollment of clinical trials

Table 7. Adjuvant treatment for patients with WHO grade 2 diffuse astrocytoma, *IDH*-wildtype by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	1) Standard RT & adjuvant temozolomide chemotherapy (Level III) 2) Standard RT alone 3) Observation
NCCN*	- For patients with KPS ≥60 1) Standard RT & followed adjuvant temozolomide chemotherapy 2) Standard RT with concurrent & adjuvant temozolomide chemotherapy - For patient with KPS <60 1) RT (hypofractionated) alone 2) Temozolomide chemotherapy, if *MGMT* promoter methylated (category 2B) 3) Palliative/best supportive care
EANO	1) Wait-and-see 2) RT (50−54 Gy in 1.8−2.0 Gy fractions) 3) RT followed by PCV or Temozolomide CCRT (determined by *MGMT* status)

*Same guideline for patients with WHO grade 3 anaplastic astrocytoma. CCRT, concurrent chemoradiotherapy; EANO, European Association of Neuro-Oncology; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; MGMT, O^6-methylguanine-DNA-methyltrasferase; NCCN, National Comprehensive Cancer Network; PCV, procarbazine, CCNU, and vincristine; RT, radiotherapy; WHO, World Health Organization

Table 8. Adjuvant treatment for patients with WHO grade 2 diffuse astrocytoma (*IDH*-mutant) and oligodendroglioma (*IDH*-mutant, 1p/19q codeletion) by KSNO, NCCN, and EANO guideline

Guidelines	Adjuvant treatment
KSNO	- High risk group* 1) Standard RT & neoadjuvant or adjuvant PCV chemotherapy 2) Standard RT with concurrent and adjuvant temozolomide chemotherapy 3) Standard RT with adjuvant temozolomide chemotherapy - Low risk group† 1) Observation 2) Standard RT alone 3) Adjuvant PCV chemotherapy alone
NCCN	- High risk group* 1) Standard RT with adjuvant PCV chemotherapy 2) Standard RT with adjuvant temozolomide chemotherapy 3) Standard RT with concurrent and adjuvant Temozolomide chemotherapy - Low risk group† 1) Consider clinical trial 2) Observation
EANO	- Diffuse astrocytoma 1) Wait-and-see or 2) RT (50−54 Gy in 1.8−2.0 Gy fractions) followed by PCV (or temozolomide CCRT) - Oligodendroglioma, *IDH*-mutant, 1p19q codeleted and Oligodendroglioma, *NOS* 1) Wait- and- see 2) RT (50−54 Gy in 1.8−2.0 Gy fractions) followed by PCV chemotherapy

*High risk includes patients who are older than 40 years or those who have not undergone gross total resection of the tumor; †Low risk includes patients who are younger than 40 years and those who have undergone gross total resection of the tumor. CCRT, concurrent chemoradiotherapy; EANO, European Association of Neuro-Oncology; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Scale; KSNO, Korean Society for Neuro-Oncology; MGMT, O^6-methylguanine-DNA-methyltrasferase; NCCN, National Comprehensive Cancer Network; PCV, procarbazine, CCNU, and vincristine; RT, radiotherapy; WHO, World Health Organization

or observation [9]. The NCCN guidelines also state that tumor size and neurological deficits can be considered as other risk factors for WHO grade 2 gliomas [9].

The EANO guidelines recommend wait-and-see or radiotherapy (50−54 Gy in 1.8−2.0 Gy fractions) followed by PCV chemotherapy (or concurrent chemoradiotherapy with temozolomide) for diffuse astrocytoma (*IDH*-mutant) and wait-and-see or radiotherapy (50−54 Gy in 1.8−2.0 Gy fractions) followed by PCV chemotherapy for oligodendrogliomas (*IDH*-mutant, 1p19q codeleted, and *NOS*) [10].

SALVAGE TREATMENT FOR RECURRENT GLIOBLASTOMA

The KSNO guidelines recommend that the true recurrence of glioblastoma be distinguished from pseudoprogression on MRI within the first 3 months after completion of concurrent chemoradiotherapy with temozolomide. These guidelines state that the following radiologic findings can suggest recurrence of glioblastomas: 1) increase of 25% or more in enhancing lesions despite stable or increasing steroid dose, 2) significant increase of the lesion in the fluid-attenuated inversion recovery (FLAIR) image and T2-weighted image, not attributable to other non-tumor causes, and 3) any new lesions. In addition, if clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease) occurs simultaneously, true progression must be strongly suggested. When the clinical and radiological features of any grade of glioma, including glioblastoma, is suggested to progress or recur, surgical resection is always recommended, if feasible. The KSNO guidelines recommend the following therapeutic options: 1) systemic chemotherapy (bevacizumab alone, bevacizumab plus irinotecan, daily temozolomide of low dose, lomustine or carmustine, and PCV or procarbazine plus lomustine), and/or 2) reirradiation (especially if there is a long interval since prior radiotherapy and/or if there was a good response to prior radiotherapy), and/or supportive treatment if the patient has poor performance status [6]. The efficacy of standard-of-care treatment, such as adjuvant temozolomide chemotherapy for recurrent glioblastoma, is suboptimal for salvage purposes. Thus, for eligible patients, clinical trials are highly encouraged [6].

The NCCN guidelines preferentially recommend clinical trial enrollment for eligible patients. If ineligible, systemic treatments, such as bevacizumab (single or combination with carmustine, lomustine, or temozolomide), temozolomide chemotherapy, lomustine or carmustine, PCV chemotherapy, and regorafenib; reirradiation; alternating electric field therapy; and palliative/best supportive care are considered. If failure or intolerance to the preferred or other recommended regimens occurs, etoposide or platinum-based regimens can also be considered [9].

The EANO guidelines recommend the selection of treatment modalities based on prior therapy, age, KPS, *MGMT* promoter methylation status, and patterns of disease progression. A second surgery can be an option for symptomatic patients with circumscribed relapses diagnosed not earlier than 6 months after the initial surgery. The main systemic treatment options for patients with disease progression include nitrosoureas, temozolomide rechallenge, and bevacizumab (depending on availability). Bevacizumab is not approved for patients with recurrent glioblastoma in the European Union (EU), although it has been approved for this indication in other countries based on the objective response rates of approximately 30% in two uncontrolled phase II trials [13,14]. When available, recruitment into appropriate clinical trials should be considered [10].

There is no significant difference among the three guidelines, but alternating electric field therapy in the NCCN guidelines is not included in the KSNO and EANO guidelines. Targeted therapy using bevacizumab is mainly recommended in the KSNO and NCCN guidelines, but not in the EANO guidelines because its use in recurrent glioblastoma has been disapproved by the EU. The common recommendation by the three guidelines for recurrent glioblastoma is patient enrollment in clinical trials (Table 9).

SUMMARIES AND FUTURE DIRECTIONS

In terms of preoperative brain imaging studies, there is no significant difference among the three guidelines. Brain MRI, including T2-weighted, T2-weighted FLAIR sequences and 3D T1-weighted sequences before and after the application of a gadolinium-based contrast agent, is routinely recommended as the diagnostic gold standard for detecting gliomas. CT scans of the brain (with and without contrast) are usually considered for patients who cannot undergo MRI. Magnetic resonance (MR) spectroscopy, MR perfusion imaging, and positron emission tomography (PET)-CT are not routine recommendations but are necessary for specific conditions in clinical practice, such as differentiation of true progression from pseudoprogression.

The common principles of surgical resection of glioma are as follows: gross total resection when appropriate, minimal surgical morbidity, and accurate diagnosis. The following factors should be considered when deciding on surgical resection: age; performance status; feasibility of decreasing the mass effect with surgery; and resectability, including number of lesions, location of lesions, time since last surgery in recurrent patients, and new versus recurrent tumor.

All the guidelines recommend histopathological diagnosis and classification of individual gliomas based on the 2016 WHO classification of CNS tumors. The classification of gli-

Table 9. Salvage treatment for patients with glioblastoma by KSNO, NCCN, and EANO guideline

Guidelines	Salvage treatment
KSNO	- Surgical resection of large or symptomatic lesion, if feasible
	- Surgically unresectable
	1) Bevacizumab alone
	2) Bevacizumab + irinotecan
	3) Daily temozolomide chemotherapy with low dose
	4) Lomustine or carmustine
	5) PCV chemotherapy
	6) Procarbazine + lomustine
	- Reirradiation
	- Supportive/best care
	- Clinical trial enroll
NCCN	- Clinical trial enroll
	- Surgical resection of large or symptomatic lesion, if feasible
	- Surgically unresectable
	1) Bevacizumab (alone or combination with carmustine, lomustine, or temozolomide)
	2) Temozolomide chemotherapy
	3) Lomustine or carmustine
	4) PCV chemotherapy
	5) Regorafenib
	- Reirradiation
	- Supportive/best care
EANO	- Clinical trial enroll
	- Surgical resection of large or symptomatic lesion, if feasible
	- Surgically unresectable
	1) Bevacizumab
	2) Nitrosourea regimen
	3) Temozolomide chemotherapy rechallenge
	- Reirradiation
	- Supportive/best care

EANO, European Association of Neuro-Oncology; KSNO, Korean Society for Neuro-Oncology; NCCN, National Comprehensive Cancer Network; PCV, procarbazine, CCNU, and vincristine

omas by the NCCN guidelines is simpler than that of other guidelines, and the EANO guidelines have a more detailed classification by application of the cIMPACT-NOW recommendation than that of the KSNO and NCCN guidelines. Ultimately, these different histopathological and molecular genetic diagnoses of gliomas should be established for global application based on an updated version of the 2021 WHO classification of CNS tumors.

Adjuvant treatment modalities for individual gliomas are recommended with various optimized protocols according to the different socio-medical environments of individual countries. The EANO guidelines are well established on evidence-based processes, such as detailed systemic reviews and scientific systems for making guidelines. However, the evidence qualities and the strength of recommendation are not the same among the three guidelines, although they have the same protocol. The most recent guidelines for diffuse astrocytoma and oligodendroglial tumors in adults by the American Society of Clinical Oncology (ASCO) and Society for Neuro-Oncology (SNO) on December 13, 2021 have several different recommendations from three guidelines [15]. For example, the ASCO-SNO guidelines in 2021 recommend deferring initial therapy until radiographic or symptomatic progression in people with oligodendroglioma (*IDH*-mutant and 1p19q codeleted) [15]. The major cause of this discrepancy is the lack of randomized clinical trials due to the rarity of the disease. Therefore, the NCCN and EANO guidelines emphasize patient enrollment in clinical trials immediately after the diagnosis of glioma.

Following the publishing of the guidelines for glioblastoma, WHO grade 2 and 3 gliomas, in adults in 2019 by the KSNO guideline working group, preparations are ongoing to update the guidelines. At the end of 2021, the working group started activating the multidisciplinary committee of the KSNO to update the guidelines. It is expected that many executive members of the disease-specific subcommittee of the multidisciplinary committee of KSNO will participate in the new KSNO guideline working group. For this updated version, a national fund of more than 5 million USD will be granted by the National Cancer Center. In the updated version of the guidelines, a more detailed evidence-based system is essential for application to the practical fields of treating patients. It is necessary for new KSNO guidelines to establish the scientific evidence quality and strength of recommendations more systemically.

Ethics Statement

Not applicable

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

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Conflicts of Interest

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