Continuing Medical Education

The Treatment of Gliomas in Adulthood

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Summary

Background: Gliomas are the most common intrinsic tumors of the brain, with an incidence of 6 per 100 000 persons per year. Recent years have seen marked changes in the diagnosis and treatment of gliomas, with molecular parameters now being an integral part of the diagnostic evaluation.

Methods: This review is based on pertinent articles retrieved by a selective search in PubMed, with special attention to the new WHO glioma classification.

Results: The classification of gliomas on the basis of additional molecular parameters enables more accurate prognostication and serves as a basis for therapeutic decision-making and treatment according to precisely specified algorithms. PET scanning with ^{18}F -fluoroethyl tyrosine and ^{11}C -methionine for the measurement of metabolic activity in gliomas has further refined the diagnostic evaluation. The median overall survival of patients with glioblastoma who have undergone resection of all tumor tissue with a disrupted blood–brain barrier (i.e., all contrast-enhancing tumor tissue) has been prolonged to up to 20 months. The 5-year survival of patients with WHO grade II gliomas is now as high as 97% after near-total resection. The surgical resection of all contrast-enhancing tumor tissue and subsequent radiotherapy and chemotherapy remain the key elements of treatment. New surgical strategies and new methods of planning radiotherapy have made these techniques safer and more effective. The percutaneous application of tumor-treating fields is a new therapeutic option that has gained a degree of acceptance. Accompanying measures such as psycho-oncology and palliative care are very important for patients and should be considered mandatory.

Conclusion: The consistent application of the existing multimodal treatment options for glioma has led in recent years to improved survival. Areas of important current and future scientific activity include immunotherapy and targeted and combined chemotherapy, as well as altered neurocognition, modern approaches to palliative care, and complementary therapies.

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Gliomas are the most common intrinsic tumors of the brain, with an incidence of 6 per 100 000 persons per year (1). The World Health Organization (WHO) classifies gliomas into four grades of differing degrees of malignancy, ranging from fully benign grade I tumors (e.g., pilocytic astrocytoma) to highly malignant grade IV tumors (e.g., glioblastoma). The grade of a glioma is, in turn, the most important factor affecting the patient's prognosis, ranging from a normal life expectancy for patients with WHO grade I tumors to a median survival time of 15 months or, according to the most recent data, 20 months for patients with glioblastoma (WHO grade IV) (2, 3). Glioblastoma, with an incidence of 3–4 per 100 000 persons per year, is the

Incidence

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most common type of glioma. WHO grade I glioma is very rare in adults and will not be discussed in this article.

Gliomas can cause a wide variety of neurologic manifestations depending on their size, growth pattern, and location, ranging from focal neurologic deficits to structural epilepsy and mental and cognitive changes. Epileptic seizures are the most common primary manifestation: they are present in 60–85% of patients with grade II gliomas (4). The detection of asymptomatic (i.e., not yet symptomatic) gliomas has become more common in recent decades owing to the widening indications for diagnostic magnetic resonance imaging (MRI).

Learning objectives

This article should enable the reader to

- name the different types of glioma in the WHO classification (whatever the reader's medical specialty),
- know the differential diagnosis of glioma, and
- gain an overview of the more important treatment algorithms.

Histopathology and molecular classification

The updated WHO classification of 2016 (5) was the first to include a fundamental implementation of molecular parameters in neuropathological diagnosis. This, in combination with tumor histology and grading based on morphological features, has made the classification of gliomas much more precise.

The main molecular markers are the following:

- Isocitrate dehydrogenase 1 and/or 2 (IDH-1/-2)
 - Considered a very early mutation in glioma pathogenesis
 - Typical of low-grade or anaplastic glioma
 - New-onset glioblastomas are typically IDH-1-wildtype (WT); a (rare) IDH-1 mutation in a glioblastoma implies that the tumor arose from a lower-grade precursor.
- Codeletion of chromosome segments 1p and 19q
 - In IDH-1-mutated tumors, this indicates that the tumor is of oligodendroglial origin. Astrocytoma is characterized by the lack of a 1p/19q codeletion.
- Histone 3 mutation (H3 K27M)
 - This defines the new entity of diffuse midline glioma, which carries an unfavorable prognosis.
- Methylation of the O6-methylguanine DNA methyltransferase (MGMT) promoter
 - This does not affect the WHO classification of the tumor, but is of high prognostic and predic-

Prognosis

The World Health Organization (WHO) classifies gliomas into four grades of differing degrees of malignancy, ranging from benign grade I tumors (e.g., pilocytic astrocytoma) to malignant grade IV tumors (e.g., glioblastoma). The grade of a glioma is an important factor affecting prognosis.

FIGURE 1

Treatment algorithm for WHO grade II glioma depending on integrated diagnosis

(1, 26, 35)

IDH: isocitrate dehydrogenase; PCV: procarbazine, CCNU (lomustine), and vincristine; RCT: radiochemotherapy; RT: radiotherapy; TMZ: temozolomide; WHO: World Health Organization

* In the presence of favorable prognostic factors (age ≤ 40, complete resection)

tive significance for patients with glioblastoma (correlated with response to temozolomide [6]).

The updated WHO classification is also the basis of the new guidelines for the diagnosis and treatment of astrocytic and oligodendroglial tumors in adulthood that have been issued under the aegis of the European Association for Neuro-Oncology (EANO) (1). The treatment recommendations in this guideline are the first to be clearly stratified according to molecular parameters, and they will serve as a basis for the coming update of the national guidelines. In this review, we present the main aspects of the diagnosis and treatment of gliomas. An overview of the main therapeutic algorithms is found in *Figures 1–3*.

In preparing this review, we selectively searched PubMed for literature on the diagnosis and treatment of gliomas published from 1 January 2001 to 30 September 2017.

Diagnostic evaluation

Imaging studies in primary diagnostic evaluation

Magnetic resonance imaging (MRI; T1 with and without contrast medium, T2, and FLAIR sequences) is now

Presenting symptoms

Gliomas can cause a wide variety of neurologic manifestations depending on their size, growth pattern, and location. Epileptic seizures are the most common primary manifestation.

FIGURE 2

Treatment algorithm for WHO grade III glioma depending on integrated diagnosis
(1, 32, 40)

IDH: isocitrate dehydrogenase; PCV: procarbazine, CCNU (lomustine), and vincristine; RCT: radiochemotherapy; RT: radiotherapy; TMZ: temozolomide; WHO: World Health Organization

the imaging method of first choice. Disruption of the blood–brain barrier, as manifested by contrast enhancement of tumor tissue, is considered evidence of a malignant glioma of WHO grade III or IV, although malignant areas can also be present in large non-contrast-enhancing tumors that are presumed to be of a lower grade. Focal malignant transformation can be demonstrated in such cases with metabolic imaging (amino acid positron emission tomography [PET] or MRI with magnetic spectroscopy) (7) (Figure 4). PET has been validated for this purpose and is performed mainly with the tracer substance ^{18}F -fluoroethyl tyrosine (FET), or, in some centers, ^{11}C -methionine (MET) (8).

Computed tomography (CT) plays a lesser role in the diagnostic evaluation of gliomas, although it is often a CT that first brings a tumor to light when performed as an emergency study on the patient's initial presentation. CT also reveals focal intratumoral calcifications (typical of oligodendroglioma) better than MRI does.

Diagnostic studies after surgery and in follow-up

As the goal of surgery is considered to be the removal of all tissue in which the blood–brain barrier is disrupted, i.e., all contrast-enhancing tissue, early post-operative MRI (within 72 hours at most, and within 48 hours if possible) is indicated to assess the extent of

resection. The patient's further course of disease and the effects of further treatment are monitored with conventional MRI as specified in the RANO criteria (9, 10). According to the guideline (1), follow-up MRI is performed every three months in patients with WHO grade IV tumors and every four to six months in patients with WHO grade II or III tumors, depending on their clinical condition.

In unclear clinical situations with possibly post-therapeutic rather than neoplastic changes on MRI, amino acid PET can be used to distinguish true tumor progression from so-called pseudoprogression induced by treatment measures such as radiotherapy (11–13). If PET yields no clear answer either in this situation, stereotactic biopsy is indicated.

Stereotactic biopsy

The treatment of gliomas in adults must always be based on a tissue diagnosis. If open tumor resection is not possible, stereotactic biopsy guided by structural and metabolic imaging (MRI/PET) is a highly reliable, low-risk method of establishing a definitive, integrated diagnosis that can serve as a basis for further neuro-oncological treatment and can be performed on patients of any age (14, 15). When a tumor biopsy, rather than gross total resection, is to be performed, stereotactic biopsy is preferable to “open” biopsy via craniotomy because of its lesser invasiveness and greater precision. Modern neuropathological methods enable the determination of all of the required histological and molecular genetic parameters even from the small tissue samples obtained by stereotactic biopsy, which are no more than a few cubic millimeters in size.

Treatment options

The treatment of patients with gliomas generally consists of a combination of the following options. The treatment algorithms for the main types of glioma are depicted in Figures 1–3.

Resection

The goal of tumor resection is the removal of all contrast-enhancing tissue (in glioblastoma) or of all T2/FLAIR-hyperintense tissue (in WHO grade II and III tumors) while minimizing neurological risk for the patient.

Multiple preoperative and intraoperative aids are available to help the neurosurgeon attain this goal. These include intraoperative imaging with MRI, CT, or ultrasonography, electrophysiologic monitoring, the visualization of tumor tissue with systemically injected

Imaging studies for primary diagnostic evaluation

Magnetic resonance imaging (MRI; T1 with and without contrast medium, T2, and FLAIR sequences) is now the imaging method of first choice. Disruption of the blood–brain barrier, as manifested by contrast enhancement of tumor tissue, is evidence of a malignant glioma of WHO grade III or IV.

Stereotactic biopsy

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fluorescent dye (5-aminolevulinic acid [5-ALA]), and surgery under local anesthesia with neurolinguistic cortical language mapping.

A newer method intended to make resection safer while also maximizing the extent of resection involves preoperative non-invasive mapping of the brain surface with identification of the motor and speech areas through the use of navigated transcranial magnetic stimulation (nTMS) (16).

Because of their growth pattern, gliomas of grade II, III, or IV cannot be cured by resection. The role of surgery is, therefore, subject to continual debate and re-evaluation.

The state of the evidence favoring tumor resection varies depending on the tumor grade. For glioblastoma, the complete removal of tissue with a disrupted blood–brain barrier has a positive effect on progression-free and overall survival, with prolongation of the mean overall survival from 12 to 15 months (level Ib evidence) (17, 18). Recent retrospective data suggest an incremental prolongation of survival depending on the percentage of resection; because of statistical problems and marked distortion, however, these data are not considered reliable enough to provide a basis for therapeutic decision-making (19). The goal of resection in the primary treatment of glioblastoma therefore remains the removal of as much contrast-enhancing tissue as possible without giving the patient a new functional deficit. The deliberate partial resection of a large tumor for the purpose of lessening intracranial pressure is very rarely indicated.

Far fewer data are available concerning the resection of recurrent glioblastoma. A number of large retrospective analyses indicate that re-resection can be beneficial as part of an overall oncological treatment plan (20).

In general, the authors consider the use of 5-ALA fluorescence or intraoperative MRI as standard in glioblastoma surgery, as each of these methods has been shown to have a marked effect on the attainment of the goal of surgery (removal of all contrast-enhancing tumor tissue) as well as on progression-free survival (17).

The state of the evidence concerning the surgical resection of WHO grade II and III gliomas is weaker than that for glioblastoma. In primary treatment, the maximal resection of tumor tissue that is visible in T2/FLAIR-weighted MRI is considered to increase the chance of recurrence-free, progression-free, and overall survival (21, 22). The 5- and 8-year overall survival of patients in whom more than 90% of the tumor has been resected is 97% and 91%, respectively, compared to 76% and 60% with a lesser extent of resection (22). Consequently,

Surgical resection

The goal of tumor resection in the primary treatment of glioblastoma is the removal of all contrast-enhancing tumor tissue while minimizing neurological risk for the patient.

FIGURE 3

Treatment algorithm for WHO grade IV glioma depending on integrated diagnosis (1, 2)
 IDH: isocitrate dehydrogenase; RCT: radiochemotherapy; RT: radiotherapy;
 TMZ: temozolomide; WHO: World Health Organization

maximal resection is recommended for these tumors as well, according to the guideline of the European Association of Neuro-Oncology (EANO) (1). The role of resection in case of tumor recurrence has been insufficiently investigated. A benefit on survival has been found only in small-scale, retrospective studies, and thus no general, evidence-based recommendation can be given regarding the treatment of recurrent WHO grade II or III glioma (23, 24). Surgery may be indicated to treat epileptic seizures, aside from the question of its potential benefit for survival.

Radiotherapy

Percutaneous, fractionated radiotherapy of gliomas is now performed in standardized fashion and is generally well tolerated. Total radiation doses of 50 Gy (for WHO grade II tumors) (25) and 60 Gy (for WHO grade III and IV tumors) are given in daily individual doses of 1.8 to 2.9 Gy five days per week, so that the total treatment time is five to six weeks. The current methods of defining the target volume and of delivering the requisite dose minimize harm to healthy brain tissue and thereby lessen the side effects of treatment.

Because most recurrences of glioma arise in the immediate vicinity of the primary tumor, local radiotherapy of the tumor region or tumor bed is performed. For malignant, contrast-enhancing gliomas, any residual tumor tissue seen on MRI after initial surgery (biopsy or resection) is included in the treatment volume, with an

Resection of recurrent gliomas

Sparse data are available concerning the resection of recurrent glioblastoma. A number of large retrospective analyses indicate that re-resection can be beneficial as part of an overall oncological treatment plan.

Figure 4:
A 27-year-old man with an extensive left frontotemporal lesion.
 MRI shows no contrast enhancement, but ^{18}F -FET PET reveals a small metabolically active area. Stereotactic biopsy and neuropathological evaluation yielded the diagnosis of anaplastic astrocytoma, WHO grade III (IDH-1 mutated, $1p/19q$ intact, methylated MGMT promoter).
 Images kindly provided by Forschungszentrum Jülich (Prof. Dr. Langen).

- a) ^{18}F -fluoroethyl tyrosine positron emission tomography (^{18}F -FET PET)
- b) Magnetic resonance imaging (MRI): T1 with contrast medium
- c) Magnetic resonance imaging (MRI): fluid-attenuated inversion recovery (FLAIR)

anatomically adapted safety margin of no more than 20 mm. For non-contrast-enhancing gliomas, the target volume is defined on the basis of the T2/FLAIR MRI, and the safety margins are adapted to the degree of malignancy (26–28). The utility of PET with radioactively marked amino acids for the planning of radiotherapy has not yet been conclusively demonstrated (13).

Radiotherapy is preferably performed as IMRT (intensity-modulated radiotherapy) and under image

guidance (image-guided radiotherapy, IGRT). This enables high spatial precision and the sparing of structures at risk (eloquent brain areas, the visual system, the hippocampi, the pituitary gland, and the lenses of the eyes). For patients over age 60, a briefer course of hypofractionated radiotherapy (10×3.4 Gy over two weeks) is probably just as effective as the standard course (29).

The treatment of recurrent glioma with a second course of percutaneous radiotherapy was looked on unfavorably in the past but has now come back into use because of the recent finding that a second course of radiotherapy can safely be delivered locally (30). This is done with markedly narrower safety margins than are used for primary radiotherapy, and preferably with the aid of stereotactic radiation methods and PET-guided radiotherapy planning.

When diagnostic imaging studies show that a primary, residual, or recurrent tumor is well circumscribed (such tumors are generally of WHO grade I or II, and less commonly of WHO grade III or IV), brachytherapy can be a further treatment option in selected cases. This consists of the stereotactically guided implantation of radioactive iodine (^{125}I) seeds (31).

Medical tumor therapy

The standard chemotherapeutic drug for gliomas is temozolomide (1); in addition, a combination of procarbazine, lomustine (CCNU), and vincristine (so-called PCV treatment) is used both for primary chemotherapy (Figures 1–3) and for the therapy of recurrent tumors. Temozolomide is a component of primary chemotherapy for glioblastoma (in the so-called Stupp protocol), while PCV is used mainly for oligodendroglial tumors (32). Elderly patients with glioblastoma can be given monotherapy with either radiation or temozolomide (33), or else a shortened course of radiotherapy combined with temozolomide (34).

Until a decade ago, chemotherapy was generally not given for WHO grade II or III tumors, except in case of recurrence or tumor progression. The long-term findings of clinical trials now clearly support early chemotherapy for these tumors (26, 32, 35).

As for anti-angiogenic drugs, phase III trials have not shown any significant prolongation of overall survival through the use of either bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), or the integrin inhibitor cilengitide (36, 37). The current research landscape in neuro-oncology, as in other areas of oncology, is dominated by immunological trials, but no significantly positive

Radiotherapy

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Chemotherapy

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TABLE 1

A selection of clinical trials that have led to changes in standard treatment

Authors	Year	Description	Trial designation	Reference
Stupp et al.	2005	Concomitant radio- and chemotherapy for glioblastoma	EORTC 26981/22981	(2)
Hegi et al.	2005	MGMT as a prognostic and predictive factor	–	(6)
Stummer et al.	2006	5-aminolevulinic acid in the resection of glioblastoma	–	(17)
Wick et al.	2009	Radiotherapy vs. chemotherapy for anaplastic glioma	NOA-04	(40)
Wick et al.	2012	Radiotherapy vs. chemotherapy for elderly patients with malignant astrocytoma	NOA-08	(33)
Cairncross et al.	2013	Radiotherapy and PCV for anaplastic oligodendroglioma	RTOG 9402	(e1)
van den Bent et al.	2013	Radiotherapy and PCV for anaplastic oligodendroglioma	EORTC 26951	(32)
van den Bent et al.	2017	Radio- and chemotherapy for non-codeleted anaplastic glioma	CATNON	(e2)
Buckner et al.	2016	Chemotherapy for grade II glioma	–	(35)
Stupp et al.	2016	Tumor-treating fields in the primary treatment of glioblastoma	EL-14	(38)
Perry et al.	2017	Radiochemotherapy for elderly patients with glioblastoma	–	(34)

MGMT, O6-methylguanine-DNA-methyltransferase; PCV, procarbazine, CCNU (lomustine), and vincristine

findings have yet been obtained. A large-scale trial of vaccination with rindopepimut (ACT IV) (3) revealed no significant effect on the survival of patients with glioblastoma. The data from a multicenter trial involving the application of dendritic cells (DCVax) have been inaccessible for some time. Multiple drugs from the checkpoint inhibitor class are now being studied in phase III trials, among them nivolumab, an antibody against PD-1 (e.g., in the CA-209-548 and -498 trials).

The uncritical use of potentially dangerous, addictive drugs such as methadone to treat patients with glioma is now receiving a great deal of attention from the news media but is not supported by evidence from controlled studies and should be avoided.

A selection of clinical trials that have led to changes in treatment standards is presented in *Table 1*.

Tumor-treating fields (TTF)

The external application of an alternating electric field (100–300 kHz) to dividing tumor cells *in vitro* has an antimitotic and apoptotic effect. A randomized clinical trial in which such fields were permanently applied through the scalp (in addition to standard treatment) for the treatment of patients with *de novo* glioblastoma yielded a statistically significant prolongation of progression-free and overall survival (38). Despite

the presence of convincing trial evidence, treatment with TTF is still heavily debated; the main reason for this is probably the visible stigmatization of patients that this form of treatment entails (the scalp must be clean-shaven, and electrodes must be fastened to the head for at least 18 hours per day). On the basis of the available evidence, this treatment option should be offered to patients with supratentorial glioblastoma.

Palliative and supportive care

Supportive therapies are now an indispensable component of the treatment strategy for glioma patients. Epilepsy or manifestations of intracranial hypertension should be treated in accordance with the guidelines, and appropriate measures should be taken for thrombosis prevention, in view of the high incidence of thrombosis. Antiemetic drugs should be given as needed, mainly while the patient is undergoing chemotherapy. Patients must receive support in dealing with their often complicated social problems (social service). Psycho-oncology also plays a central role, providing essential help for patients and their families.

The natural course of gliomas places complex demands on symptomatic palliative care. Little evidence specifically relating to glioma patients is currently available, but many aspects of palliative

Chemotherapy for WHO grade II and III tumors

Until a decade ago, chemotherapy was generally not given for WHO grade II or III tumors, except in case of recurrence or tumor progression. The long-term findings of clinical trials now clearly support early chemotherapy for WHO grade II and III tumors.

Trials of immunotherapy

The current research landscape in neuro-oncology, as in other areas of oncology, is dominated by immunological trials, but no significantly positive findings have yet been obtained.

care have been shown to be beneficial in patients with other types of cancer, particularly the symptomatic treatment of pain and delirium. According to the most recent guideline (39), patients should be offered palliative care as early as possible.

Complementary medicine

There are no valid data supporting any of the methods of so-called complementary medicine (traditional Chinese medicine, phytotherapy, homeopathy, and others). There is nonetheless a heavy demand for these treatments from the patients themselves, and, when used in addition to evidence-based treatment, they often yield subjective benefit in terms of general physical and emotional stabilization and the improvement of treatment-associated symptoms (nausea, fatigue, and the like). Accompanying complementary therapy can be accepted in routine clinical practice if the patient desires it and if a reputable practitioner is available to provide it.

Therapeutic decision-making

According to the guidelines, the treatment measures presented here should be combined to create an individualized treatment approach based on the integrated tumor diagnosis and on the patient's clinical condition and special needs (Figure 1–3). This is the responsibility of an interdisciplinary neuro-oncological tumor board, which should include representatives of the key disciplines—neurosurgery, neurology, radiation oncology—as well as medical oncology, palliative medicine, and the diagnostic specialties. In addition to recommending primary treatment, the tumor board should monitor and assess patients who have a complex course of disease after primary treatment. A tumor board that meets weekly, alongside other quality-assurance measures such as the rapid management of complications, is an essential criterion for a properly functioning neuro-oncological center.

Future prospects

The main goal of research in the near future will be the development of targeted local or systemic treatments that are based on the molecular signature of the tumor. Immunotherapy will remain a central object of investigation. Meanwhile, increasing attention will be paid to the scientific understanding of patient-oriented factors such as cognitive changes and the effect of early palliative care, and even of complementary methods, on the quality of life and overall survival of patients with malignant gliomas.

Complementary medicine

Although there is no evidence for its efficacy, complementary therapy as an add-on to evidence-based treatment can be accepted in routine clinical practice if the patient desires it and if a reputable practitioner is available to provide it.

Conflict of interest statement

Prof. Goldbrunner has served as a paid consultant for MagForce and has received reimbursement of meeting participation fees and of travel and accommodation expenses from Roche.

Dr. Grau has served as a paid consultant for Roche. He has received reimbursement of travel and accommodation expenses, as well as honoraria for preparing scientific presentations, from Roche.

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► **Supplementary material**
 For eReferences please refer to:
www.aerzteblatt-international.de/ref2018

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Only one answer is possible per question. Please choose the most appropriate answer.

Question 1

What is the most common primary manifestation of grade II tumors?

- a) Diminished visual acuity
- b) Personality change
- c) Aura
- d) Epileptic seizure
- e) Cluster headache

Question 2

Which molecular marker has a high prognostic value in glioblastoma patients as a predictor of the response to treatment with temozolomide?

- a) APLP
- b) IDH-2
- c) MGMT
- d) H3 K27M
- e) IDH-1

Question 3

What is the most common type of glioma?

- a) Astrocytoma
- b) Glioblastoma
- c) Oligodendroglioma
- d) Ependymoma
- e) Pleomorphic xanthoastrocytoma

Question 4

According to the treatment algorithm for WHO grade II gliomas, what is the next step in the treatment of a diffuse astrocytoma (IDH-wildtype) after resection?

- a) Radiotherapy
- b) Radiotherapy with procarbazine
- c) Chemotherapy with 5-fluorouracil
- d) Chemotherapy with bleomycin/vinblastine
- e) Methadone treatment

Question 5

What is the method of first choice in the primary diagnostic evaluation of glioma?

- a) Electroencephalography
- b) Ultrasonography
- c) Magnetic resonance imaging
- d) Plain x-ray
- e) Computed tomography

Question 6

What is the incidence of gliomas?

- a) 6/100 000/year
- b) 12/100 000/year
- c) 18/100 000/year
- d) 24/100 000/year
- e) 32/100 000/year

Question 7

What is the goal of primary surgical treatment of glioblastoma?

- a) Limited resection to spare cognitive ability
- b) One-time decompressive surgery to normalize intracranial pressure
- c) Complete resection of contrast-enhancing tissue without a functional deficit
- d) Partial resection followed by second-look surgery for completion
- e) Extensive, radical resection to include all potentially suspect areas

Question 8

Where do recurrences of glioma generally arise?

- a) In the cerebellum
- b) In the limbic system
- c) Far away from the primary tumor
- d) In the diencephalon and brainstem
- e) In the immediate vicinity of the primary tumor

Question 9

Which of the following drugs plays a role in the primary treatment of glioblastoma?

- a) Dexamethasone
- b) Doxorubicin
- c) Temozolomide
- d) Dacarbazine
- e) Etoposide

Question 10

For what new method of treating glioblastoma are convincing trial data available?

- a) Angiogenesis inhibitors
- b) Tumor-treating fields
- c) Propolis therapy
- d) Oil-protein diet
- e) Immunotherapy

► Participation is possible only via the Internet:
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Supplementary material to:

The Treatment of Gliomas in Adulthood

by Roland Goldbrunner, Maximilian Ruge, Martin Kocher, Carolin Weiß Lucas, Norbert Galldiks*, and Stefan Grau

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