CONTINUING MEDICAL EDUCATION

Gliomas in Adults

by Thomas Schneider, Christian Mawrin, Cordula Scherlach, Martin Skalej, and Raimund Firsching

SUMMARY

Background: Primary brain tumors are among the ten most common causes of cancer-related death. There is no screening test for them, but timely diagnosis and treatment improve the outcome. Ideally, treatment should be provided in a highly specialized center, but patients reach such centers only on the referral of their primary care physicians or other medical specialists from a wide variety of fields. An up-to-date account of basic knowledge in this area would thus seem desirable, as recent years have seen major developments both in the scientific understanding of these tumors and in clinical methods of diagnosis and treatment.

Methods: Selective search of the pertinent literature (PubMed and Cochrane Library), including the guidelines of the German Societies of Neurosurgery, Neurology, and Radiotherapy.

Results and Conclusion: Modern neuroradiological imaging, in particular magnetic resonance imaging, can show structural lesions at high resolution and provide a variety of biological and functional information, yet it is still no substitute for histological diagnosis. Gross total resection of gliomas significantly improves overall survival. New molecular markers can be used for prognostication. Chemotherapy plays a major role in the treatment of various different kinds of glioma. The median survival, however, generally remains poor, e.g., 14.6 months for glio-blastoma.

▶ Cite this as:
Schneider T, Mawrin C, Scherlach C, Skalej M, Firsching R: Gliomas in adults. Dtsch Arztebl Int 2010; 107(45): 799–808. DOI: 10.3238/arztebl.2010.0799

Klinik für Neurochirurgie, Otto-von-Guericke Universität Magdeburg: PD Dr. med. Schneider, Prof. Dr. med. Firsching

Institut für Neuropathologie, Otto-von-Guericke Universität Magdeburg: Prof. Dr. med. Mawrin

Institut für Neuroradiologie, Otto-von-Guericke Universität Magdeburg: Dr. med. Scherlach, Prof. Dr. med. Skarlej

Gliomas account for 30% to 40% of all intracranial tumors. About half of all gliomas in adults are glioblastomas. The incidence of primary brain tumors in the USA is estimated to be 10 per 100 000 persons per year, in a male-female ratio of 6:4. Gliomas are typical tumors of middle age, with peak incidence between the ages of 40 and 65 years (1).

As for their etiology, only 1% to 5% of the gliomas can be classified as hereditary (2, e1). The vast majority of gliomas are thus sporadic, and their cause is unknown in most cases. The only known and generally accepted risk factor is ionizing radiation, which confers a relative risk that is reportedly as high as 22. In one study, for example, 23 of 9720 persons who had been irradiated developed gliomas, while only 1.06 cases of gliomas would have been expected from epidemiological data relating to the general population (2, e1).

Although gliomas are rare, they are of major medical importance because the affected patients often have a poor clinical course. Gliomas have highly varied clinical manifestations; thus, the care of patients with gliomas can involve physicians from multiple specialties. An up-to-date review of current basic knowledge about gliomas and their treatment seems appropriate, in view of the many recent scientific advances in the field.

Learning objectives

The learning objectives for readers of this article are:

- to become acquainted with important aspects of the varied clinical manifestations of these tumors,
- to understand the main diagnostic and therapeutic techniques that are used, including supportive measures,
- and to gain insight into recently developed therapeutic strategies, as well as others that are just beyond the horizon.

This review article is based on a selective review of literature retrieved from the PubMed and Cochrane

Epidemiology

Gliomas make up 30% to 40% of all intracranial tumors. They typically affect middle-aged adults, with peak incidence between the ages of 40 and 65.

TABLE 1

The incidence of brain tumors[*1]

Tumor type	WHO grade	% of all brain tumors[*2]	Incidence (per 100 000 per year)
Neuroepithelial tumors	**I–IV**	**34.3**	**6.46**
Glioblastoma	IV	17.1	3.17
Anaplastic astrocytoma	III	2.1	0.4
Pilocytic astrocytoma	I	1.7	0.33
Oligodendroglioma	II	1.4	0.27
Ependymoma	II/III	1.4	0.26
Mixed glioma	II/III	1.0	0.19
Anaplastic oligodendroglioma	III	0.7	0.12
Diffuse astrocytoma	II	0.5	0.09

[*1] Central Brain Tumor Registry of the United States (CBTRUS; www.cbtrus.org/)
[*2] Not all brain tumors are gliomas

Library databases with the search terms "glioma" und "brain neoplasm." Current specialty society guidelines and the authors' own scientific studies and clinical experience were also taken in to account.

Neuropathology

Most primary brain tumors are of neuroepithelial origin, including gliomas, which constitute the largest subgroup. Gliomas, in turn, are classified by their prevailing cell type as astrocytoma (including glioblastoma), oligodendroglioma, ependymoma, and mixed oligodendroglial and astrocytic tumors. There are also rare tumors with both glial and neuronal components.

In the current World Health Organization (WHO) classification of brain tumors, the gliomas are assigned Grades I through IV *(Table 1)*. The most recent version of the WHO classification, dated 2007, is the product of a historical evolution that began with the work of Bailey and Cushing (e3) and continued with the development of a number of subsequent brain tumor classification schemes on the basis of histopathological and prognostic data (2).

Gliomas generally grow by diffuse infiltration into the white matter of the brain and are therefore often not directly visible on the brain surface. They do, however, cause visible thickening and flattening of the gyri. At the periphery of the lesion, the vessels are often massively dilated, while thrombosed vessels are found in the center of the lesion, especially in aggressive tumors. Gliomas are most commonly found in the cerebral hemispheres; in children, they often arise in the brainstem and cerebellum. "Butterfly glioma" is the name given to tumor growth across the corpus callosum into both frontal poles. 5% to 10% of glioblastomas are already multifocal at the time of diagnosis (3). The tumor is usually surrounded by extensive white-matter edema.

Pilocytic astrocytoma is a special case. This benign tumor (WHO Grade I) primarily affects children and has biological properties that are distinct from those of the diffuse astrocytomas (WHO Grades II–IV).

The ability of glioma cells to migrate is an important factor rendering glial tumors aggressive. Consequently, gliomas cannot be totally removed by any form of local treatment, surgery included. Cytotoxic therapy may fail, too, because migrating cells are less likely than non-migrating cells to be in the chemosensitive cell-division phase .

Diagnostic evaluation

Physical examination

Brain tumors can cause practically any kind of neurological disturbance. The type of disturbance that is present depends, not on the histology of the tumor, but on its location (e4). The clinical manifestations can be local, such as weakness, somatosensory loss, visual loss, or aphasia, or global, such as headache, nausea, vomiting, papilledema, or impaired consciousness. These global manifestations are due to intracranial hypertension. Epileptic seizures, which may be either focal or generalized, are common and are a typical mainfestation of low-grade gliomas.

Rapid worsening of the clinical manifestations may indicate either malignant growth or impaired flow of cerebrospinal fluid (CSF). Only 7% of patients with glioblastoma have had symptoms for more than one year at the time of diagnosis (e5); the corresponding figure for astrocytoma is reportedly 34% (e6). The initial presentation is sometimes sudden ("apoplectiform"). This may be due to acute hemorrhage into the tumor.

Acute clinical manifestations that are a sign of life-threatening brain herniation due to intracranial

Neuropathology

Most primary brain tumors are of neuroepithelial origin. The gliomas are the largest subclass of primary brain tumors.

Typical symptoms and signs

Weakness, somatosensory loss, visual loss, aphasia, headache, vomiting, papilledema, impaired consciousness, focal or generalized epileptic seizures.

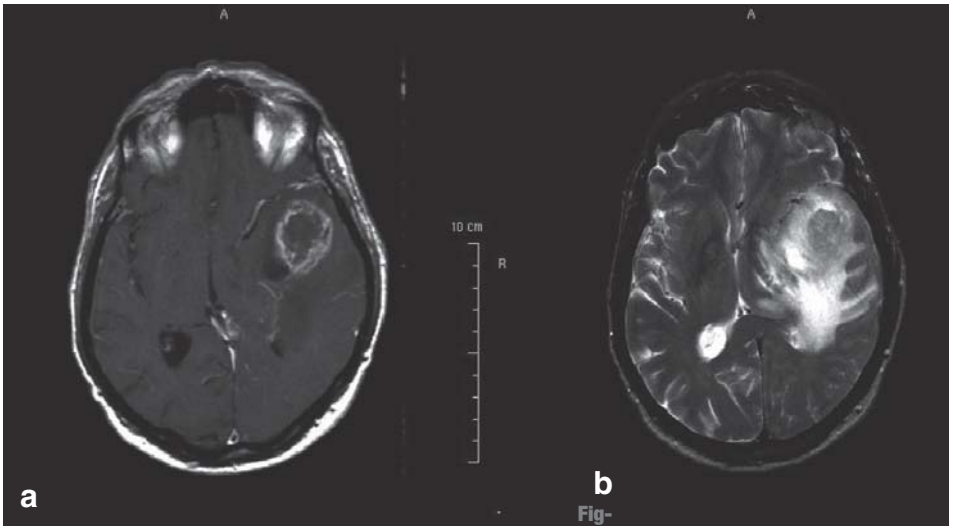

Figure 1:
Magnetic resonance images of a glioblastoma: centrally necrotic mass with strong peripheral contrast enhancement and marked perifocal edema
a) T1-weighted image with contrast medium
b T2-weighted image clearly showing the perifocal edema

Fig-

hypertension include headache, vomiting, and deterioration of consciousness leading to coma. Once unconscious, the patient may display pupillary abnormalities and extensor posturing. Both slowly-growing and rapidly-growing tumors can ultimately cause fatal brain herniation. Even though gliomas are histologically highly malignant, they hardly ever metastasize (e7)

The Karnofsky performance score, which reflects the general functional status of patients with tumors or other illnesses, should be determined at each clinical follow-up visit. A low Karnofsky score and advanced age predict a poor outcome and must be taken into account in the planning of diagnostic measures and treatment.

CSF examination is usually not indicated but may aid in the differential diagnosis of glioma from lymphoma, brain abscess, or a germ-cell tumor. It can also be useful in the evaluation of possible diffuse meningeal spread of tumor cells.

No means are now available for the early detection, prevention, or screening of gliomas, nor are any specific tumor markers available. Their differential diagnosis includes cerebral hemorrhage, ischemia, inflammation, infection, post-traumatic state, impaired flow of CSF, mental illness, and endocrine/metabolic disturbances.

General neuroradiological aspects

The neuroradiological investigation of gliomas generally involves tomographic studies. Magnetic resonance imaging (MRI) is far superior to computerized tomography (CT) for this purpose, for a number of reasons:

- higher sensitivity,
- higher soft-tissue contrast,
- better depiction of the extent of tumors,
- and the ability to display data in three planes.

The basic MRI protocol for the depiction of a brain tumor should include T2- and T1-weighted native and contrast-enhanced sequences, as well as a fluid-attenuated inversion-recovery (FLAIR) sequence. We also recommend displaying the images in three planes (axial, sagittal, and coronal) and, in some cases, performing a T2-weighted gradient-echo sequence (abbreviated as T2*, where the * denotes a special kind of T2-weighted sequence) to show blood and calcifications, or a diffusion-weighted sequence to differentiate glioma from abscess. The slices should be no more than 5 to 6 mm thick (e8).

Intravenous contrast medium should be given in order to reveal the full extent of the tumor and to enable distinctions to be made between tumor tissue and perifocal edema, between vital and non-vital tumor tissue, and between low- and high-grade portions of the tumor, as well as to detect any small satellite lesions that may be present (e9).

If the tumor disrupts the blood-brain barrier and thus takes up contrast medium, a repeated scan in the early postoperative phase (up to 48 hours after surgery) can

Prevention

No means are now available for the early detection, prevention, or screening of gliomas, nor are any specific tumor markers available.

Neuroradiological aspects

Tomographic imaging techniques play the most important role. Magnetic resonance imaging is decidedly superior to computerized tomography.

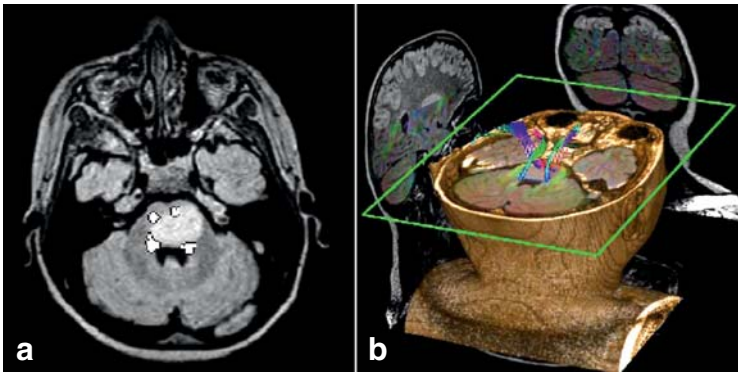

Figure 2: Magnetic resonance images of a pontine glioma with anatomical fiber tracking.
Figure 2 a) (axial) shows color-coded fiber pathways; the craniocaudal fibers on the left side are clearly displaced and spread apart
Figure 2 b) shows the same finding in a three-dimensionally reconstructed color image

detect any residual tumor that may be present (4). CT can be helpful in the evaluation of tumors that contain calcification or infiltrate bone.

Newer imaging techniques

MR proton spectroscopy can be used to measure the signal strength of a number of brain metabolites (N-acetyl-aspartate, choline, creatine, lactate, lipids), thereby enabling better differentiation of tumors from non-neoplastic brain lesions, such as infarcts, and also providing an indication of the degree of malignancy of the tumor (e10). Regional cerebral blood flow (rCBV) measurement provides evidence of the malignant transformation of low-grade gliomas, which aids in the prognostication of recurrence-free and overall survival times (12, e11).

Functional magnetic resonance imaging (fMRI) displays brain activity, making use of the principle that elevated neuronal activity is associated with a change in local perfusion. It can thus be used to depict various areas of the cerebral cortex that subserve specific sensory or motor functions, or to determine the lateralization of language, by means of active testing paradigms (finger-tapping, language) or passive ones (sensorimotor nerve stimulation). Diffusion-tensor imaging displays the anatomical relationship of the tumor to major white-matter pathways such as the pyramidal tract ("fiber tracking") (e13) *(Figure 2)*. These methods are regularly used to narrow the differential diagnosis of tumors with an atypical appearance on MRI, and to aid in neurosurgical planning.

(Amino-acid) PET and SPECT can be used to pinpoint the region of most pronounced anaplasia more specifically than MRI; in some circumstances, this may increase the diagnostic yield and accuracy of tumor biopsy. PET and SPECT are also more specific than MRI for the differentiation of recurrent tumor from treatment sequelae such as radiation-induced necrosis (15, e14).

Treatment

The treatment of gliomas is highly individualized at present, based on the histological diagnosis and other factors, and will be even more so in future. It is now well established that the prognosis of a patient with a glioma depends, in general, on the histological classification of the tumor, the tumor grade, the patient's Karnofsky performance score and neurological deficits as well as and the patient's age. New molecular markers, such as loss of heterozygozity (LOH) of chromosome 1p/19q, methylation of the methylguanine methyltransferase (MGMT) promoter, and mutations of isocitrate dehydrogenase-1 (IDH-1), now enable more accurate prognostication (*Table 2)*. In the following paragraphs, we will present the treatment measures recommended by current guidelines. The recommendations for Grade III and Grade IV tumors are based on class 1b evidence, while those for Grade I and Grade II tumors are still only based on class 3 evidence. Patients with such tumors live considerably longer, and studies of treatment efficacy therefore require much longer follow-up (for a summary, see *Table 3*).

Particular tumors

Pilocytic astrocytoma (WHO Grade I)

Pilocytic astrocytoma classically arises in the cerebellum of a child, usually adjacent to the fourth ventricle. It is rarely seen in patients over age 30. The typical neuroradiological finding is a cystic mass with a nodular portion that is strongly and inhomogeneously contrast-enhancing. This type of tumor can also arise in the optic chiasm; in such cases, the tumor is usually not cystic and displays homogeneous contrast enhancement (5). Gross total resection is the treatment of choice. If only partial resection is possible, adjuvant radiotherapy can be considered, although its benefit

Newer diagnostic methods

The measurement of metabolite signal intensities with MR proton spectroscopy enables better differentiation of neoplastic from non-neoplastic brain lesions.

Treatment

The treatment of gliomas is highly differentiated, mainly based on the histological diagnosis. Treatment will become even more individualized in the future.

TABLE 2

The function and significance of the main molecular markers of glioma

Molecular marker	Function and significance
MGMT (methylguanyl methyltransferase) promoter methylation*1,*2	MGMT is a repair enzyme that protects cells from damage by ionizing radiation or alkylating agents. Glioblastoma patients with a methylated (and therefore functionally impaired) MGMT promoter have better overall survival and better responses to radio- and chemotherapy than glioblastoma patients with an unmethylated MGMT promoter (17). 40% to 50% of glioblastomas have a methylated MGMT promoter. The MGMT status of a recurrent tumor may differ from that of the primary tumor (e35). MGMT status is currently the most important molecular parameter in the treatment of glioblastoma (23, 24).
Isocitrate dehydrogenase (IDH)-1 and -2*1,*2	Heterozygous mutations (mainly of the IDH-1 enzyme) are seen in over 80% of all low-grade gliomas and secondary glioblastomas (i.e., those that arise from low-grade precursor tumors). 12% of glioblastomas have IDH-1 mutations (e36). IDH-1 and -2 mutations are associated with a better prognosis; in patients with glioblastoma, they are associated with longer progression-free survival and longer overall survival (23).
Loss of allele on chromosome 1p/19q*1	Loss of allele on chromosome 1p and 19q is seen in 60% to 80% of anaplastic oligodendrogliomas (WHO Grade III) and predicts chemosensitivity in oligodendroglioma (11, 25). Patients with 1p/19q allele loss have longer progression-free survival and better overall survival after radiotherapy or chemotherapy.
BRAF fusion gene	This gene can be found in more than 60% of pilocytic astrocytomas, but only rarely in diffuse astrocytomas (e37)

*1 Current therapeutic trials must be stratified according to these markers in view of their major clinical importance
*2These markers are suitable for routine clinical use

remains unclear. The prognosis is excellent, with recurrence-free survival times of well over 20 years. Documented cases of malignant transformation are extremely rare (6, e16).

Low-grade glioma (WHO Grade II)

Low-grade gliomas tend to lie in the cortical and subcortical regions of the temporal and frontal lobes. They appear on MRI scans as areas of homogeneous T2 hyperintensity and mild T1 hypointensity, usually without any surrounding edema or contrast enhancement. Contrast enhancement that is seen in subsequent MRI scans is a neuroradiological correlate of malignant transformation. The differential diagnosis of low-grade glioma includes infarct and gliosis; thus, histological confirmation by open tumor resection or stereotactic needle biopsy is recommended. The operation should be planned in such a way as to avoid any risk of creating an additional neurologic deficit.

This can be done with the aid of modern intraoperative ancillary techniques (7):

- neuronavigation,
- open, intraoperative MRI,
- intraoperative electrophysiological monitoring,
- intraoperative language testing in the awake patient (awake surgery).

The preoperative evaluation may include any or all of the following functional imaging methods:

- magnetoencephalography (MEG),
- functional MRI (fMRI),
- magnetic resonance fiber tracking,
- functional topographic mapping with implanted electrodes.

Anatomically well-circumscribed Grade II gliomas that are symptomatic and surgically accessible should be resected as completely as possible as the treatment of choice. McGirt et al. reported 5-year survival rates of up to 95% after total resection (e17). There is level 2b evidence to support the conclusion that gross total resection improves overall survival not only for low-grade glioma, but also for glioblastoma (e17).

No advantage in terms of overall survival has been found for immediate postoperative radiotherapy of Grade II gliomas as compared to follow-up observation after resection (8), despite the demonstrated advantage with respect to the time to tumor progression. Thus, once the diagnosis of Grade II glioma has been histologically confirmed, it is best to adopt a wait-and-see strategy. This is particularly true for patients under age 40, whose prognosis is better than others' by virtue of

Pilocytic astrocytoma

Pilocytic astrocytoma arises in children and is usually located in the cerebellum adjacent to the fourth ventricle. It rarely affects patients above age 30.

Low-grade gliomas

Low-grade gliomas tend to be located in the cortical and subcortical regions of the temporal and frontal lobes. In MRI scans, they appear homogeneously hyperintense on T2-weighted images and mildly hypointense on T1-weighted images. They usually do not take up contrast medium and are not surrounded by perifocal brain edema.

TABLE 3

The primary treatment of different types of glioma*[1]

Pilocytic astrocytoma (WHO Grade I)	Surgical resection (level III evidence)
Astrocytoma (WHO Grade II)	Surgical resection, or biopsy and wait-and-see, or radiotherapy*[2] (level III evidence)
Anaplastic astrocytoma, oligodendroglioma/oligoastrocytoma (WHO Grade III)	Surgical resection (or biopsy) and chemotherapy (or radiotherapy) (level 1b evidence)
Glioblastoma (WHO Grade IV)	Surgical resection (or biopsy) and radiotherapy and chemotherapy (temozolomide) (level Ib evidence)

*[1] from the treatment recommendations of the Neuroonkologische Arbeitsgemeinschaft (NOA)
*[2] The available evidence from clinical trials does not permit any definite recommendation

their age. Selected patients with very clearly circumscribed tumors can alternatively benefit from stereotactic brachytherapy with iodine-125 (9).

The standard treatment for tumor progression after initial resection of a low-grade glioma is fractionated low-dose radiotherapy to 45 or 50.4 Gy (10), possibly preceded by resection of the recurrent tumor. No benefit has yet been documented for chemotherapy instead of, or in addition to, radiotherapy in the treatment of diffuse Grade II astrocytoma.

Newly diagnosed Grade III glioma

Newly diagnosed gliomas of WHO Grade III include anaplastic astrocytoma, oligoastrocytoma, and oligodendroglioma. These lesions are all inhomogeneous on both T1- and T2-weighted images and display a moderate degree of contrast enhancement, in a mottled pattern. Oligodendroglial tumors also often have areas of calcification (best demonstrated on T2*-weighted MR images, or by CT) and mild perifocal edema (5).

There is no substitute for histological confirmation of the diagnosis, because Grade III tumors cannot be securely differentiated from Grade II tumors on radiological grounds alone, nor can imaging studies conclusively show the presence or absence of an oligodendroglial component. As much of the tumor as possible should be removed by open, microsurgical resection, if the location of the tumor permits (11).

After resection, a combination of chemotherapy and radiotherapy has no advantage over either of these modalities alone with respect to overall survival (12), nor is there any difference beween chemotherapy alone and radiotherapy alone (multi-center trial of the Neuro-Oncology Working Group [*Neuroonkologische Arbeitsgemeinschaft*] of the German Cancer Society, NOA-04 Study [11]). The median overall survival time in the NOA-04 Study was 72.1 months after radiotherapy and 82.6 months after chemotherapy; the difference was not statistically significant. It did not matter, either, whether the chemotherapy consisted of temozolomide or procarbazine. Nonetheless, if one takes the potential side effects and long-term sequelae into account, one can interpret these data as showing an advantage when adjuvant chemotherapy with temozolomide is given after primary surgery.

The NOA-04 Study confirmed that the histological demonstration of an oligodendrial component within the tumor is associated with a markedly better outcome, as has long been known. Furthermore, it impressively confirmed the positive prognostic significance of factors such as 1p/19q loss of heterozygosity (LOH), MGMT promoter methylation, and IDH-1 mutations.

Newly diagnosed glioblastoma

Just as the histopathological features of glioblastoma are highly variable, so, too, are its neuroradiological features. Most commonly, MRI reveals a centrally necrotic mass with marked peripheral contrast enhancement and marked edema in the surrounding brain tissue *(Figure 1)*.

Metastasis, abscess, and lymphoma should be considered in the differential diagnosis (4). Histological confirmation of the diagnosis is essential; tissue for histopathological examination must be obtained surgically, i.e., either by stereotactic biopsy or by open microsurgical resection. It was only in the last few years that clinical studies were finally able to document the benefit of extensive tumor resection (13, e18). In particular, the multicenter trial of Stummer et al., which involved microsurgical resection aided with the intraoperative administration of the fluorescent tissue dye 5-aminolevulinic acid (5-ALA), revealed that patients who had no contrast-enhancing residual tumor on their immediate postoperative MRI scan lived significantly longer than patients who did have contrast-enhancing residual tumor (median survival time 16.7 versus 11.8 months, $p<0.0001$) (14, e19). The standard technique of microsurgical resection is associated with less than 2% operative mortality and less than 5% permanent neurological morbidity (15). R0

Radiotherapy

A recent study demonstrated no overall survival advantage of immediate postoperative radiotherapy over a wait-and-see strategy for patients with Grade II gliomas.

Newly diagnosed WHO Grade III gliomas

These include anaplastic astrocytoma, oligoastrocytoma, and oligodendroglioma.

resection of glioblastoma is a practical impossibility, because of the migration of glioma cells into the surrounding brain tissue; therefore, further treatment is still needed even after the gross total resection of all contrast-enhancing tumor tissue.

A trial conducted under the joint auspices of the European Organisation for Research and Treatment of Cancer (EORTC) and of the National Cancer Institute of Canada (NCIC) and published in 2005 by Stupp et al. resulted in the establishment of a new treatment standard, which consists of postoperative radiotherapy accompanied by temozolomide chemotherapy for six weeks, and adjuvant temozolomide chemotherapy thereafter (six cycles in a 28-day rhythm). This protocol resulted in a prolongation of median survival from 12.1 to 14.6 months ($p = 0.001$) (13). The side effects that arose were mostly no more than moderately severe; for example, only 1% of patients suffered from vomiting of clinical grade 3 or 4. Severe myelosuppression (grade 3 or 4) does arise, however, in up to 16% of treated patients (13).

The radiotherapy of glioblastoma involves the delivery of an overall dose of ca. 55 to 60 Gray (in fractions of 1.8 to 2 Gy each) focused on the tumor target volume, with a marked dose fall-off in the surrounding brain tissue (16). Whole-brain radiotherapy (WBRT) for this application is now obsolete.

Subgroup analysis in the Stupp trial yielded the first, impressive evidence of the usefulness of MGMT promoter methylation as a predictive molecular marker for responsiveness to temozolomide and probably also to any other form of treatment. The median survival time of patients with a methylated MGMT promoter was 21.7 months (compared to 12.7 months without), and their two-year survival rate was 46% (compared to 13.8% without) (17).

Recurrent glioma (WHO Grade III or IV)

The available data on recurrent glioma are less informative and are mainly based on small-scale phase II trials. Reoperation is generally recommended when:

- the tumor is surgically accessible,
- the operation is expected to result in significant debulking of the residual tumor,
- reoperation is thought likely to improve the patient's neurological condition in view of the location of the tumor, and
- the patient's general condition is satisfactory.

For a minority of patients with well-circumscribed lesions, repeated radiotherapy (usually hyperfractionated, e.g., 4 × 5 Gy) or single-shot stereotactic irradiation can be considered (e20, e21).

The decision whether to perform a new round of chemotherapy must be made individually. Repeated chemotherapy, e.g., with nitrosoureas (ACNU) or PCV combination chemotherapy, usually improves the prognosis. In one study, raising the dose of temozolomide to 150 mg/m² in weekly alternation was found to prolong the median progression-free survival time from 13 weeks (in a historical control group) to 21 weeks (18). These patients' quality of life is highly variable and unpredictable.

Supportive treatment

Corticosteroids

Perifocal vasogenic edema typically accompanies brain tumors and can cause markedly increased mass effect. The specific pharmacotherapy of tumor-associated brain edema with dexamethasone can rapidly improve neurologic deficits and the patient's overall condition (e22–e24). This very effective form of treatment was first described in 1961 by Galicich et al. (e25) and has since come to be used all over the world. To our knowledge, there has never been a high-quality, randomized, controlled clinical trial on this subject; thus, all recommendations about dexamethasone treatment for tumor-associated brain edema are of an empirical nature. Long-term steroid treatment can cause multiple complications, some of them severe. It follows that the dose of dexamethasone should always be lowered as rapidly as possible to the lowest dose that is clinically necessary.

In view of such problems, it would seem reasonable to look for an alternative to dexamethasone. Boswellic acids are terpenes with anti-inflammatory activity, derived from the frankincense plant, that have been tested as a possible treatment for tumor-associated brain edema. This type phytotherapeutic agent, which can be obtained in Germany through international pharmacies, can reduce peritumoral edema by up to 40% in some patients, or at least enable reduction of the dexamethasone dose (19, e26).

Anti-angiogenic therapy with bevacizumab also reduces perifocal edema by lowering vascular permeability. Its use for supportive treatment cannot yet be recommended. Future clinical trials will show whether this drug can truly improve patients' quality of life, and, if so, to what extent (20).

Newly diagnosed glioblastoma

Newly diagnosed glioblastoma has a highly varied appearance on MRI scans. The typical findings are a central zone of necrosis, a strongly contrast-enhancing periphery, and marked perifocal edema.

Reoperation for recurent glioma when:

- the tumor is surgically accessible,
- significant reduction of the residual tumor mass is achievable, and
- reoperation is thought likely to improve the patient's neurological condition.

Antithrombotic drugs

Patients with malignant glioma are at a markedly increased risk of developing venous thromboses of the lower limbs and pulmonary embolism. Anticoagulant drugs such as heparin or, preferably, low-molcular weight heparins are therefore given in many hospitals, even in the early postoperative phase, even though they have not been approved for use after surgery on the brain. Practical experience has shown that the risk of intracranial hemorrhage in this situation is relatively low. The available published data on this subject are derived only from a small number of small-scale studies, in which no intracranial hemorrhage occurred in cohorts of up to 50 treated patients (e24, 27). Oral anticoagulants, such as phenprocoumone, cannot be recommended as strongly; if possible, they should not be given until at least four weeks after surgery (e28).

Anticonvulsants

About half of all glioma patients have epileptic seizures at some point in their course. Focal seizures are more common than generalized ones. The main types of anticonvulsant are roughly equally effective in preventing seizures in glioma patients. They interact to differing extents with simultaneously administered cytostatic agents, such as temozolomide, as they can either inhibit or induce metabollic enzymes. Such interactions are less marked with newer anticonvulsants, such as lamotrigine, topiramate, and levetiracetam, than with older ones, such as phenytoin, cabamazepine, and valproic acid. The newer agents are better tolerated in general, but they have certain individual disadvantages. Lamotrigine, for example, must be introduced at a low dose that is then slowly increased. Levetiracetam is still an expensive drug at present. Anticonvulsants should be given as a practical, protective treatment whenever a patient in whom a glioma is suspected on radiological grounds has a first epileptic seizure, even though no direct evidence is available from clinical trials to support this practice (e24). Giving anticonvulsants prophylactically to all patients with glioma, or to all glioma patients who have undergone surgery, is not recommended (e29).

New treatments

In recent years, improved scientific knowledge of the molecular genetic changes that are present in gliomas has led to the development of specific molecular genetic drugs. Among such drugs are inhibitors of the epidermal growth factor receptor (EGFR), such as gefitinib and erlotinib; integrin inhibitors, such as cilengitide; and tyrosine kinase inhibitors, such as imatinib. These agents have not yet been demonstrated to provide a therapeutic benefit (21).

Initial, positive results have already been seen, however, from angiogenesis inhibition with bevacizumab, an antibody against vascular entdothelial growth factor (VEGF), in combination with irinotecan. Multiple phase I and II trials have shown that treatment with this combination markedly improves the six-month progression-free survival rate to 43% in glioblastoma and to as high as 59% in anaplastic glioma, compared to 15% and 31%, respectively, in historical control groups (20). No statistically significant change in overall survival was found. The effects of this form of treatment will soon be the subject of a larger-scale randomized and controlled study under the aegis of the Radiation Therapy Oncology Group (RTOG).

Another therapeutic approach is the local application of antisense oligonucleotides directed against TGF-β2, a highly immunosuppressive cytokine, through a catheter that is surgically inserted into the tumor. This seems to be a possible treatment option for WHO Grade III astrocytoma in particular (22) and is currently being studied for this application in an international, multicenter phase III trial. A number of trials of other types of passive or active immunotherapy have been performed to date and have met all of the preconditions for immunotherapy in the brain and demonstrated its feasibility in principle. These trials, however, did not yield any clear evidence of clinical benefit (e30, e31).

The latter statement holds for gene therapy as well. Both direct and indirect forms of gene therapy are of interest as potentially effective treatments for glioma (e32).

The clinical results in the trials of intratumoral infusion of exotoxins or oncolytic viruses that have been performed to date have not lived up to the expectations originally placed in this form of treatment (e33, e34).

Continuing research in neuro-oncology probably will not lead to the development of a single type of treatment that is optimal for all patients. Rather, future improvements are likely to involve individualized therapy based on the molecular properties of the tumors that are to be treated.

Antithrombotic therapy

Patients with malignant gliomas are at markedly elevated risk of deep venous thrombosis and pulmonary embolism.

New forms of treatment

Initial positive results have been seen from the inhibition of angiogenesis with bevacizumab, an antibody against VEGF, given in combination with irinotecan.

Conflict of interest statement
PD Schneider has received financial support in the framework of joint research projects from Merck and Antisense-Pharma.
Prof. Mawrin has received support for travel to scientific meetings and for research projects from the following companies: Merck, Pfizer, Wyeth and DAKO.
Dr. Scherlach and Prof. Skalej are involved as radiologists in the Sapphire Study of Antisense-Pharma GmbH.
Prof. Firsching stastes that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

Manuscript submitted on 6 October 2009; revised version accepted on 9 August 2010.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

1. Zülch KJ: Brain Tumors. Their biology and pathology. Berlin-Heidelberg-New York: Springer Verlag, 1986.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: WHO classfication of tumours of the central nervous system. Lyon, IARC 2007.
3. Wiestler OD: Pathologische Anatomie und WHO-Klassifikation der Tumoren des Nervensystems, in Schlegel U, Westphal M (eds.): Neuroonkologie. Stuttgart, New York: Georg Thieme Verlag, 1998: 4–46.
4. Uhlenbrock D, Forsting M: MRT und MRA des Kopfes. Stuttgart, New York: Georg Thieme Verlag, 2007.
5. Ricci PE, Dungan DH: Imaging of low- and intermediate-grade gliomas. Semin Radiat Oncol 2001; 11(2): 103–12.
6. Bell D, Chitnavis BP, Al Sarraj S, et al.: Pilocytic astrocytoma of the adult–clinical features, radiological features and management. Br J Neurosurg 2004; 18(6): 613–6.
7. Simon M, Schramm J: Surgical management of intracranial gliomas. Recent Results Cancer Res 2009; 171: 105–24.
8. van den Bent MJ, Afra D, De Witte O, et al.: Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005; 366(9490): 985–90.
9. Schramm J, Blumcke I, Ostertag CB, et al.: Low-grade gliomas–current concepts. Zentralbl Neurochir 2006; 67(2): 55–66.
10. Shaw E, Arusell R, Scheithauer B, et al.: Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002; 20(9): 2267–76.
11. Wick W, Hartmann C, Engel C, et al.: NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 2009; 27(35): 5874–80.
12. Cairncross G, Berkey B, Shaw E, et al.: Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 2006; 24(18): 2707–14.
13. Stupp R, Mason WP, van den Bent MJ, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352(10): 987–96.
14. Stummer W, Pichlmeier U, Meinel T, et al.: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006; 7(5): 392–401.
15. Schlegel U, Westphal M: 2. Primäre Tumoren des Gehirns und seiner Häute: Gliome, in Schlegel U, Westphal M (eds.): Neuroonkologie. Stuttgart, New York: Thieme Verlag, 1998: 170–203.
16. Laperriere N, Zuraw L, Cairncross G: Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol 2002; 64(3): 259–73.
17. Hegi ME, Diserens AC, Gorlia T, et al: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005; 352(10): 997–1003.
18. Wick W, Steinbach JP, Kuker WM, et al.: One week on/one week off: a novel active regimen of temozolomide for recurrent glioblastoma. Neurology 2004; 62(11): 2113–5.
19. Böker DK, Winking M: Die Rolle von Boswellia-Säuren in der Therapie maligner Gliome. Dtsch Arztebl 1997; 94(18): A-1197–1199.
20. de Groot JF, Yung WK: Bevacizumab and irinotecan in the treatment of recurrent malignant gliomas. Cancer J 2008; 14(5): 279–85.
21. Minniti G, Muni R, Lanzetta G, Marchetti P, Enrici RM: Chemotherapy for glioblastoma: current treatment and future perspectives for cytotoxic and targeted agents. Anticancer Res 2009; 29(12): 5171–84.
22. Hau P, Jachimczak P, Schlingensiepen R, et al.: Inhibition of TGF-beta2 with AP 12009 in recurrent malignant gliomas: from preclinical to phase I/II studies. Oligonucleotides 2007; 17(2): 201–12.
23. Weller M, Felsberg J, Hartmann C, et al.: Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. J Clin Oncol 2009; 27(34): 5743–50.
24. Weller M, Stupp R, Reifenberger G, et al.: MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol 2010; 6(1): 39–51.
25. Cairncross JG, Ueki K, Zlatescu MC, et al.: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998; 90(19): 1473–9.

Corresponding author
PD Dr. med. Thomas Schneider
Klinik für Neurochirurgie
Otto-von-Guericke Universität Magdeburg
Leipziger Str. 44
39120 Magdeburg, Germany
thomas.schneider@med.ovgu.de

For eReferences please refer to:
www.aerzteblatt-international.de/ref4510

Further information about CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (Länder). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire within 6 weeks of publication of the article. See the following website: **cme.aerzteblatt.de**

Participants in the CME program can manage their CME points with their 15-digit "uniform CME number" (*einheitliche Fortbildungsnummer,* EFN). The EFN must be entered in the appropriate field in the **cme.aerzteblatt.de** website under "meine Daten" ("my data"), or upon registration. The EFN appears on each participant's CME certificate.

The solutions to the following questions will be published in issue 1-2/2011.

The CME unit "The Diagnosis and Treatment of Dyslexia" (issue 41/2010) can be accessed until 26 November 2010.

For issue 49/2010 we plan to offer the topic "Idiopathic Scoliosis."

Solutions to the CME questionnaire in issue 37/2010:
Keller F: Pharmacotherapy in Patients with Chronic Renal Failure
Solutions: 1e, 2b, 3c, 4a, 5d, 6b, 7b, 8d, 9a, 10b.

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

According to the current understanding of the neuropathology of gliomas, which of the following statements is true?

a) Gliomas are multiple in fewer than 1% of cases.
b) The aggressiveness of gliomas is due to the marked ability of glioma cells to migrate.
c) At the present time, the molecular differentiation of these tumors plays an important role in determining their appropriate treatment.
d) Oligodendroglioma is a special type of glioma and is therefore not included in the WHO classification scheme.
e) The current WHO classification scheme for gliomas grades their degree of malignancy on a 5-point scale.

Question 2

From what age onward should persons undergo a screening test for glioblastoma?

a) Not at all
b) From age 20 onward
c) From age 30 onward
d) From age 40 onward
e) From age 50 onward

Question 3

Magnetic resonance imaging of a glioma without intravenous contrast medium is informative for what purpose?

a) Detecting small satellite lesions
b) Judging the size of the tumor
c) Displaying calcifications
d) Identifying vital tumor tissue
e) Differentiating higher- from lower-grade portions of the tumor

Question 4

What property is typical of low-grade gliomas (WHO Grade II)?

a) They tend to be located in the occipital lobe and cerebellum.
b) They usually do not take up radiological contrast medium.
c) They have homogeneous perifocal edema.
d) They do not undergo malignant transformation.
e) They appear inhomogeneously hypointense on T2-weighted MR images.

Question 5

What do recent study findings imply about the prognosis and treatment of newly diagnosed glioblastoma?

a) Contrast-enhancing residual tumor on an early postoperative MRI scan has no relevance to overall survival.
b) Modern microsurgical resection of these tumors has an operative mortality of less than 2%.
c) Chemotherapy followed by radiotherapy can be performed without histological confirmation of the diagnosis of glioblastoma.
d) In clinical experience with temozolomide to date, there has not been any grade 3 or 4 myelotoxicity.
e) Radiotherapy for glioblastoma is currently administered to the whole brain.

Question 6

According to current studies, which of the following statements is true of newly diagnosed WHO Grade III gliomas?

a) After surgical resection of the tumor, adjuvant chemotherapy is associated with significantly longer survival than adjuvant radiotherapy.
b) Grade III oligodendroglioma is diagnosed on the basis of calcifications that are visible on neuroimaging studies.
c) Oligodendroglioma has a better prognosis than astrocytoma.
d) For chemotherapy, a procarbazine protocol is preferable to temozolomide.
e) Chromosome 1p/19q deletions and IDH-1 mutations are prognostically irrelevant.

Question 7

In the treatment of low-grade gliomas (WHO Grade II), which of the following is currently considered to be a correct statement?

a) For patients under age 40, histological confirmation of the diagnosis can be followed by observation, i.e., a wait-and-see strategy, at least initially.
b) The extent of surgical debulking of the tumor is prognostically irrelevant if the tumor is surgically accessible, even in older patients; thus, no attempt should be made to remove as much of the tumor as possible.
c) Radiotherapy has no effect on progression-free survival times in patients with low-grade gliomas.
d) If a Grade II astrocytoma shows progression, reoperation should preferably be followed by adjuvant chemotherapy.
e) Well-demarcated and well-circumscribed tumors should be managed with stereotactic needle biopsy rather than complete surgical resection.

Question 8

In the clinical trials that have been performed to date on new therapeutic approaches for newly diagnosed glioblastoma, what drug has been found to prolong progression-free survival significantly?

a) Imatinib
b) Gefitinib
c) Erlotinib
d) Bevacizumab in combination with irinotecan
e) Dexamethasone

Question 9

A patient with an already diagnosed glioblastoma complains of worsening headache and fatigue. MRI shows that the residual tumor is no larger than on previous scans, but there is more brain edema around it. What would improve this patient's neurological function and overall condition in the short term?

a) Treatment with a stinging nettle extract
b) Discontinuation of a frankincense-derived preparation
c) Administration of imatinib
d) Administration of dexamethasone
e) Lumbar puncture

Question 10

Which of the following is true of anticonvulsant and antithrombotic treatment in patients with gliomas?

a) Prophylactic administration of an anticonvulsant is indicated in the early postoperative phase.
b) Newer anticonvulsants, such as lamotrigine, interact with cytostatic agents to a lesser extent than older ones, such as phenytoin.
c) Carbamazepine is much more potent than other anticonvulsants.
d) Low-molecular-weight heparins should not be used in the early postoperative phase because of the high risk of intracranial hemorrhage.
e) The risk of pulmonary embolism after glioma surgery is low.

CONTINUING MEDICAL EDUCATION

Gliomas in Adults

by Thomas Schneider, Christian Mawrin, Cordula Scherlach, Martin Skalej, and Raimund Firsching

eReferences

e1. Narod SA, Stiller C, Lenoir GM: An estimate of the heritable fraction of childhood cancer. Br J Cancer 1991; 63(6): 993–9.

e2. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS: Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol 2002; 4(4): 278–99.

e3. Bailey P, Cushing H: A classification of the tumors of the glioma group on a histogenetic basis with a correlation study of prognosis. Philadelphia: Lippincott, 1926.

e4. Cobb C, Youmans JR: Glial and neuronal tumors of the brain, in Youmans JR (ed): 2nd edition. Philadelphia: Saunders Comp, 1982.

e5. Busch EA: Indications for surgery in glioblastomas. Clin Neurosurg 1963; 9: 1–17.

e6. Russel DS, Rubinstein LJ: Pathology of tumors of the nervous system. Baltimore: Williams and Wilkins, 1989.

e7. Firsching R, Schroder R, Koning W, Frowein RA: Spinal drainage metastasis in cerebral glioblastoma/gliosarcoma. Nervenarzt 1985; 56(11): 629–34.

e8. Jenkinson MD, Du Plessis DG, Walker C, Smith TS: Advanced MRI in the management of adult gliomas. Br J Neurosurg 2007; 21(6): 550–61.

e9. Cha S: Neuroimaging in neuro-oncology. Neurotherapeutics 2009; 6(3): 465–77.

e10. Martinez-Bisbal MC, Celda B: Proton magnetic resonance spectroscopy imaging in the study of human brain cancer. Q J Nucl Med Mol Imaging 2009; 53(6): 618–30.

e11. Danchaivijitr N, Waldman AD, Tozer DJ, et al.: Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology 2008; 247(1): 170–8.

e12. Essig M, Giesel F, Stieltjes B, Weber MA: Functional imaging for brain tumors (perfusion, DTI and MR spectroscopy). Radiologe 2007; 47(6): 513–9.

e13. Schonberg T, Pianka P, Hendler T, Pasternak O, Assaf Y: Characterization of displaced white matter by brain tumors using combined DTI and fMRI. Neuroimage 2006; 30(4): 1100–11.

e14. Langen K, Tatsch K, Grosu A, Jacobs A H, Weckesser M, Sabri O: Diagnostics of cerebral gliomas with radiolabeled amino acids. Dtsch Arztebl Int 2008; 105(4): 55–61.

e15. Minn H: PET and SPECT in low-grade glioma. Eur J Radiol 2005; 56(2): 171–8.

e16. Garcia DM, Fulling KH: Juvenile pilocytic astrocytoma of the cerebrum in adults. A distinctive neoplasm with favorable prognosis. J Neurosurg 1985; 63(3): 382–6.

e17. McGirt MJ, Chaichana KL, Attenello FJ, et al.: Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery 2008; 63(4): 700–7.

e18. Lacroix M, Abi-Said D, Fourney DR, et al.: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001; 95(2): 190–198.

e19. Stummer W, Reulen HJ, Meinel T, et al.: Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008; 62(3): 564–76.

e20. Pouratian N, Crowley RW, Sherman JH, Jagannathan J, Sheehan JP: Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma. J Neurooncol 2009; 94(3): 409–18.

e21. Vordermark D, Kolbl O, Ruprecht K, et al.: Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. BMC Cancer 2005; 5: 55

e22. Piette C, Munaut C, Foidart JM, Deprez M: Treating gliomas with glucocorticoids: from bedside to bench. Acta Neuropathol 2006; 112(6): 651–64.

e23. Wick W, Kuker W: Brain edema in neurooncology: radiological assessment and management. Onkologie 2004; 27(3): 261–6.

e24. Batchelor TT, Byrne TN: Supportive care of brain tumor patients. Hematol Oncol Clin North Am 2006; 20(6): 1337–61.

e25. Galicih JH, French LA, Melby JC: Use of dexamethasone in treatment of cerebral edema associated with brain tumors. J Lancet 1961; 81: 46–53.

e26. Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M: Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. Neurology 2001; 56(9): 1219–21.

e27. Hamilton MG, Hull RD, Pineo GF: Prophylaxis of venous thromboembolism in brain tumor patients. J Neurooncol 1994; 22(2): 111–26.

e28. Willis BK: Timing of anticoagulant therapy for thromboembolic complications after craniotomy for brain tumors. Neurosurgery 1991; 28(6): 929–30.

e29. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR: Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev 2008(2): CD004424

e30. Schneider T, Gerhards R, Kirches E, Firsching R: Preliminary results of active specific immunization with modified tumor cell vaccine in glioblastoma multiforme. J Neurooncol 2001; 53(1): 39–46.

e31. Grauer OM, Wesseling P, Adema GJ: Immunotherapy of diffuse gliomas: biological background, current status and future developments. Brain Pathol 2009; 19(4): 674–93.

e32. Weber F, Schackert G, Burger KJ, Floeth FW: Somatic gene therapy of glioblastoma. Dtsch Arztebl 2000; 97(18): A-1228–32.

e33. Hall WA: Targeted toxin therapy for malignant astrocytoma. Neurosurgery 2000; 46(3): 544–51.

e34. Todo T: Oncolytic virus therapy using genetically engineered herpes simplex viruses. Hum Cell 2002; 15(3): 151–9.

e35. Brandes AA, Franceschi E, Tosoni A, et al.: O(6)-methylguanine DNA-methyltransferase methylation status can change between first surgery for newly diagnosed glioblastoma and second surgery for recurrence: clinical implications. Neuro Oncol 2010; 12(3): 283–8.

e36. Parsons DW, Jones S, Zhang X, et al.: An integrated genomic analysis of human glioblastoma multiforme. Science 2008; 321(5897): 1807–12.

e37. Jones DT, Kocialkowski S, Liu L, et al.: Oncogenic RAF1 rearrangement and a novel BRAF mutation as alternatives to KIAA1549:BRAF fusion in activating the MAPK pathway in pilocytic astrocytoma. Oncogene 2009; 28(20): 2119–23.