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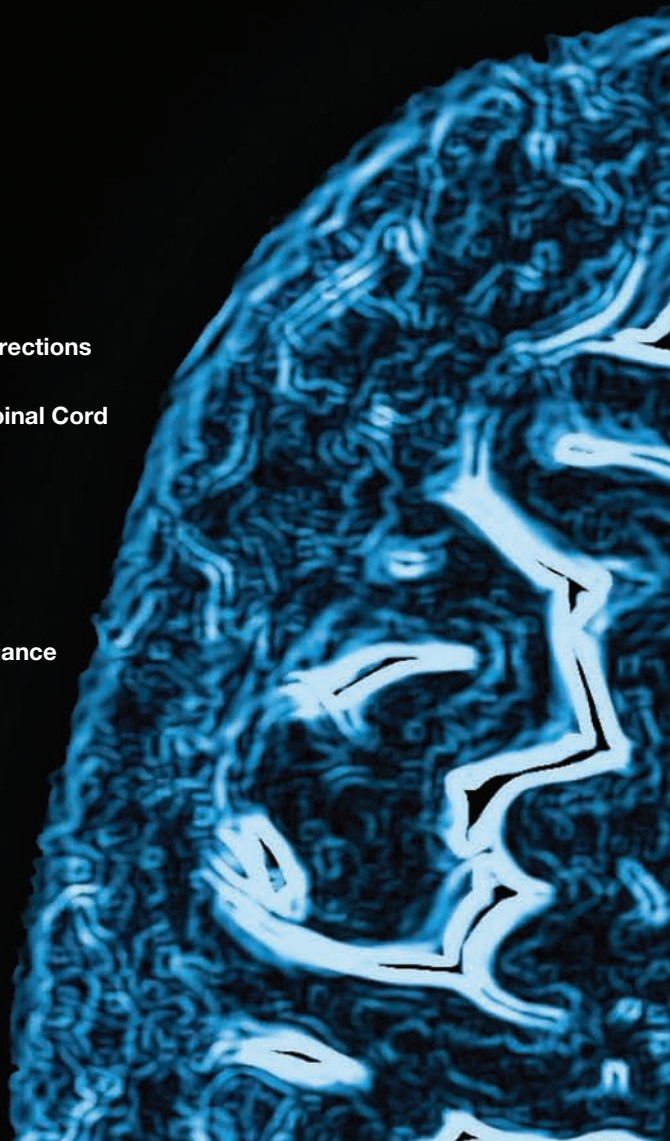

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Editorial

On behalf of the *World Federation of Neuro-Oncology Societies* (WFNOS), we invite you to read the second issue of the WFNOS Magazine. The new WHO classification for brain tumors provides an important novel perspective for the diagnosis and consecutively also clinical decision making for patients with many brain tumors. In the current issue of our magazine, G. Reifenberger provides an update on the most important changes introduced in 2016. Our colleagues from Torino summarize recent developments and future directions for the diagnosis and management of epilepsy in brain tumor patients. We enclose a report of the James Lind Alliance Priority Setting Partnership in Neuro-oncology on the top priorities for clinical research in primary brain and spinal cord tumors. Drs Ricklefs and Chiocca summarize recent trends in the treatment of gliomas—further, we enclose a report on the current state of immuno-oncology as it relates to neuro-oncology. As part of our snapshot presentations of important clinical trials, we introduce the Alliance Cooperative Group umbrella trial of molecularly targeted therapy for patients with meningiomas. We introduce the South American Society of Neuro-Oncology (SNOLA) and conclude with viewpoints of our colleagues A. Brandes and A. Malmström on the treatment of elderly patients with glioblastoma.

Kind regards,
on behalf of EANO & SNO

Michael Weller, MD
President, EANO & WFNOS
E. Antonio Chiocca, MD, PhD
President, SNO

WHO classification of central nervous system tumors 2016: integration of histological features and molecular biomarkers for improved glioma diagnostics

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Key points

- The WHO classification 2016 has changed histological glioma diagnostics to an integrated classification system considering morphological features and molecular biomarkers for more precise tumor classification.
- Diagnostic biomarkers mandatory for glioma classification are IDH mutation, 1p/19q codeletion, H3-K27M mutation, and *C11orf95-RELA* fusion. Other markers may provide additional information for diagnostic purposes and/or for guiding adjuvant therapy.
- Integrated WHO classification of gliomas sharpens diagnostic accuracy, reduces interobserver variability, and improves clinically relevant patient stratification.
- The integrated approach requires establishment of novel molecular diagnostic tests and appropriate quality control measures. In addition, reimbursement of novel molecular diagnostic procedures needs to be established.
- Time to the final integrated diagnosis is prolonged compared with purely histological diagnosis but should not lead to postponement of postsurgical treatment.

Keywords: 1p/19q codeletion, glioma, integrated diagnostics, isocitrate dehydrogenase mutation, World Health Organization (WHO) classification

Molecular genetic studies using next generation sequencing and microarray-based approaches have revealed comprehensive mutational and epigenetic landscapes for all major types of gliomas. These impressive advancements have not only improved our understanding of pathomechanisms underlying glioma development and progression but also identified novel biomarkers that may be employed for more precise tumor classification and better prediction of therapy response and prognosis. The revised World Health Organization (WHO) classification of tumors of the CNS published in May 2016 takes advantage of these developments and introduces a novel diagnostic approach that combines traditional histological features with molecular information in an "integrated diagnosis."[1] Thus, the WHO classification 2016 no longer relies on histological criteria alone but additionally employs molecular biomarkers for more accurate classification of primary brain tumors, in particular gliomas and embryonal CNS tumors. This paradigm shift has a major impact on the daily diagnostics and management of patients. Here, the general principles of the new classification system and its implications for glioma diagnostics are briefly illustrated. More detailed information is provided in the WHO classification 2016 itself and an accompanying review article.[1,2]

The Integrated Diagnosis Concept of the WHO Classification 2016

The integrated diagnosis concept of the WHO classification 2016 consists of a layered approach that combines the traditional histological tumor typing (eg, diffuse astrocytoma) and WHO grading (eg, WHO grade II) with results of molecular testing for defined diagnostic biomarkers (eg, IDH mutation) to a final (top layer) integrated diagnosis (eg, diffuse astrocytoma, IDH-mutant, WHO grade II). Thus, many glioma entities are now defined more precisely by combined histological and molecular criteria, which reduces interobserver variability and allows for more reliable prognostic predictions. At the same time, continuity to the former histology-based WHO classification is kept, as histological features for tumor typing and grading remain essential parts of the integrated diagnosis.

In total, 4 molecular aberrations have been considered as relevant diagnostic biomarkers for WHO classification of gliomas, namely mutation of the isocitrate dehydrogenase (IDH) genes 1 or 2 (IDH mutation), whole-arm codeletion of the chromosomal arms 1p and 19q (1p/19q codeletion), mutations in codon 27 of the histone 3 family

genes *H3F3A* or *HIST1H3B/C* leading to substitution of the amino acid lysine to methionine (H3-K27M mutation), and the formation of *C11orf95/RELA* fusion genes (v-rel avian reticuloendotheliosis viral oncogene homolog A [RELA] fusion). Other biomarkers, including loss of nuclear α-thalassaemia/mental retardation syndrome X-linked (ATRX) protein expression, telomerase reverse transcriptase (*TERT*) promoter mutation, v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) codon 600 mutation, *BRAF* fusion genes like *KIA1549/BRAF*, and *H3F3A* codon 34 mutation may additionally provide diagnostically helpful information for glioma classification but have not been recognised as diagnostic markers for defining integrated diagnoses. O^6-DNA methylguanine-methyltransferase (*MGMT*) promoter methylation is also mentioned in the explanatory text of the new WHO classification as important predictive biomarker for benefit from alkylating agent chemotherapy in patients with IDH-wildtype glioblastoma. However, *MGMT* promoter methylation is of limited value as a diagnostic biomarker and hence not included in the actual classification scheme.

In the rare case that molecular testing for an entity-defining biomarker is not possible or remains inconclusive, the term NOS (not otherwise specified) has been introduced into the WHO classification 2016 to indicate that the diagnosis is based on histology only and that decisive information on the relevant biomarker(s) was not available for an integrated diagnosis. Table 1 summarizes the major changes in glioma classification between the former WHO classification of 2007[3] and the revised WHO classification of 2016.[1]

WHO Classification of Diffuse Astrocytic and Oligodendroglial Tumors

A major novelty in the WHO classification 2016 is the distinction of different entities of diffuse gliomas according to the IDH mutation status. This reflects the fact that IDH mutation separates glioma entities with distinct biology and clinical behavior across the former histologically defined tumor types. Consequently, the new WHO classification groups all diffusely infiltrating gliomas, including astrocytic and oligodendroglial tumors, together under the header of *diffuse astrocytic and oligodendroglial tumors*. This main glioma group includes the IDH-mutant astrocytic gliomas (diffuse astrocytoma, IDH-mutant, anaplastic astrocytoma, IDH-mutant, and glioblastoma, IDH-mutant), the IDH-mutant and 1p/19q-codeleted oligodendroglial gliomas (oligodendroglioma, IDH-mutant and 1p/19q-codeleted, and anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted), and the IDH-wildtype glioblastomas. In addition, the entity of diffuse midline glioma, H3-K27M-mutant (WHO grade IV) has been newly introduced. Thus, the WHO classification 2016 comprises 7 main entities of diffusely infiltrating gliomas, each defined by an integrated diagnosis.

In the case of oligodendroglial tumors, diagnostic testing for 2 distinct biomarkers is mandatory, namely IDH mutation and 1p/19q codeletion. Gliomas that are positive for both markers suffice for the diagnoses of oligodendroglioma, IDH-mutant and 1p/19q-codeleted or anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted, even when histology shows a mixed oligoastrocytic or ambiguous phenotype. In other words, genotype trumps phenotype in oligodendroglioma classification. Oligoastrocytic gliomas are no longer considered distinct tumor entities because they lack disease-specific genetic profiles but carry either astrocytic or oligodendroglial genetic alterations. Depending on the results of testing for IDH mutation and 1p/19q codeletion, diffuse gliomas with histological features of oligoastrocytoma are either classified as IDH-mutant and 1p/19q-codeleted oligodendroglioma, IDH-mutant astrocytoma or, IDH-wildtype astrocytoma. This applies for both WHO grade II and WHO grade III (anaplastic) gliomas. Thus, the diagnoses of oligoastrocytoma and anaplastic oligoastrocytoma, which were associated with high interobserver variability, are discouraged in the new WHO classification. In the exceptional case when testing for IDH mutation and/or 1p/19q codeletion could not be performed or remained inconclusive, assignment to an NOS category is still possible but should be avoided whenever possible.

The two remaining groups of diffuse gliomas designated as IDH-wildtype diffuse astrocytoma and IDH-wildtype anaplastic astrocytoma are provisional WHO categories, meaning that they are less precisely defined as the 7 main entities of diffuse gliomas and likely consist of yet to be clarified mixtures of different glioma types. In adult patients, most tumors in these groups carry genetic aberrations associated with IDH-wildtype glioblastoma, such as monosomy of chromosome 10, *PTEN* mutation, and *EGFR* amplification. These cases likely represent tumors in which histological assessment of the available tissue specimens underestimated the actual tumor grade, e.g. due to limited tissue sampling. On the other hand, the provisional group of IDH-wildtype diffuse astrocytoma also may contain tumors with favorable outcome, including low-grade diffuse gliomas with *BRAF*, fibroblast growth factor receptor 1 *(FGFR1*), v-myb avian myeloblastosis viral oncogene homolog (*MYB*) or *MYB*-like 1 (*MYBL1*) aberrations commonly seen in pediatric glioma patients. Further molecular analyses beyond determination of the IDH mutation status may aid tumor classification in these cases and help to better predict their biology and clinical behaviour.

Table 1. Changes in the WHO classification of gliomas from 2007 to 2016

WHO classification of gliomas 2007		WHO classification of gliomas 2016	
Tumour entity or variant	**WHO grade**	**Tumour entity or variant**	**WHO grade**
Astrocytic tumours		***Diffuse astrocytic and oligodendroglial tumours***	
Pilocytic astrocytoma	I	Diffuse astrocytoma, IDH-mutant	II
Pilomyxoid astrocytoma	II	Gemistocytic astrocytoma, IDH-mutant	II
Subependymal giant cell astrocytoma	I	**Diffuse astrocytoma, IDH-wildtype*	*II*
Pleomorphic xanthoastrocytoma	II	Diffuse astrocytoma, NOS	II
Diffuse astrocytoma	II	Anaplastic astrocytoma, IDH-mutant	III
Fibrillary astrocytoma	II	**Anaplastic astrocytoma, IDH-wildtype*	*III*
Gemistocytic astrocytoma	II	Anaplastic astrocytoma, NOS	III
Protoplasmic astrocytoma	II	Glioblastoma, IDH-wildtype	IV
Anaplastic astrocytoma	III	Giant cell glioblastoma	IV
Glioblastoma	IV	Gliosarcoma	IV
Giant cell glioblastoma	IV	**Epithelioid glioblastoma*	*IV*
Gliosarcoma	IV	Glioblastoma, IDH-mutant	IV
Gliomatosis cerebri	III	Glioblastoma, NOS	IV
		Diffuse midline glioma. H3K27M-mutant	IV
Oligodendroglial tumours		Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Oligodendroglioma	II	Oligodendroglioma, NOS	II
Anaplastic oligodendroglioma	III	Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
		Anaplastic oligodendroglioma, NOS	III
Oligoastrocytic tumours		**Oligoastrocytoma, NOS	II
Oligoastrocytoma	II	**Anaplastic oligoastrocytoma, NOS	III
Anaplastic oligoastrocytoma	III		
		Other astrocytic tumours	
Ependymal tumours		Pilocytic astrocytoma	I
Subependymoma	I	Pilomyxoid astrocytoma	
Myxopapillary ependymoma	II	Subependymal giant cell astrocytoma	I
Ependymoma	II	Pleomorphic xanthoastrocytoma	II
Cellular ependymoma	II	Anaplastic pleomorphic xanthoastrocytoma	III
Papillary ependymoma	II		
Clear cell ependymoma	II	***Ependymal tumours***	
Tanycytic ependymoma	II	Subependymoma	I
Anaplastic ependymoma	III	Myxopapillary ependymoma	I
		Ependymoma	II
Other neuroepithelial tumours		Clear cell ependymoma	II
Astroblastoma		Papillary ependymoma	II
Chordoid glioma of the third ventricle	II	Tanycytic ependymoma	II
Angiocentric glioma	I	Ependymoma, RELA fusion-positive	II or III
		Anaplastic ependymoma	III
		Other gliomas	
		Chordoid glioma of the third ventricle	II
		Angiocentric glioma	I
		Astroblastoma	

Entities and variants in the WHO classification 2007[3] that have been deleted in the WHO classification 2016[1] are printed in red. The main integrated diagnoses that have been newly introduced in the WHO classification 2016 are printed in green. Blue indicates the new histologically defined entity of anaplastic pleomorphic astrocytoma and epithelioid glioblastoma, a new provisional variant of IDH-wildtype glioblastoma. *Provisional tumor entities or variants in the WHO classification 2016 are printed in italics. **The WHO classification 2016 discourages the diagnoses of oligoastrocytoma NOS or anaplastic oligoastrocytoma NOS, since oligoastrocytic gliomas should be assigned to either an astrocytic or an oligodendroglial tumor entity based on IDH mutation and 1p/19q codeletion status.

Concerning histological variants, gemistocytic astrocytoma remained as a distinct variant of IDH-mutant diffuse astrocytoma, while the former protoplasmatic astrocytoma has been deleted and fibrillary astrocytoma is now considered as the standard type of IDH-mutant diffuse astrocytoma. Among the IDH-wildtype glioblastomas, epithelioid glioblastoma has been added as a provisional variant characterized by epithelioid and sometimes rhabdoid tumor cell morphology as well as frequent BRAF-V600E mutation. Gliomatosis cerebri is no longer regarded as a distinct glioma entity but rather as a particularly infiltrative growth pattern that may occur in different types of diffuse astrocytic and oligodendroglial tumors. In line, molecular studies demonstrated various genetic and epigenetic profiles in gliomatosis cerebri corresponding to either IDH-mutant astrocytomas, IDH-mutant and 1p/19q-codeleted oligodendrogliomas, or IDH-wildtype glioblastomas.

WHO Classification of Other Gliomas

Changes in the WHO classification of the overall less common groups of other astrocytic tumors, ependymal tumors and other gliomas, are less pronounced as in diffuse gliomas (Table 1). Except for the new entity of RELA fusion–positive ependymoma, integrated diagnoses have not been introduced. Nevertheless, assessments of molecular biomarkers, such as demonstration of KIA1459/BRAF fusion or BRAF-V600E mutation, may be useful for differential diagnostic purposes. Anaplastic pleomorphic xanthoastrocytoma, WHO grade III, has been introduced as a new entity that differs from pleomorphic xanthoastrocytoma, WHO grade II, by an elevated mitotic count (5 or more mitoses per 10 microscopic high-power field). It substitutes the former descriptive diagnosis of pleomorphic xanthoastrocytoma with anaplastic features. Distinction of these tumors from epithelioid glioblastoma may be difficult, as histological features overlap and BRAF-V600E mutation is common in both. The grading of pilomyxoid astrocytoma as WHO grade II tumor is no longer recommended, as genetic alterations overlap with those in classic pilocytic astrocytoma and the clinical course may not always be more aggressive.

In the ependymal tumor group, the cellular ependymoma variant has been deleted and the new entity of RELA fusion–positive ependymoma has been introduced (Table 1). The latter tumors make up the majority of supratentorial ependymomas in children. Histology may correspond to WHO grade II or III, but clinical outcome is overall less favorable compared with supratentorial ependymomas without RELA fusions. Classification of chordoid glioma of the third ventricle, astroblastoma, and angiocentric glioma has remained unchanged.

Some Practical Consequences of the WHO Classification 2016

Implementation of the new WHO classification system in the routine diagnostic setting has several immediate implications. First, pathology laboratories need to update their repertoire of diagnostic methods to cover assessment of the required biomarkers. While several biomarkers, like IDH1-R132H mutation, H3-K27M mutation, BRAF-V600E mutation, and loss of nuclear ATRX expression, can be determined by immunohistochemical assays, other markers need molecular (cyto)genetic approaches, including fluorescence *in situ* hybridization (FISH), PCR-based analyses, and DNA (pyro)sequencing. As false results of molecular testing can lead to misclassification of tumors, standard operating procedures and internal quality control measures must be established for each molecular test. Separate pre- and post-PCR laboratories are recommended to reduce contamination problems. Moreover, external quality assurance programs, including interlaboratory trials, are required to ensure testing proficiency across different laboratories and reduce interlaboratory variability.

Another practical consequence relates to the fact that integrated histological and molecular classification takes longer as purely histological classification. Time to final (integrated) diagnosis may be even longer when cases are sent out to external laboratories for molecular testings. Thus, care needs to be taken to ensure that prolonged diagnostic procedures do not delay the start of postsurgical treatment and that follow-up pathology reports indeed reach responsible physicians even when a patient has been referred to an outside institution. Finally, reimbursement of the expenses for molecular diagnostic procedures needs to be solved. However, these issues should not detract from the enormous benefits that the markedly improved diagnostic accuracy of the new WHO classification provides to patients and physicians.

Conclusions

Recent studies have provided convincing evidence that certain molecular biomarkers can improve diagnostic accuracy of gliomas. These developments have been taken up in the WHO classification 2016, which no longer relies on histological criteria alone but incorporates relevant diagnostic biomarkers in an integrated approach. Thereby, accuracy and reproducability of glioma cassification is markedly improved, resulting in better stratification of gliomas into biologically and clinically more homogeneous groups. Moreover, the improved classification also facilitates future clinical trials on more precisely defined patient populations. Although certain practical consequences still need to be addressed and the number of clinically relevant diagnostic, prognostic, and predictive biomarkers will continously increase, the WHO classification 2016 certainly is a major step forward toward precision medicine in neuro-oncology.

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Epilepsy in Patients with Gliomas: New Insights and Future Directions

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Abstract

Purpose of review. To present an overview of the recent findings in pathophysiology and management of epileptic seizures in patients with gliomas.
Recent findings. Low-grade gliomas are the most epileptogenic brain tumors. Regarding pathophysiology, the role of peritumoral changes (hypoxia and acidosis, blood–brain barrier disruption, increase or decrease of neurotransmitters and receptors) are of increasing importance. Tumor-associated epilepsy and tumor growth could have some common molecular pathways. Total/subtotal surgical resection (with or without epilepsy surgery) allows seizure control in a high percentage of patients. Radiotherapy and chemotherapy as well have a role. New anti-epileptic drugs are promising, in terms of both efficacy and tolerability. Resistance to anti-epileptic drugs is still a major problem: new insights into pathogenesis are needed to develop strategies to manipulate the pharmacoresistance.

Keywords: epileptogenesis, gliomas, seizures, therapies.

Introduction

Epilepsy is a common cause of morbidity among glioma patients. Clinically seizures are localization related and manifest as simple or complex seizures with or without secondary generalization and respond less frequently to conventional anti-epileptic therapy. Epileptogenesis in brain tumor patients is multifactorial and still not fully understood. Antineoplastic treatments (surgical resection, radiotherapy and chemotherapy, targeted agents) are increasingly recognized as effective not only for tumor control but for epileptic control as well. Old anti-epileptic drugs (AEDs) have many interactions with antineoplastic agents and steroids, thus newer AEDs are increasingly investigated.

Factors Predisposing to Seizures

The frequency of seizures depends mainly on tumor location and histologic type.

Intractable epilepsy is particularly frequent in tumors which involve the temporo-mesial and insular structures.[1–4] Glioneuronal tumors, such as gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs), are typically associated with a chronic pharmacoresistant epilepsy in 80%–100% of patients.[5–8] Seizures are usually the first and isolated clinical symptom: of these, 50%–80% are focal seizures with alteration of consciousness, with or without secondary generalization.[9] Glioneuronal tumors occur predominantly in children and young adults, are located in the temporal lobe, and comprise largely grade I neoplasms with favorable outcome after surgery alone, with rare instances of recurrence and malignant transformation in gangliogliomas.[10]

Regarding the molecular genetics signature, glioneuronal tumors generally lack isocitrate dehydrogenase (IDH)1/2 mutations, while BRAF V600E mutations have been identified in up to 50% of gangliogliomas,[11] while being more rare in DNETs.[12]

The brain tissue adjacent to a ganglioglioma or a DNET may frequently show an atypical cortical development or cortical dysplasia.[5,13] BRAF V600E mutations can be present not only in glioneuronal tumors but also in focal cortical dysplasias that accompany glioneuronal tumors[14]: thus, a common origin of glioneuronal tumors and focal cortical dysplasia from the same precursor cell has been hypothesized. Moreover, a dual pathology, such as hippocampal sclerosis, in association with the epileptogenic tumor, may occur. The majority of gangliogliomas of the temporal lobe, unlike those in other locations, are positive for CD34 glycoprotein staining,[15] which could represent a possible marker of dysembryoplastic differentiation, contributing to epileptogenesis.[9]

Other rare grade I gliomas (supratentorial pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and angiocentric glioma), which prevail in children and young adults, represent a cause of seizures.[5] Similar to glioneuronal tumors, pilocytic astrocytomas and pleomorphic xanthoastrocytoma have frequently BRAF V600E mutations.[11]

Diffuse grade II gliomas, the so-called low-grade gliomas, are more common in young adults, have seizures in 70%–90% of patients, representing more often the first clinical symptom, and have an inherent tendency to progress toward higher-grade tumors. Among low-grade gliomas, seizures are much less frequent in older patients (≥50–60 y) compared with younger patients.[16] Grade II gliomas arise in the cerebral hemispheres, and compared with glioneuronal tumors, focal seizures with alteration of consciousness (complex partial seizures) are less frequent than simple partial seizures and secondary generalized seizures.[17] Tumors with an oligodendroglial component are more likely to present with seizures.[3] The rare protoplasmic astrocytoma, which is predominantly based in the cortex, can be linked to chronic epilepsy.

IDH1 and 2 mutations are common in diffuse low-grade gliomas (60%–75%), separating them from the glioneuronal tumors and pilocytic astrocytomas, in which they are absent or extremely rare.[18] IDH1/2 mutations have been associated with seizures as the initial symptom,[19–21] and this could be independent of tumor localization. Due to the structural similarity to glutamate, 2-hydroxyglutarate, the metabolic product of IDH1 mutation, is able to activate receptors of N-methyl-D-aspartate,[22] providing evidence for an epileptogenic potential. Interestingly, a high level of IDH1 mutations has been found in protoplasmic astrocytomas,[20] which are known to have a higher incidence of seizures.

However, a relationship between molecular markers and seizure risk has not been confirmed in a large French dataset of low-grade gliomas.[4] Thus, this issue is still open.

Diffuse grade III gliomas tend to overlap with grade II tumors in terms of age of presentation, location in the cerebral hemispheres, frequency of seizures at presentation, and positivity for IDH1/2 mutations.

BRAF V600E mutations are extremely rare in large series of diffuse gliomas.[11] Recently, 4 out of 5 BRAF V600E mutated diffuse grade II gliomas have been described as having long-standing, frequent, sometimes refractory, seizures, and all 4 tumors were located within the temporal lobe.[23] The same authors also reported 2 cases of glioblastoma with BRAF V600E mutations, both presenting with focal seizures. All these data suggest that the BRAF mutations occur in a setting specifically linked to epileptogenesis.

The incidence of epilepsy in patients with glioblastoma multiforme (GBM) varies between 30% and 60% — in about two thirds as a presenting symptom and in one third developing during the course of the disease.[9]

Tumor-associated seizures are more likely to occur with smaller lesions in high-grade tumors and vice versa in low-grade tumors[24]; however, among low-grade gliomas, no significant association between seizures and tumor volume or growth speed has been found.[4]

Patients with preoperative seizures have been reported with a longer overall survival compared with those without seizures across the different grades of malignancy.[25–27] Seizure recurrence is generally associated with tumor recurrence.[28]

Mechanisms of Epileptogenesis

The pathogenesis of tumor-related seizures is multifactorial and still not fully understood.[29,30] The mechanisms of epileptogenesis differ among tumor types. Intrinsic epileptogenicity of glioneuronal tumors is supported by electrocorticography and surgical and immunocytochemical studies, suggesting the presence of a hyperexcitable neuronal component.[31] The associated dysplastic disorganization of the adjacent cortex contributes to the mechanism of seizure generation.

The role of changes in peritumoral tissue is being increasingly recognized.[32] Morphologic changes include aberrant migration with persistent neurons in the white matter and pyramidal neurons with fewer inhibitory and more excitatory synapses. Intercellular connections between adjacent glial cells occur via connexin transmembrane gap junction proteins, and altered expression of connexins in tumor cells and reactive astrocytes of the perilesional cortex of patients with low-grade gliomas and epilepsy has been found by immunohistochemical studies.[33]

The peritumoral microenvironment in brain tumors is substantially different from that of normal brain tissue. Modern neuroimaging techniques have provided new evidence: MR spectroscopy has demonstrated decreased levels of N-acetylaspartate, a marker of neuronal viability and function, in lesional epileptogenic cortex.[34] Several alterations predispose to seizure generation. The tumor can mechanically compress the surrounding normal tissue because of mass effect, inducing ischemia, hypoxia, and acidosis, which in turn induce glial cell swelling and damage. A functional consequence of acidic pH is the deregulation of sodium and calcium influx across cell membranes. Further, the influence of pH on the activity of AEDs is uncertain. Changes in ionic concentrations can also contribute to neuronal excitability, and a focal disruption of the blood–brain barrier leads to the development of a seizure focus.[35]

Brain tumors and the peritumoral tissue have an altered expression of neurotransmitters and their receptors. A greater concentration of glutamate, the major excitatory amino acid neurotransmitter in the brain, has been found

in brain tumor samples from patients with active epilepsy.[36] When invading the normal tissue, glioma cells could react to spatial constraints by releasing high levels of glutamate into the extracellular space, which induces seizures and later causes excitotoxic neuronal cell death, thereby facilitating invasion and migration.[37–40*] Ionotropic and metabotropic glutamate receptors have been shown to be overexpressed both in glioma cells and in peritumoral astrocytes.[41–42] Activation of these receptors by glutamate could downregulate gamma-aminobutyric acid (GABA)–mediated inhibitory stimuli as a second mechanism of epileptogenesis. Alterations in GABA levels, the main inhibitory neurotransmitter, may also contribute to tumor-associated seizures,[43] but it remains unclear whether decreased inhibition or new excitatory activity, together with altered receptor subtype expression, may be responsible for neuronal hyperexcitability.

Recent molecular–genetic findings have been described in glioneuronal tumors. A common role for the phosphatidylinositol-3 kinase–mammalian target of rapamycin pathway in the pathogenesis of glioneuronal tumors, focal cortical dysplasias type IIB, and cortical tubers has been suggested.[44] Overall there is increasing evidence of common pathways between epileptogenicity and growth of gliomas.[45]

Regarding diffuse low-grade gliomas, susceptibility candidate genes associated with tumor-related seizures have not yet been identified.

Factors Influencing Preoperative Seizure Control

There is a lack of information on factors associated with preoperative seizure control in diffuse low-grade gliomas in the contemporary MRI era. In a recent large single institution study, about half of the patients had uncontrolled seizures.[3] The presence of simple partial seizures, a longer duration from seizure onset, and temporal lobe involvement were associated with uncontrolled preoperative seizures. Conversely, the presence of generalized seizures was associated with better seizure control.

Current Treatment of Seizures

Surgical resection, radiation therapy with various modalities, chemotherapy, and AEDs (Tables 1, 2) all have a potential role in controlling seizures. Overall, an integration of the different options is critical for a successful outcome.[46–49]

Table 1. Impact of antineoplastic treatments on seizures in gliomas

Treatments	Freedom from Seizures	Median Follow-up
Surgical resection		
Grade I tumors	80-85%	< 6 mo – 8 y
Grade II tumors	62-67%	12%–34 mo
Grades III–IV tumors	77%	14 mo
Brachytherapy/radiosurgery		
Grade II tumors	40%–100%	Up to 24 mo
Conventional radiotherapy		
Grades II and III tumors	32%–38%	12 mo
Chemotherapy (PCV, TMZ)		
grade II tumors	13%–55%	Up to 3 y

Abbreviations: PCV, procarbazine/lomustine/vincristine; TMZ, temozolomide. Modified from R. Rudà and R. Soffietti, Curr Treat Options Neurol. 2015.

Role of Surgical Resection

Seizure control after resection of glioneuronal tumors has been studied extensively. In contrast to diffuse gliomas, where the primary goal of surgery is to impact progression-free and overall survival rather than epileptologic considerations, the primary objective of surgery in glioneuronal tumors is to alleviate disabling seizures and side effects of AEDs. Seizure freedom rates are significantly higher following gross total resection compared with subtotal resection[50]: among gangliogliomas, values of 96% versus 54% are reported.[51] Duration of epilepsy of less than 1 year and secondarily generalized seizures preoperatively were factors associated with a better seizure outcome, while there were no differences between children and adults, temporal and extratemporal location, DNET and ganglioglioma and medically controlled and refractory seizures preoperatively.[50] The incomplete removal of the cortical dysplasia adjacent to tumors represents an important cause of failure.[52]

Among diffuse low-grade gliomas, the extent of resection (EOR) is an independent predictor of control of the epileptic seizures at 6 and 12 months following surgery, and gross total resection is strongly associated with seizure freedom (62%–67% range).[3,4,17,26,53] Simply partial seizures are associated with less favorable control. An early resection has been suggested in the context of recurrence.[54] A recent study has investigated the seizure outcome following surgery in a series of 52 insular low-grade

gliomas with preoperative drug-resistant epilepsy.[55] At 12 months following surgery, 67% of patients were seizure free (Engel Class I), 8% had rare seizures (Class II), 15% a meaningful improvement (Class III), and only 10% showed no improvement (Class IV). Seizure freedom significantly prevailed among patients who had seizures for less than 1 year before surgery (88%) compared with a preoperative seizure history of more than 1 year (12%), and among patients with monthly seizures compared with those with daily seizures. These findings confirm previous reports favoring an early surgical resection of low-grade gliomas,[3] even if they are small and not progressive.

In line with the other studies, the series of Ius et al[55] confirmed the importance of the EOR (measured by postoperative tumor volume) as predictor of seizure control: seizure outcome was worse for patients with an EOR $<$70%, and no or little postoperative seizure improvement occurred in cases with a prevalent infiltrative growth pattern. Interestingly, the authors reported that the patients in whom preoperative EEG demonstrated epileptic activity had a worse seizure outcome at 1 year follow-up.

Among high-grade gliomas, an extensive resection is associated with improved seizure control, with seizure freedom at 12 months of 77% in a large recent series,[28] while less extensive resections are associated with a higher risk of recurrence.[56]

An extensive surgical resection allows a reduction of AED use,[57] and patients who achieve a condition of seizure freedom following gross total resection are candidates for AED discontinuation.[3,53,55] However, factors predicting the safety of discontinuation are still not well known.[16] The prophylactic use of AEDs in patients with no preoperative seizures is still a controversial issue. An increased risk of intraoperative seizures during awake surgery has been either reported[58] or denied.[59,60] Patients with tumors located in the supplementary motor area could have a higher incidence of intraoperative seizures.[61] However, in the absence of data from prospective randomized trials, most authors favor a perioperative prophylaxis in patients undergoing awake craniotomy. It must be noted that in all studies, surgical resection was performed using intraoperative functional cortical and subcortical mapping allowing extensive resection while preserving eloquent areas.

Impact of Radiotherapy

The role of radiation therapy as a means of improving seizure control in diffuse gliomas, especially in low-grade gliomas, has been suggested for many years. Old studies reported seizure control in 40%–100% of patients with inoperable tumors by using either interstitial or γ-knife irradiation, and a usefulness of conventional radiotherapy has been described in inoperable or incompletely resected low-grade gliomas.[46] A recent retrospective study has analyzed the seizure outcome following conformal radiotherapy in a cohort of 43 patients diagnosed with grades II and III gliomas and medically intractable epilepsy.[62] A significant reduction of seizure frequency (reduction $\geq$50% from baseline) was obtained in 72% of patients at 3 months and in 76% at 12 months. Seizure reduction was observed more often among patients displaying an objective tumor response on MRI, but patients with no change on MRI had a significant seizure reduction as well. Seizure freedom (Engel Class I) was achieved at 12 months in 32% of all patients and in 38% of patients with grade II tumors. This study also demonstrated that early versus delayed radiotherapy at tumor progression is equally effective in seizure control. Prospective studies are needed to precisely define the role of radiation therapy for management of seizures in high-risk low-grade gliomas. Conversely, there are no data on seizure control following radiotherapy or radiotherapy plus temozolomide in glioblastomas.

Impact of Chemotherapy

The efficacy of chemotherapy with alkylating agents (procarbazine/lomustine/vincristine, temozolomide) in treating low-grade gliomas either at recurrence following radiotherapy or as initial treatment in symptomatic/progressive patients is well established.[46,63] Overall, a seizure improvement has been reported in 48%–100% of patients, with 20%–40% becoming seizure free. As already observed with radiotherapy, clinical improvement is not reflected by radiographic response on MRI, which is often unchanged or demonstrates only minor responses. In a recent retrospective study on 102 patients, 44% achieved a 50% reduction of seizure at 6 months after the start of temozolomide.[64] Interestingly, responding patients showed a significant longer progression-free survival of 24 months compared with only 12 months in patients without seizure reduction, and this translated into a superior overall survival as well. Moreover, the prognostic effect of seizure reduction was independent of age, histology, neurological symptoms, and previous antitumor therapies. Studies that prospectively collect the data regarding epileptic seizures following both radiotherapy and chemotherapy are needed. In particular, when analyzing the potential prognostic effect of response of seizures to treatments, molecular makers of known prognostic significance (1p/19q codeletion, IDH1/2 mutation) must be evaluated, as seizure response could be a surrogate biomarker for certain favorable prognostic molecular signatures.[65]

Last, seizure control following either radiotherapy or chemotherapy is similar in terms of rates of seizure reduction, early appearance, and lack of strict correlations with tumor response on MRI. All these findings reinforce the

Table 2. Efficacy of AEDs in brain tumors

AED	Study	*N*/Histology	Median Follow-up (mo)	Monotherapy	Add-on	Seizure-free	Reduction > 50%	Adverse Event	Neuropsicological Assessment
LEVETIRACETAM									
Wagner et al, 2003	P	26 8 LGG 18 HGG	9.3 (3.5–20)	–	YES	20%	65%	35%	NO
Newton et al, 2006	R	34 7 LGG 25 HGG 2 PCNSL	1–2	YES (7)	YES (27)	52.9%	35.3%	61.7%	NO
Newton et al, 2007	R	13 MTS	13	–	YES	77%	23%	23%	NO
Lim et al, 2009	P	15 5 LGG 10 HGG	6	YES	–	87%	12%	53%	NO
Maschio et al, 2011	P	29 6 LGG 19 HGG 4 others*	12	YES	–	93.3%	6.7%	17.2%	YES
Rosati et al, 2010	P	82 13 LGG 69 HGG	13	YES	–	91%	–	1.5%	NO
Bahr et al, 2012	P	25 5 LGG 17 HGG 3 MEN	1	YES	–	76%	–	0%	YES (23)
OXCARBAZEPINE									
Maschio et al, 2012	P	25	7.1	YES	–	40%	–	28%	YES
VALPROIC ACID									
You et al, 2012	R	431 LGG	12	YES	–	30.4%	14.4%	–	NO
Kerkhof et al, 2013	R	152 HGG	9	YES (36)	YES (116)	Mon 77.8% Add–on 60.3%	–	–	NO

AED	Study	*N*/Histology	Median Follow-up (mo)	Monotherapy	Add-on	Seizure-free	Reduction > 50%	Adverse Event	Neuropsicological Assessment
TOPIRAMATE									
Maschio et al, 2008	P	47 13 LGG 28HGG 4 MEN	16.5 (3–48)	YES (14)	YES (33)	58.8%	14.7%	6.4%	NO
Lu et al, 2009	R	54 LGG	10.3	–	YES	61%	74%	36.1%	NO
LACOSAMIDE									
Maschio et al, 2011	R	14 3 LGG 11 HGG	5.4	–	YES	42.9%	35.7%	7.1%	NO
Saria et al, 2013	R	70 25 LGG 40 HGG 5 others	5.4–6.2	–	YES	42.9%	35.7–54.3	22.9%	NO

Abbreviations: LGG, low-grade glioma; HGG, high-grade glioma; P, prospective; R, retrospective

hypothesis that the impact of these treatments on seizures is not exclusively related to an impact on the tumor cells; probably also involved are other mechanisms, such as changes of microenvironment, downregulation of neuronal epileptogenicity, etc.[46]

Efficacy of Anti-epileptic Drugs

Epilepsy in patients with brain tumors belongs to the type of partial epilepsy in adults, either with or without secondary generalized seizures. For this type of seizure, the International League Against Epilepsy has recently updated the most appropriate AED choices, based on a meta-analysis of a large number of randomized controlled trials.[66] Levetiracetam (LEV), carbamazepine, phenytoin, and zonisamide have been classified as level A anticonvulsants; valproate (VPA) represents the only level B anticonvulsant, while gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are level C. In neuro-oncology, consensus exists to avoid enzyme-inducing AEDs, such as phenobarbital, carbamazepine, and phenytoin, to avoid interactions with antineoplastic drugs. A recent meta-analysis by the Cochrane Collaboration[67] concluded that there is a lack of robust, randomized, controlled evidence to support the choice of AED for the treatment of seizures in patients with brain tumors. Moreover, it is important to realize that the excellent figures in terms of response rate of seizures to the different drugs that have been reported probably include the beneficial effects of surgery or other concomitant antineoplastic treatments.

LEV is the preferred monotherapy choice in patients with gliomas, based on numerous studies carried out either as add-on therapy or monotherapy, reporting seizure freedom in 76%–91% of patients, a 50% seizure reduction in up to 100%, and a superior tolerability.[68–70] In a recent randomized comparison, LEV yielded a seizure freedom at 12 months of 65% compared with 75% with pregabalin.[71] VPA monotherapy yielded a seizure freedom in 30%–78% of patients.[72] VPA may induce or aggravate thrombocytopenia in combination with chemotherapy.[73] However, a recent study on a cohort of GBM patients receiving radiotherapy plus temozolomide (Stupp regimen) did not show any significant difference between LEV and VPA in terms of neutrophil granulocyte, lymphocyte, and thrombocyte decrease.[74] Both LEV and VPA (to a lesser extent) could improve verbal memory in high-grade glioma patients.[75] Lacosamide is a third-generation AED that has a novel mechanism of action of selectively enhancing slow inactivation of voltage-gated sodium channels. It is approved by the FDA and the European Medicines Agency as add-on treatment for partial-onset seizures in adults with epilepsy. Lacosamide has many good properties for use in patients with brain tumors. It

has a favorable pharmacokinetic profile, which includes low protein binding; a 13-hour half-life, allowing twice daily administration; rapid and complete oral assumption not affected by food intake; no induction or inhibition of hepatic enzymes; and a very low potential for drug interactions. Lacosamide is available also in an intravenous form with easy 1:1 dose conversion to/from the oral preparation. A recent study[76] of 70 patients with primary brain tumors (mainly gliomas) with seizures reported a decrease of seizure frequency in 66%: the activity was even greater (73%) in the subset of patients who suffered from seizure unresponsive to previous therapy. Lacosamide showed activity regardless of the prior AED class. No data on seizure freedom rate were reported. Toxicities were mild. Future prospective trials should confirm these preliminary interesting data. In our experience, when seizure control is insufficient using LEV or VPA alone, a polytherapy combining the 2 drugs is preferred; in case this combination lacks activity, our policy is to add lacosamide before trying alternative AEDs (lamotrigine or zonisamide). Status epilepticus, which is more likely associated with frontal tumors and advanced disease, appears paradoxically more responsive to simple AED regimens than tumor-associated epilepsy.[77] Our preliminary experience suggests an important activity of i.v. lacosamide in treating status epilepticus resistant to phenytoin and valproate.[78]

In glioma patients with seizure freedom after antitumor therapy, the question emerges whether AEDs should be continued, particularly in those in whom antitumor treatment has been successful. Few studies suggest that in this subgroup of patients a safe withdrawal of AED medication is feasible,[79,80] but overall the benefit versus risks and timing of a withdrawal of AEDs in patients with gliomas are still unclear. A prospective observational study is ongoing in the Netherlands.[80]

The use of VPA in patients with GBM has recently drawn attention because of its potential beneficial antitumor activity as a histone deacetylase inhibitor.[81] Some clinical papers have suggested an improvement of survival when using VPA in combination with temozolomide[72,82–84]; however, this hypothesis has not been confirmed in a large recent study.[85]

Conclusions

Tumor-associated epilepsy is an important clinical problem. Low-grade gliomas are the most epileptogenic brain tumors. In this patient population, early total/subtotal surgical resection shows a strong tendency to predict better seizure outcome. This supports early operation not only based on oncological considerations, but also to avoid the risk of chronic epilepsy and optimize the patients' quality of life. Radiation and chemotherapy can be proposed as a first-line choice, instead of AED polytherapy, when uncontrollable seizures develop during follow-up, even if a true tumor recurrence is not evident. Advances into the distinct pathophysiologies of epilepsy associated with different tumor histologies will promote an even more rational choice of therapies, including prophylaxis.

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Top 10 Priorities for Clinical Research in Primary Brain and Spinal Cord Tumors

Final report of the James Lind Alliance Priority Setting Partnership in Neuro-oncology

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Executive Summary

After a very successful and productive collaboration among brain and spinal cord tumor patients, carers, major brain and spinal cord tumor charities, and multidisciplinary professional organizations, we present the top 10 UK clinical research uncertainties in brain and spinal cord tumors.

Top 10 Priorities*

(1) 1 Do **lifestyle factors** (e.g., sleep, stress, diet) influence tumor growth in people with a brain or spinal cord tumor?
(2) 2 What is the effect on prognosis of **interval scanning** to detect tumor recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumor?
(3) 3 Does **earlier diagnosis** improve outcomes, compared with standard diagnosis times, in people with a brain or spinal cord tumor?
(4) 4 In **second recurrence glioblastoma**, what is the effect of further treatment on survival and quality of life, compared with best supportive care?
(5) 5 Does **earlier referral to specialist palliative care** services at diagnosis improve quality of life and survival in people with a brain or spinal cord tumor?
(6) 6 Do **molecular subtyping** techniques improve treatment selection, prediction and prognostication in people with a brain or spinal cord tumor?
(7) 7 What are the **long-term effects** (physical and cognitive) of surgery and/or radiotherapy when treating people with a brain or spinal cord tumor?
(8) 8 What is the effect of interventions to help **carers** cope with changes that occur in people with a brain or spinal cord tumor, compared with standard care?
(9) 9 What is the effect of additional strategies for managing **fatigue**, compared with standard care, in people with a brain or spinal cord tumor?
(10) 10 What is the effect of **extent of resection** on survival in people with a suspected glioma of the brain or spinal cord?

*relate to any age

Background

Brain and spinal cord tumors are rare conditions that can be devastating for those affected and their families. The UK government has expressed commitment to improving the lives of those with rare diseases by 2020. The UK strategy for rare diseases recommends commissioning of high-quality research and recognizes the value of involving patients at every stage of the research journey. This positive approach to treating rare diseases is also now evident beyond the UK, where other countries are developing rare disease plans to better serve patients and improve outcomes.

One important way of involving patients in research has been developed by the James Lind Alliance (JLA; http://www.lindalliance.org/), which was established in 2004 and is coordinated by the National Institute for Health Research (NIHR). The JLA brings patients, carers, and clinicians together in a "priority setting partnership" (PSP) to ensure that researchers, and those who fund health research, are aware of what matters to those most directly affected by a disease.

Preparation

In July 2013, Dr Robin Grant, consultant neurologist at the Edinburgh Centre for Neuro-Oncology, gathered support for embarking upon a brain and spinal cord tumor PSP. The Neuro-Oncology Group was initiated and thus began an 18-month process aimed at identifying the clinical research questions of greatest importance to people living with brain and spinal cord tumors, those who care for them, and those involved in their diagnosis and treatment. The Neuro-Oncology JLA PSP is giving patients, carers, and clinicians the opportunity to influence the research agenda and to ensure that the time and money available for research is directed to the issues that matter most.

At the first Neuro-Oncology JLA PSP Steering Group meeting, the scope of the project was agreed as being clinical uncertainties of interventions for primary brain or spinal cord tumors, any age, from diagnosis to terminal stages. The following project objectives were agreed:

- To work with patients, carers, and clinicians to identify uncertainties about the effects of neuro-oncology interventions
- To agree by consensus on a prioritized list of those uncertainties
- To translate these prioritized uncertainties into research questions which are amenable to hypothesis testing
- To raise public awareness of why research into brain and spinal cord tumors is necessary
- To improve the prevention, diagnosis, treatment, and care of patients and their families, both during and after active treatment
- To publicize the results of the Neuro-Oncology PSP
- To take the results to research commissioning bodies to be considered for funding

Several months were spent planning, producing a protocol, engaging with the JLA team in Southampton, inviting major brain and spinal cord charities to become partners, involving patients, sourcing funding, and producing

project documentation. We developed a website (http://www.neuro-oncology.org.UK/) for the purpose of promoting the collaborative venture to seek unanswered clinical questions around brain and spinal cord tumors.

Process

In March 2014, the Neuro-Oncology Group invited questions from members of the public who had experience or interest in brain and spinal cord tumors, and professionals dealing with this group of patients. Following JLA guidelines, we undertook a dynamic collaborative process of continually refining and prioritizing questions until we established a "top 10" of the clinical uncertainties that exist in the area of brain and spinal cord tumor diagnosis and treatment. There were four main stages in the refinement process:

(1) **Gathering questions:** the main source of questions was from a survey on our website which was publicized widely through the press and relevant charity, health, and research organizations. Demographic data were requested but were optional. This was augmented with a small number of questions from a brain tumor charity patient forum and from UK DUETs (UK Database of Uncertainties about the Effects of Treatments).

(2) **Collating and formatting questions:** we merged duplicate questions and rejected out of scope questions and questions that research has already answered. Questions were categorized and were standardized as far as possible into a PICO (**p**articipants, **i**nterventions, **c**omparisons, **o**utcomes) format to ensure we selected questions that could be explored in a clinical trial. Formatted questions were checked by pairs of stakeholders.

(3) **Prioritizing questions:** the number of questions was narrowed down by stakeholders working as a whole group then in pairs and then individually. Once we had what we considered a manageable number, we sent out a second survey to patients, carers, and health professionals and more widely, with a request that they vote for their top 10.

(4) **Agreeing on the top 10:** at the final prioritization workshop in London in November 2014, JLA facilitators used a modified delphi and nominal group technique to help stakeholders reach consensus on the final top 10.

Participation

Our first survey generated over 600 initial individual questions from around 200 people. We were able to ascertain that all age groups had contributed, as had both males and females. Most importantly, we received questions from the 3 key groups: patients, carers (ie, family members or friends), and health professionals. Submissions were primarily from the UK, with a few from elsewhere (Australia, France, Ireland, Italy, the Netherlands, and the USA).

Two hundred twenty-seven people took part in a second public survey in September 2014, to choose which of 44 questions should be prioritized. Although there appeared to be less representation from the youngest age group and spinal cord patients at this stage, we were confident that we had a sufficiently representative response that included relevant questions pertaining to these demographics. Crucially, our 3 key groups of patients, families, and professionals were well represented.

Our stakeholder group comprised 11 men and 18 women, ranging in age from 14 to 76 years. Stakeholders were patients, relatives, charity representatives, doctors from a breadth of specialties, nurses, and allied health professionals. Fourteen people were primarily involved to represent the patient perspective and 15 to represent the professional, but many stakeholders wore more than one hat.

Next Steps

Working together, we successfully identified and prioritized 10 crucial questions, structured in a form suitable for clinical trials.

To promote these top 10 priorities, we will engage with governmental organizations such as the NIHR and Chief Scientist Office (CSO), Medical Research Council (MRC), the National Institute for Health and Care Excellence (NICE); independent charities such as Wellcome Trust, Cancer Research UK (CRUK), Marie Curie, UK Brain Tumor Charities; and clinical trials support such as through Cochrane, the National Cancer Research Institute (NCRI), and UK Clinical Research Collaboration (UKCRC) clinical trials units. We will encourage the commissioning of high-quality clinical trials run by specially trained research clinicians and supported by the NCRI clinical studies groups run through the UKCRC clinical trials units. It is hoped that the outputs of these trials will inform guidelines and quality performance indicators.

Our ultimate goal is to find answers to these uncertainties in diagnosis, treatment, and care, so that people with a brain or spinal cord tumor will receive the best treatment possible, will live longer, and will have better quality of life.

For more information about the project, see our website at www.neuro-oncology.org.UK or contact us at jlagroup@exseed.ed.ac.UK

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Therapies for Glioma: New Trends

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Malignant gliomas evade therapy because of their complex and adaptive cellular composition, their ability to evade most therapies through compensatory mechanisms, and the difficulty to deliver drugs. By definition they are unresectable and recur, as history has shown, even after radical complete lobectomies. So, whereas advances in surgery, radiotherapy, chemotherapy, and as of recently immunotherapy have made therapies mostly safer and somewhat more effective, strong efforts are being made to find new approaches to improve the efficacy of antiglioma treatments.

The development of therapeutic strategies that will target glioma cells by a combination of surgery, radiation, and chemotherapy as well as priming the patient's immune system against the tumor are now gaining momentum in clinics[1]. Multiple strategies to enhance or prime the patient's immune system against the tumor are being investigated, including vaccine therapy, oncolytic viruses, checkpoint inhibition, as well as gene therapy. Every strategy aims to induce an immune response against tumor antigens, which seem to remain unnoticed during tumor development.

Apart from immune therapy, another promising approach to tackle glioma cells is the use of microRNAs (miRs). MiRs are associated with various types of human cancers, with some having an oncogenic activity, while others are tumor suppressors. Due to their ability to mirror the tumor stage, subtype[2], and adaption[3], they also have an appealing potential to act as biomarkers in glioma[4,5].

Vaccines

Most vaccine strategies involve the administration of a tumor-associated antigen[6], mostly peptides, which are coadministered with immunostimulatory adjuvants to induce a cross-presentation of the antigen[7–9]. Probably the most well-known peptide vaccine is rindopepimut, which is directed against epidermal growth factor variant III (EGFRvIII). It is now being tested in an international, randomized, double-blind, controlled phase III study with standard of care and granulocyte-macrophage colony-stimulating factor in primary, surgically resected, EGFRvIII-positive glioblastoma multiforme (ACT IV study). Unfortunately, it was reported that results did not show evidence of a benefit over control.

Oncolytic Virus Therapy

Besides vaccinating patients against a specific tumor-associated antigen, another approach is to trigger the immune response against tumor cells by oncolytic virus therapy. A couple of viruses are being investigated for their capability for selective tumor cell killing without harming the normal brain and their potential to direct the immune system against upcoming tumor antigens. The overall goal of oncolytic virus therapy is to achieve a sophisticated tumor cell killing and recruit effector immune cells to the tumor microenvironment to produce a long-lasting response and control of tumor cells. Next to mutant herpes simplex viruses (HSV)[10,11] (NCT02031965), oncolytic parvovirus H1[12], replication competent adenovirus[13] (NCT02197169), and measles virus (NCT00390299), there is a genetically recombinant, polio/rhinovirus chimera (PVS-RIPO) currently in the spotlight. PVS-RIPO was recently fast-tracked by the FDA because of its promising results in a phase I clinical trial occurring since 2012 (NCT0191893). It achieved a 20% three-year survival rate in patients with glioblastoma, compared with a historical 4% survival rate[14].

Checkpoint Inhibitors

These treatments work by targeting molecules that serve as checks and balances on immune responses, with its most prominent members being programmed cell death protein 1 (PD1) and its ligand (PDL1) and cytotoxic T lymphocyte antigen (CTLA-4)[15–17]. Both molecules play an important role in the secondary interaction of T cells to their target, while CTLA-4 inhibits T-cell priming and PD1 T-cell activation at the target site, if the ligand is bound, namely being CD80/CD86 and PDL1/PDL2[15,17]. By blocking these inhibitory molecules with either anti-PD1 (nivolumab) or anti–CLTA-4 (ipilimumab), these treatments are designed to unleash or enhance preexisting anticancer immune responses. CTLA-4 was one of the first molecules to be studied and showed an antitumor effect within a murine model for melanoma by CTLA-4 blockade[18]. Several preclinical studies have shown that anti–CTLA-4 and anti-PD1 improved survival in mice glioma models[19,20]. Current trials are investigating several aspects with either anti-PD1 and/or anti–CTLA4 treatment in newly diagnosed (NCT02617589) or recurrent glioblastoma (NCT02017717). Further trials are trying to block PDL1 (NCT02336165) or using PD1 blockade in addition to dendritic cell vaccine in patients with recurrent glioma, astrocytoma, or glioblastoma (NCT02529072).

Gene Therapy

Genetic therapy for glioblastoma has been postulated and attempted for the past 20 years, with different degrees of success[21,22]. Viruses targeting mammalian cells have evolved as the most promising vehicles for horizontal gene transfer and have been used to deliver so-called suicide genes into tumor cells[21–24]. These suicide genes are envisioned to act as drug-activating enzymes which will convert an inactive prodrug, given systemically, into its deadly derivative. One of the best-studied suicide genes

is the HSV-derived enzyme thymidine kinase (HSV-TK)[23,25]. It activates ganciclovir into its toxic nucleotide metabolite, leading to disruption in DNA replication and therefore halting cell division[26]. Since the prodrug is a poor substrate for human TK, the toxic effect is limited to cells that have been transduced with the HSV-TK using nonreplicating herpesvirus or adenovirus[23,27]. However in a randomized, open-label phase III clinical trial using and HSV-TK retroviral vector, no significant improvement of median survival or progression-free survival was found, probably due to low delivery of both vector-producing cells and the ganciclovir prodrug[28]. Whereas recent advances using the local delivered aglatimagene besadenovec (AdV-tk), an adenoviral vector containing the HSV-TK gene and administration of the prodrug, showed improvement in patients with minimal residual disease after gross total resection, but this result needs to be confirmed in a formal randomized 2-arm trial [27].

MicroRNAs

MicroRNAs are endogenous, small noncoding RNAs that regulate gene expression by antisense complementarity to specific RNAs. Evidence is present that miRs regulate specific biologic processes such as cell invasion, migration, proliferation, apoptosis, stress resistance, stem cell migration, and cell identity[29–32]. MiRs are currently the focus of several brain tumor research groups, and a significant number of miRs have been found to be deregulated in gliomas and to contribute to the development of the disease and its prognosis[30,32–36]. For example, miR-124 and miR-137 are postulated to induce differentiation of neural stem cells and human glioma-derived stem cells, as well as induce a cell cycle arrest in glioblastoma multiforme cells[32]. MiR-128 has been shown to be critical in the self-renewal of glioma cells through the targeting of at least 2 of the epigenetic polycomb repressor complex mRNAs[30,36]. Furthermore, it was shown for miR-10b to positively affect the growth and invasion of glioma cells and to reduce apoptosis in vitro[35], whereas miR-1 functions as a tumor suppressor in glioma by inactivating multiple oncogenic signaling pathways[33].

Apart from their therapeutic potential, miRs are a promising class of molecular biomarkers[4,37] and have been reported to have tissue-specific signatures, as they can mirror the profile of their tissue of origin[2,5,38]. Patients treated with immunological therapies, locally applied oncolytic viruses, or intracavitary chemotherapies often show radiological alterations after therapy. In conventional radiotherapy/chemotherapy-treated patients, these alterations would be interpreted as tumor progression[39], but in patients treated with novel therapy modalities, especially with an immunological component, they might in fact represent treatment response. To distinguish tumor growth from therapy reaction, a need for reliable tumor markers is emerging, which might be met by circulating miRs.

Conclusion

Multiple strategies have demonstrated safety and shown early signs of efficacy in phase I and II clinical trials. Many agents are currently undergoing phase III investigations with results being anticipated within the next 1–2 years.

Since gliomas display cellular heterogeneity and adaptation capability to therapy, combining various therapy modalities to tackle each aspect of tumor development and progression will most probably determine the best treatment approach for patients.

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Immunotherapy for Primary Brain Tumors

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Abstract

The limited efficacy of conventional treatment modalities such as surgery, radiation therapy, and alkylating agent chemotherapy against various primary brain tumors as well as the failure of other approaches such as anti-angiogenic therapy have resulted in a continued interest in novel therapies which may improve the prognosis of patients affected by intracranial neoplasms, particularly glioblastoma. Immunotherapy such as vaccination against the tumor has been used for more than 2 decades in clinical neuro-oncology with only limited progress. This situation may now change with the introduction of advanced vaccines, the availability of immune checkpoint inhibitors, and most importantly, an overall improved understanding of the interaction between the tumor and its microenvironment in the central nervous system. Currently, several peptide vaccines and drugs targeting checkpoint molecules such as programmed cell death protein 1 (PD1) are in late-stage clinical trials for glioblastoma patients. Among the challenges for immunotherapy are the identification of patients who may be the most appropriate candidates for these treatments as well as the implementation of an immune monitoring which may help to trace antitumor immune activity. Only a thorough clinical development will ultimately result in the incorporation of any immunotherapy into the standard of care and clinical practice.

The Immunosuppressive Microenvironment in Primary Brain Tumors

Immunotherapy has been one of the most quickly evolving research areas in oncology. Driven by the successful implementation of immunotherapeutics in the melanoma field,[1,2] there has been a strong interest in exploiting these drugs as well as other immunotherapeutic strategies also against primary brain tumors. Among these, glioblastoma has remained a major challenge because of its unfavorable prognosis. Accordingly, glioblastoma has been in the focus of most immunotherapeutic studies conducted so far. Compared with other tumor types, glioblastoma is characterized by its poor immunogenicity.[3] Furthermore, its localization in the brain may impede strong immune responses because of the particular immunological situation in the CNS. Trafficking of lymphocytes to the CNS, a prerequisite for sustained immune surveillance of the tumor, is limited by various obstacles. First, the blood–brain barrier does not allow for uncontrolled entrance of lymphocytes to the brain parenchyma.[4] Second, professional antigen-presenting cells are absent or, in the case of microglial cells, possess only limited equipment to sufficiently mount immune responses.[5] Furthermore, it has long been doubtful whether lymphatic vessels exist in the CNS. Findings from rodent models suggest the presence of lymphatic structures.[6,7] If these findings can be confirmed in humans, they would stress the rationale for active immunotherapy also against malignant neoplasms in the brain.

The immunological situation in the CNS is additionally compromised by immunosuppressive signals derived from the tumor which dominate the local microenvironment. Although several mechanisms contributing to the immunosuppressive environment in gliomas have been characterized in detail,[8–11] no therapeutic approach targeting any of these molecules has shown relevant clinical activity so far. One of the major immunosuppressive cytokines secreted by glioma cells is transforming growth factor (TGF)-β.[12,13] Despite intense preclinical work suggesting that inhibition of TGF-β activity may result in reduced tumor growth, this approach can so far not be translated successfully into a clinical setting with human patients. Among the strategies which have been explored in order to interfere with the TGF-β pathway are blocking antibodies, antisense molecules, and, most recently, pharmacological inhibitors of the cognate receptor. The clinical development of almost all of these drugs has been abandoned because of lack of activity or systemic toxicity.[14,15] Another pathway which has been considered as a promising target for therapeutic purposes is the tryptophan metabolism. Depletion of tryptophan is carried

out by tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO), which results in kynurenine metabolites that ultimately confer local immunosuppression. Although inhibitors of IDO or TDO have reached the clinic,[16] their activity against primary brain tumors remains to be proved. Clinical trials assessing this approach in more detail are ongoing.

Vaccination

Harnessing the immune system against a tumor by vaccination has been investigated for several decades in neuro-oncology. While the use of unspecific vaccines derived from whole cell lysate or RNA has been largely abandoned, more specific, typically peptide-based vaccines have been developed and investigated within the last 10 years. This approach, however, requires defined targets which are overexpressed or ideally exclusively expressed on tumor cells. Such tumor-specific antigens are rare in glioblastoma with variant III of epidermal growth factor receptor (EGFRvIII) as the most prominent example.[17,18] However, EGFRvIII is expressed in only ~25% of all glioblastomas. Rindopepimut is a vaccine derived from EGFRvIII composed of a 14-mer peptide that is conjugated to keyhole limpet hemocyanin. It is administered in conjunction with macrophage colony-stimulating factor. Following several smaller single-arm trials with promising results in glioblastoma patients,[19–21] rindopepimut was assessed in a double-blind, randomized phase III study in patients with newly diagnosed glioblastoma (ACT IV; NCT01480479). However, according to a press release of the company in March 2016, the trial was stopped because of lack of activity of the vaccine. In contrast to this disappointing result in the first-line setting, a smaller randomized, placebo-controlled phase II study in patients with recurrent glioblastoma receiving either rindopepimut or placebo in combination with bevacizumab demonstrated prolonged survival of patients treated with rindopepimut (hazard ratio 0.57 for the intention-to-treat population).[22] Whether the administration of rindopepimut in combination with bevacizumab will be further explored needs to be awaited.

More advanced vaccines comprise several peptides aiming at targeting the tumor more efficiently.[23] The clinically most advanced multipeptide vaccine is ICT-107, which is generated from patient-derived dendritic cells pulsed with 6 peptides originating from glioblastoma-associated antigens. Following the promising results of a phase II study,[24] the vaccine is currently being assessed in a randomized, controlled phase III trial in human leukocyte antigen A2–positive patients with newly diagnosed glioblastoma (NCT02546102).

Finally, the characterization of mutations in the isocitrate dehydrogenase (IDH)-1 gene, frequently found in World Health Organization grades II and III gliomas, but rarely in glioblastoma, has launched the search for vaccines derived from the mutated IDH protein that may be suitable to mount powerful immune responses against IDH-1-mutated tumors.[25] This approach is currently being explored in first clinical trials.

Immune Checkpoint Inhibition

Immune cell receptors or their ligands which regulate immune cell responses are called “immune checkpoints.” Typically, these ligand-receptor pairs downregulate immune responses in order to preclude overwhelming and potentially destroying immune cell activity. Immune checkpoints have been recognized as promising therapeutic targets within the last years. Antibodies which block immune cell receptors with inhibiting properties such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), PD1, and its ligand PDL1 aim at boosting the lytic activity of immune cells against a tumor and prolong the duration of these responses. Following the approval of ipilimumab, an antibody directed against CTLA-4, for patients with metastatic melanoma, anti-PD1 antibodies such as nivolumab and pembrolizumab entered the clinical area and have been approved for the treatment of melanoma and lung cancer. It still remains unclear whether the activity of these drugs against tumor manifestations in the brain is similarly effective compared with tumor manifestations outside the CNS.[26,27] Based on promising preliminary results in patients with brain metastases as well as preclinical glioma models,[28–30] PD1 inhibitors are currently being investigated in recurrent and newly diagnosed glioblastoma. A phase III trial assessing nivolumab compared with bevacizumab in patients with first recurrence of glioblastoma has completed accrual (NCT02017717). Further trials exploring the addition of nivolumab to radiation therapy or combined radiochemotherapy in patients with newly diagnosed glioblastoma are ongoing (NCT02617589; NCT02667587). Importantly, checkpoint blockade does not mount immune responses specifically against tumor cells. In contrast, checkpoint inhibitors may induce off-target effects resulting in a variety of immune-related adverse events which require a close monitoring of the patients.

Other Immunotherapeutic Strategies in Clinical Development

EGFR has not only been used as a target for vaccination as described above but may also serve as a point of

attack for monoclonal antibodies. Antibodies that are coupled to toxins or chemotherapeutic agents are commonly called "immunoconjugates." ABT-414 is an antibody linked to monomethylauristatin, a cytotoxic agent, which is directed against amplified or mutated EGFR. Following the successful completion of a phase I trial in patients with recurrent glioblastoma,[31] the drug is currently being investigated in larger trials in patients with newly diagnosed and recurrent glioblastoma (NCT02573324; NCT02343406).

The administration of immune cells to patients is referred to as "adoptive cell therapy." Typically, immune cells are harvested from patients, subsequently expanded and/or modified ex vivo in order to enhance their antitumor activity, and finally transferred back to the patient. The genetic modification of immune cells using chimeric antigen receptors (CARs) which specifically recognize a predefined target molecule has resulted in striking effects in hematological cancers.[32] This concept is currently also evaluated in patients with primary brain tumors, foremost patients with EGFRvIII-positive glioblastoma.[33,34]

Conclusion and Future Directions

Immunotherapy may represent a powerful weapon against glioblastoma and other primary brain tumors. Compared with other treatment modalities, immunotherapeutic approaches may allow for long-lasting tumor control or even cure because of the memory function of the immune system, which can confer durable antitumor responses. Beyond the vaccines and checkpoint inhibitors that are currently being explored within large trials, even more specific, patient-tailored vaccines as well as novel checkpoint inhibitors targeting further immune cell regulators will enter clinical neuro-oncology. Finally, the ideal timing for implantation of any immunotherapy into the standard of care needs to be established within appropriate trials.

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Targeted therapies for meningiomas: a phase II trial of the Alliance Cooperative Group

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Synopsis

Meningiomas are the most common primary brain tumor. Although surgery and radiation are effective in treating the majority of meningiomas, there are no effective chemotherapeutic agents when surgery and radiation fail. In nearly all prior clinical studies investigating systemic therapies in meningiomas, response rates have been close to 0%.[1] Recently, potentially clinically actionable genetic mutations have been identified in meningiomas.[2,3] The most common genetic alterations are inactivating mutations in *NF2*.[2,3]Approximately 10% of *NF2*-wildtype meningiomas harbor *AKT1 E17K* mutations,[2–4] which are known oncogenic drivers in other tumors.[5] A small subset of *NF2*-wildtype meningiomas (3%–5%) have oncogenic mutations in *SMO* which have been previously described in basal cell carcinoma[6] and desmoplastic medulloblastoma.[7] Notably, *SMO* and *AKT1* mutations commonly occur in the skull base,[2–4] which are often the most difficult meningiomas to treat surgically. Therapies that target these alterations are currently in clinical use or clinical trials in other cancers.

Based on these data, the Alliance, a National Cancer Institute sponsored cooperative group in the US, has initiated A071401, a multicenter biomarker-driven phase II trial of Smoothened (Smo)/Akt/focal adhesion kinase (FAK) inhibitors in patients with recurrent, residual, or progressive meningiomas harboring *SMO/AKT1/NF2* mutations. Tumors are centrally screened at Massachusetts General Hospital for the presence of an *AKT1*, *SMO*, and *NF2* mutation, and if present, patients receive the respective inhibitor that targets the mutations. The primary objective of the study is to determine the activity of Smo, Akt1, and FAK inhibitors in patients as measured by co-primary endpoints 6-month progression-free survival and response rate. Secondary endpoints are overall survival, median time to progression, and toxicity of Smo, Akt1, and FAK inhibitors. Twenty-four evaluable patients will be assigned to each treatment group based on their tumor mutations. With each mutation treatment arm group, 12 patients will be accrued to the grade I cohort and 12 patients to the grade II/III cohort. Key inclusion criteria include: intracranial meningioma, presence of Smo, Akt, or neurofibromin 2 (NF2) mutation, and progressive or residual measurable disease. If successful, this study represents a potential new therapeutic approach in recurrent meningioma, a disease with a critical need for effective systemic therapy.

A071401 is open to patient enrollment. Questions concerning this protocol can be directed to Priscilla Brastianos, pbrastianos@mgh.harvard.edu or Samantha Sublett, Protocol Coordinator, at ssublett@uchicago.edu.

Study synopsis

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SNOLA's *Update on Neuro-Oncology* Conference Overview

The **Society for Neuro-Oncology Latin America**'s (SNOLA) first conference, the *Update on Neuro-Oncology*, is now over, but there is still much to talk about it in the following months. The meeting took place on March 24–26 in Rio de Janeiro, Brazil, and was a huge attainment for the Latin American community.

With more than 25 international speakers sharing their knowledge in neuro-oncology, nearly 600 attendees, and 137 research abstracts submitted for the oral and poster awards, we can definitely assure that our 2018 conference will be magnificent. It is already being planned, will be held in São Paulo, Brazil, and will be called *State of the Art in Neuro-Oncology*.

During the meeting, we had special moments, such as the awards ceremony, where we rewarded with a plaque renowned names within the different national and international areas of neuro-oncology (pathology, imaging, radiotherapy, oncology, pediatric oncology, and neurosurgery). Also, rewarding the best poster and oral presentations of research carried out by individuals all around the world was a chance the society had to thank these researchers, as well as, to a certain extent, encourage them to continue with their practices, as SNOLA recognizes the need and importance of the role of research to develop neuro-oncology around the world.

Furthermore, the quality of the lessons was remarkable, highlighting cases, discussions with multidisciplinary experts, and interactive firing squad sessions. Feedback from attendees could not have been better. According to our reasearch 98,6% of attendees classified the knowledge level of the conference as excellent/good, the median conference grade was 8,74, and 99,3% would recommend the event to a friend. It was therefore an amazing experience for the first conference. We thank all those involved in making the event possible, such as sponsors, the organizing committee, and the scientific committee. It has been a great pleasure to offer this event for our needy Latin American society. We are looking forward to the 2018 *State of the Art in Neuro-Oncology*.

Best wishes,

Marcos V. C. Maldaun, MD, PhD

SNOLA's Founding President

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Report from ASCO Meeting, Chicago, June 3–7, 2016

By Riccardo Soffietti,

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With regard to CNS tumors, the annual meeting of the American Society of Clinical Oncology (ASCO), included 1 plenary lecture, 9 oral presentations, and 268 posters.

In the plenary session, J. Perry presented the final results of an international phase III trial headed by the Canadian Cancer Trials Group (CCTG) and the European Organisation for Research and Treatment of Cancer (EORTC) on elderly patients (>65 y) with glioblastoma multiforme (GBM). Overall, the addition of temozolomide (TMZ) chemotherapy to standard short course radiotherapy (RT) significantly improved overall survival (OS; primary endpoint) compared with short course RT alone (9.3 vs 7.6 mo). The benefit was particularly evident in patients with O^6-DNA methylguanine-methyltransferase (MGMT) promoter methylation, where median survival was nearly doubled.

At the start of CNS oral session, M. van den Bent presented the results of a preliminary analysis of the EORTC phase III CATNON trial in anaplastic gliomas without 1p/19q codeletion (751 patients randomized).

OS was significantly longer for patients with adjuvant TMZ (not reached) compared with those without TMZ (4.1 mo), and the same was true for progression-free survival (PFS; 42.8 mo vs 19 mo); conversely, no data are mature so far regarding the impact of TMZ concurrent with radiotherapy.

W. Wick presented the final results of the EORTC phase III trial 26101 in glioblastoma at first relapse after chemoradiation. The combination of bevacizumab and lomustine yielded a modest improvement of PFS (4.17 vs 1.54 mo) but not OS (9.10 vs 8.64 mo) over lomustine alone.

M. T. Walsh discussed the results of a single arm phase II trial employing standard TMZ in a cohort of low-grade gliomas following subtotal resection or biopsy. The response rate (complete response + partial response) was 6% only with 87% stable disease. PFS and OS were extended in the subgroup of patients with 1p/19q codeletion and low residual tumor after surgery. Interestingly, the study reported that >50% of patients had not received RT for a median of 5.8 years.

The phase III randomized trial JCOGO504 (Japanese study) on patients with up to 4 brain metastases from solid tumors was presented by T. Kayama. This was a non-inferiority trial that showed no differences in OS between surgery + whole brain RT (standard arm) and surgery with stereotactic radiosurgery at salvage.

P. Kumthekar illustrated the results of a single arm phase II trial on AMG1005, a novel brain-penetrant taxane derivative, for treatment of recurrent brain metastasis and/or leptomeningeal disease (LMD) from breast cancer. The authors reported a response rate up to 14% in both human epidermal growth factor receptor (HER)2+ and HER 2− patients, with a significant clinical benefit. Interestingly, partial responses were higher (22%) in patients with LMD.

A large retrospective study from Cleveland Clinic (S. Balasubramamian) on brain metastases from non-small-cell lung carcinoma reported that the number of brain metastases was prognostically relevant only for patients without epidermal growth factor receptor and anaplastic lymphoma kinase mutations.

The analysis of a large cohort of wild-type GBM patients treated with chemoradiation (A. Lai) showed that telomerase reverse transcriptase (TERT) promoter mutation does not predict OS while interacting with MGMT methylation status; in fact, the benefit from MGMT methylation was only seen in the TERT mutation GBM.

The poster session covered almost all subfields of neuro-oncology.

In addition to free papers, there were educational and scientific symposia on brain metastases, immunotherapy in glioblastomas, and low-grade gliomas.

Treatment of Elderly Patients with Glioblastoma

Interview with Annika Malmström and Alba Brandes

Considering that the median age of patients with newly diagnosed isocitrate dehydrogenase wild-type glioblastoma multiforme (GBM) is 62 years, the treatment of patients with GBM requires from us management skills for treating elderly patients—with all implications of reduced organ functions, multimorbidity, and needs for social support.

Two leading experts in this difficult field, Alba Brandes from Bologna and Annika Malmström from Linköping, Sweden were asked their opinions for designing treatment plans for elderly glioblastoma patients and to provide insights in their current practice.

How would you define an optimal treatment for an elderly person with GBM?

Alba Brandes: The heterogeneity and the complexity of the elderly population represent the main challenges to the treatment of cancer in those patients.

Aging is an ongoing process that leads to the loss of the functional reserve of multiple organ systems, increased susceptibility to stress, an association with increased prevalence of chronic disease, and functional dependence. Determined by a combination of genetic and environmental factors, this process is highly individualized and poorly reflected in chronologic age.

We should discern the "fit" elderly, in whom standard cancer treatment appears to be comparable to a younger population, and the "unfit" or "frail" elderly, in which the risks of the treatment may overwhelm potential benefits. There are many aspects that have to be assessed before treating an elderly patient, or before choosing the treatment itself.

To date, we have data in "elderly" populations who are considered >65 years old and trials on the "general" population that cover the ages from 18 to 70 years.

This overlap generated confusion and debates in recent years.

We have also to keep in mind that the 6- or 7-week temozolomide (TMZ) continuative treatment came from a phase I study that enrolled 24 patients with a median age of 46 years. Moreover, in the phase II trial that was performed by Stupp before the EORTC 26981-22981/NCIC CE3 phase III trial, inclusion criteria did not limit the upper age of patients. However, the authors enrolled patients with ages ranging from 18 to 70 years, even in the absence of age restrictions. In consideration of these findings and remembering that bone marrow toxicity is age related, the EORTC 26981-22981/NCIC CE3 phase III trial included patients younger than 70 years. Thus, the hematologic toxic effects of protracted TMZ schedule were unknown in elderly patients.

However, the results of the recent randomized phase III trial conducted by the Canadian Cancer Trials Group (CCTG), the European Organisation for Research and Treatment of Cancer (EORTC), and the Trans-Tasman Radiation Oncology Group (TROG) provided the new evidence for the treatment of glioblastoma in the elderly (CCTG CE.6–EORTC 26062-22061–TROG 08.02).

In this trial, 562 newly diagnosed glioblastoma patients 65 years and older were enrolled to receive either short-course radiation therapy (RT) (40 Gy in 15 fractions over 3 wk) with concurrent and adjuvant TMZ or short-course RT alone. Of note is that the median patient age was 73 years, and two-thirds were older than 70 years. The 3-week chemoradiation extended the median overall survival from 7.6 months with RT alone to 9.3 months.

In addition, tumor growth was slower in the TMZ group, with median progression-free survival of 5.3 months versus 3.9 months. The 1-year and 2-year survival rates were 37.8% and 10.4% with radiation plus TMZ versus 22.2% and 2.8% with RT alone.

This significant result was enhanced in the population of patients with O^6-DNA methylguanine-methyltransferase (MGMT) methylation, where the median overall survival was 13.5 months with TMZ and 7.7 months with RT alone. Patients who received TMZ had a 47% lower risk of death than those who received RT alone.

Importantly, quality-of-life analyses using the standardized EORTC 30-item core quality-of-life (QLQ-C30) and 20-item brain neoplasm (BN20) questionnaires showed no differences in physical, cognitive, emotional, and social functioning between the 2 groups.

Even if decisions about therapy in elderly patients are individual and based on a patient's performance status and family support, these results have now modified our clinical practice, introducing chemoradiation in elderly GBM patients.

Future work needs to better determine the role for comprehensive geriatric assessments (CGAs) in this patient population to better identify the patients who may most benefit from our therapies.

Annika Malmström: According to our National Glioma Guidelines, elderly patients will be offered maximal safe resection. Patients >65 years old will have their tumor assessed for MGMT methylation status. Oncological treatment has until now been TMZ in standard dosing (5 d every 4 wk) for those with MGMT methylated GBM, while those with unmethylated tumor have received hypofractionated radiotherapy (3,4 Gyx10), if not considered fit enough for regular radiochemotherapy to 60 Gray followed by adjuvant TMZ. With the report at the American Society of Clinical Oncology of the results of the NCIC/EORTC elderly trial showing an advantage of combined treatment with 3 weeks of RT together with and followed by TMZ, we now have an additional treatment option mainly for those with methylated MGMT.

Our National Guidelines also point out that an assessment of rehabilitation needs and a plan for rehabilitation should be provided to all patients already before start of any oncological treatment.

From data from our Quality Registry for Primary Brain Tumors we can see that a more active attitude toward treating elderly patients has been adopted throughout Sweden and has led to increased survival over time.

Is some geriatric assessment routine for treatment planning in elderly patients in your institution?

Annika Malmström: In general, no formal geriatric assessment is done before treatment planning neither before surgery nor before decision regarding the oncological treatment. A thorough assessment of the patient's health status is done, including performance status, comorbidity, and neurological functional status. The different therapy options available and felt to be adequate, together with their pro's and con's, are discussed with the patients and their proxies before any decision is taken.

Alba Brandes: Management of cancer in the elderly population is one of the major challenges for clinical research in medical oncology. Multidisciplinary evaluation of the malignant disease and multidimensional assessment of the host represent the key element for correct decision making.

The CGA is commonly used to predict life expectancy and functional reserve and to unearth conditions that may jeopardize cancer prevention and treatment, but it is time-consuming and difficult to use in daily practice. In the interest of cost and time, we try to apply shortened forms of CGA in selected elderly patients.

How do you define the goals of treatment in the elderly with glioma? Is advance care planning part of the services offered by your institution?

Alba Brandes: The goals of treatment in these patients are to improve the quality of life and survivorship: this means maximal safe resection, which likely includes an incremental benefit with increasing completeness of resection, and RT that extends survival, and hypofractionation appears to be more tolerable than standard fractionation. In addition, TMZ chemotherapy is safe and improves the survival of patients. Moreover, the importance of tumor biomarkers is increasingly apparent in elderly patients, for whom the therapeutic efficacy of any treatment must be weighed against its potential toxicity. MGMT promoter methylation status has specifically demonstrated utility in predicting the efficacy of TMZ and should be considered in treatment decisions when possible.

Concomitantly to all these treatments the best supportive care has a central role in supporting patients and proxy, and we currently integrate the expertise of oncologists with the palliative care team early after the diagnosis of glioblastoma in elderly patients.

Annika Malmström: The goal of treatment is to achieve tumor stabilization/regression. This will hopefully lead to a progression-free period and translate into prolongation of the patient's life. It is essential that toxicity is minimal so that the patient's neurological and cognitive functioning and quality of life are maintained/improved. Surgery and carefully chosen oncological treatment can often be part of this.

Good palliative care is essential for elderly people with glioblastoma, as survival is expected to be limited. Advanced care planning is, despite this, not routine throughout the country. In the different parts of Sweden, health care is organized in various ways. In some institutions the patients are referred to a palliative care unit parallel with their oncological treatment, while in other areas this is available for patients not considered fit enough for further treatment or at the time of tumor progression. Referral to a palliative care unit will depend on the patient's general condition, neurological function, social status, and the patient and proxies' needs. For some patients, end-of-life care will be provided in a nursing home.