Cancer Letters 375 (2016) 263–273

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Original Articles

CGCG clinical practice guidelines for the management of adult diffuse gliomas

Tao Jiang [a,b,c,d,*], Ying Mao [e,**], Wenbin Ma [f,***], Qing Mao [g,****], Yongping You [h,*****], Xuejun Yang [i,******], Chuanlu Jiang [j], Chunsheng Kang [i], Xuejun Li [k], Ling Chen [l], Xiaoguang Qiu [m], Weimin Wang [n], Wenbin Li [o], Yu Yao [e], Shaowu Li [a], Shouwei Li [p], Anhua Wu [q], Ke Sai [r], Hongmin Bai [n], Guilin Li [a], Baoshi Chen [b], Kun Yao [s], Xinting Wei [t], Xianzhi Liu [t], Zhiwen Zhang [u], Yiwu Dai [v], Shengqing Lv [w], Liang Wang [x], Zhixiong Lin [p], Jun Dong [y], Guozheng Xu [z], Xiaodong Ma [l], Jinquan Cai [j], Wei Zhang [b], Hongjun Wang [j], Lingchao Chen [e], Chuanbao Zhang [a], Pei Yang [a], Wei Yan [h], Zhixiong Liu [k], Huimin Hu [a], Jing Chen [a], Yuqing Liu [a], Yuan Yang [g], Zheng Wang [a], Zhiliang Wang [b], Yongzhi Wang [b], Gan You [b], Lei Han [i], Zhaoshi Bao [b], Yanwei Liu [a], Yinyan Wang [b], Xing Fan [b], Shuai Liu [f], Xing Liu [b], Yu Wang [f], Qixue Wang [i] on behalf of the Chinese Glioma Cooperative Group (CGCG)

[a] *Beijing Neurosurgical Institute, Beijing 100050, China*
[b] *Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China*
[c] *Center of Brain Tumor, Beijing Institute for Brain Disorders, Beijing 100069, China*
[d] *China National Clinical Research Center for Neurological Diseases, Beijing 100050, China*
[e] *Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai 200040, China*
[f] *Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China*
[g] *Department of Neurosurgery, West China Hospital, West China Medical School, Sichuan University, Chengdu 610041, China*
[h] *Department of Neurosurgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China*
[i] *Department of Neurosurgery, Key Laboratory of Post-trauma Neuro-repair and Regeneration in Central Nervous System, Ministry of Education, Tianjin Medical University General Hospital, Tianjin 300052, China*
[j] *Department of Neurosurgery, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China*
[k] *Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China*
[l] *Department of Neurosurgery, Chinese PLA General Hospital, Beijing 100853, China*
[m] *Department of Radiotherapy, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China*
[n] *Department of Neurosurgery, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, Guangdong 510010, China*
[o] *Department of Oncology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China*
[p] *Department of Neurosurgery, Beijing Sanbo Brain Hospital, Capital Medical University, Beijing 100093, China*
[q] *Department of Neurosurgery, The First Affiliated Hospital of China Medical University, Shenyang 110001, China*
[r] *Department of Neurosurgery, Sun Yat-Sen University Cancer Center, Guangzhou 510060, China*
[s] *Department of Pathology, Beijing Sanbo Brain Hospital, Capital Medical University, Beijing 100093, China*
[t] *Department of Neurosurgery, The 1st Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*
[u] *Department of Neurosurgery, The First Hospital Affiliated to the Chinese PLA General Hospital, Beijing 100048, China*
[v] *Department of Neurosurgery, Beijing Military Region General Hospital, Beijing 100700, China*
[w] *Department of Neurosurgery, Xinqiao Hospital, The Third Military Medical University, Chongqing 400038, China*
[x] *Department of Neurosurgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an 710038, China*
[y] *Department of Neurosurgery, Medical College of Soochow University, Suzhou 215123, China*
[z] *Department of Neurosurgery, Wuhan General Hospital of Guangzhou Military Command, Guangzhou, Wuhan 430070, China*

* Corresponding author.
E-mail address: taojiang1964@163.com (T. Jiang).
** Corresponding author. Tel.: +8613801769152; fax: +862152489191.
E-mail address: maoying@fudan.edu.cn (Y. Mao)
*** Corresponding author. Tel.: +8613701364566; fax: +86010651254875.
E-mail address: mawb2001@hotmail.com (W. Ma)
**** Corresponding author. Tel.: +8618980601506; fax: +862885422023.
E-mail address: qingmao2000@163.com (Q. Mao)
***** Corresponding author. Tel.: +8613770694258; fax: +862583716602.
E-mail address: yypl3@sohu.com (Y. You)
****** Corresponding author. Tel.: +8613011329950; fax: +862260814469.
E-mail address: ydenny@yahoo.com (X. Yang).

http://dx.doi.org/10.1016/j.canlet.2016.01.024

ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 15 January 2016
Accepted 15 January 2016

Keywords:
CGCG
Glioma
Management
Guideline

ABSTRACT

The Chinese Glioma Cooperative Group (CGCG) Guideline Panel for adult diffuse gliomas provided recommendations for diagnostic and therapeutic procedures. The Panel covered all fields of expertise in neuro-oncology, i.e. neurosurgeons, neurologists, neuropathologists, neuroradiologists, radiation and medical oncologists and clinical trial experts. The task made clearer and more transparent choices about outcomes considered most relevant through searching the references considered most relevant and evaluating their value. The scientific evidence of papers collected from the literature was evaluated and graded based on the Oxford Centre for Evidence-based Medicine Levels of Evidence and recommendations were given accordingly. The recommendations will provide a framework and assurance for the strategy of diagnostic and therapeutic measures to reduce complications from unnecessary treatment and cost. The guideline should serve as an application for all professionals involved in the management of patients with adult diffuse glioma and also as a source of knowledge for insurance companies and other institutions involved in the cost regulation of cancer care in China.

Introduction

There is currently no clear national consensus for the optimal diagnosis and treatment of adult gliomas. This guideline developed is primarily an effort to assess the evidence for management of adult gliomas in a manner that sets a benchmark for further improvement, and to document the recommendations of the Chinese Glioma Cooperative Group (CGCG) in patients with gliomas. It covers WHO grade II/III astrocytomas, oligodendrogliomas, and oligoastrocytomas; and WHO grade IV glioblastomas. The guideline includes diagnosis (including neuroimaging, pathology and molecular information), general management strategy and specific treatment plans for gliomas, supportive care and response evaluation and follow-up. It has also been circulated to CGCG members, including neurosurgeons, medical and radiation oncologists, neuropathologists, neuroradiologists and epidemiologists for comments before the final consensus document was drawn up.

These recommendations provided are set forth for conscientious use by the practicing physician who must take into account all of the circumstances in the supervision of a given individual illness. Furthermore, the recommendations could serve as a valuable source of information for multidisciplinary medical professionals, patients, relatives, and official health departments.

Epidemiology and survival

According to the multicenter cross-sectional study on brain tumor (MCSBT) in China [1], age standardized prevalence of primary brain tumor is 22.52 per million for all populations and gliomas account for 31.1% in those aged 20–59 years. Diffuse gliomas are diagnosed as astrocytomas, oligoastrocytomas and oligodendrogliomas of grades II and III and glioblastomas (GBM) of grade IV based on the 2007 World Health Organization (WHO) CNS tumors classification [2]. Diffuse and anaplastic astrocytomas represent about 25.2% of gliomas. Oligoastrocytic tumors and oligodendrogliomas, including anaplastic oligodendrogliomas, account for about 18% of gliomas. And glioblastomas occupy about 30% of CNS gliomas [3].

Based on the Chinese Glioma Genome Atlas (CGGA) statistics, malignant gliomas have an unfavorable prognosis with median overall survival times (OS) of 78.1 months for low-grade gliomas (WHO Grade II), 37.6 months for anaplastic gliomas and 14.4 months for GBMs. For low-grade gliomas, the 6-month, 1-, 3-, and 5-year OS rates were 99, 94, 79 and 67%, respectively; for anaplastic gliomas, they were 88, 75, 51 and 36%, respectively; and for GBMs, they were 87, 61, 15 and 9%, respectively [4].

Diagnosis and pathology

Gliomas are diagnosed using morphological criteria according to WHO classification [2]. Diffuse astrocytoma cells histologically represent stellate, spindle-shaped with fiber like processes, or plump with a large eosinophilic cytoplasmic mass. Anaplastic astrocytomas show more malignant cytological features – cellularity, anaplasia and mitoses. Glioblastoma arises most commonly *de novo* (primary glioblastoma). Some glioblastomas arise by malignant transformation of lower-grade astrocytomas (secondary glioblastoma) [5]. Primary glioblastomas are more common in older patients and are more aggressive. Microscopically, glioblastoma shows high cellularity, cellular and nuclear anaplasia, mitoses, microvascular proliferation, and necrosis. Oligodendroglioma cells, microscopically, are uniform and have round central nuclei with fine chromatin surrounded by a clear halo (unstained cytoplasm), which is an artifact of processing. Oligodendrogliomas are traversed by a delicate capillary network and have a tendency to calcify, which is helpful in radiological and histological diagnoses. Some oligodendrogliomas contain neoplastic astrocytes which are mixed with the oligodendroglial cells or grow in adjacent but separate areas. Such mixed tumors are called oligoastrocytomas. Oligodendrogliomas and oligoastrocytomas can be classified as low-grade (WHO grade II) or high grade/anaplastic (WHO grade III) based on cellularity, anaplasia, mitotic activity, microvascular proliferation, and necrosis.

Molecular biomarkers

IDH *mutation*

Mutations in the isocitrate dehydrogenase (*IDH*) gene primarily locate at codon R132 in *IDH1* and R172 in *IDH2*. *IDH1/2* mutations are the earliest genetic alteration and mainly occur in WHO grade II and III astrocytic and oligodendroglial tumors and in secondary GBMs, which develop from lower grade astrocytomas [6]. *IDH2* mutations are less frequent compared with IDH1 mutations. However, *IDH 1/2* play the same role, catalyzing the oxidative carboxylation of isocitrate to a-ketoglutarate, resulting in the reduction of NADP to NADPH [7]. *IDH1/2* mutational status is of notable diagnostic value, and particularly rare in primary glioblastoma [8]. *IDH1/2* mutations commonly indicate a favorable prognosis independent of WHO grades [7,9,10].

Codeletion of chromosomal arms 1p and 19q

Combined loss of chromosomal arms 1p and 19q resulting from an unbalanced t(1;19)(q10;p10) leads to loss of heterozygosity [11],

associated with oligodendroglial histology and rarely found in other tumors [12]. Patients with tumors lacking 1p and 19q have longer median survival times and progression-free survival [13,14]. Most oligodendrogliomas with 1p and 19q codeletion also carry mutations in the *CIC* gene on chromosome 19q and the *FUBP1* gene on chromosome 1p [15–17].

MGMT *promoter methylation and* miR-181d

Methylation of O(6)-methylguanine-DNA methyl transferase (*MGMT*) promoter, a prognostic and predictive factor [18,19], correlates with benefit from alkylating agent chemotherapy in patients with *IDH1* wild type malignant gliomas of WHO grades III/IV [20]. Besides epigenetic silencing, *miR-181d* also leads to decreased mRNA stability and/or reduced protein translation by binding to the 3′ untranslated region of *MGMT* transcripts, and predicts the survival and response of alkylating agent chemotherapy in glioblastoma [21–23].

EGFRvIII

The *EGFRvIII*, a characteristic deletion exons 2–7 of the *EGFR* gene, is expressed in approximately 20–30% of primary GBM, resulting in constitutive and ligand-independent receptor activity and regarded as an important oncogenic mutation [24,25]. Long-term survival might be worse in patients whose tumors carry this mutation than in those who do not. As *EGFRvIII* is most common in primary GBM and is not expressed on normal tissues, it is an effective target for immunotherapy [26].

ATRX *mutations or loss*

Mutations of alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) strongly correlated with its loss of expression, and may predict better prognosis in astrocytic tumors with *IDH* mutations [15,27]. *ATRX* mutation or loss of expression results in ALT and genomic instability [28,29]. The protein encoded by *ATRX* plays multiple cellular roles, including chromatin remodeling at telomeres [30,31]. Furthermore, loss of ATRX expression may define a subgroup of astrocytic tumors with a more favorable prognosis [9,27].

TERT *promoter mutation*

Telomerase reverse transcriptase (*TERT*), which is essential in maintaining telomere length and its activity, is pathologically increased in gliomas. Recurrent mutations in the promoter region of *TERT* most occurred in oligodendroglial tumors and primary glioblastoma, leading to *TERT* upregulation [32]. The prognostic value of *TERT* promoter mutation remains controversial in *IDH* wild type glioblastoma [33,34]. Combined analysis of 1p/19q codeletion, *IDH* and *TERT* promoter mutational status may contribute to define prognostic subgroups of gliomas [35–38].

Ki-67

Ki-67 is a nuclear protein expressed during the G1, S, G2 and M phases of the cell cycle, and has been widely used as a stable marker of cell proliferation in various types of human tumors, including malignant gliomas [39]. Ki-67 is an independent prognostic indicator, associated with poor survival in gliomas regardless of WHO grades [4,9].

Recent published studies [35,40–42] validated prior reports that specific combinations of genetic alternations in *IDH1/2*, *TERT*, *ATRX* and codeletion of 1p/19q have the ability to reclassify gliomas into rational subsets, defining a glioma's biological and clinical behaviors more accurately than stratifications based solely on histopathology. Lower grade gliomas (WHO grade II and III gliomas) have an extremely high frequency of *IDH1/2* mutation, which is accompanied either by 1p and 19q codeletion and a mutated *TERT* promoter or by *TP53* mutations with or without *ATRX* mutations. Grade II or III astrocytomas mainly depicted the mutations in *IDH1/2*, *ATRX* and *TP53*, while grade II and III oligodendrogliomas are characterized by 1p/19q codeletion and the mutations in *IDH1/2* and *TERT* promoter. Numerous evidence showed that oligoastrocytomas (WHO grades II and III) may segregate into two groups, genetically matching oligodendroglioma on one and astrocytoma on the other side based on the molecular information, for example, *IDH1/2*, 1p/19q and *ATRX*, and so on [43,44]. Most lower grade gliomas without an *IDH* mutation were molecularly and clinically similar to glioblastoma [40]. The detailed information of these molecular markers above and their clinical relevance are listed in Table 1.

Disease management

General recommendations

Management of gliomas requires a multidisciplinary approach and involves neuroimaging, surgery, neuropathology, radiation therapy (RT), chemotherapy and supportive care. Karnofsky performance score, neurological function, and age need to be considered in clinical decision making in neuro-oncology.

Neuroimaging enables the noninvasive evaluation of glioma and is considered to be one of the key factors for individualized therapy and patient management, since accurate diagnosis and demarcation of viable tumor tissue is required for treatment planning as well as assessment of treatment response [45]. Computed tomography (CT) scanning can demonstrate the tumor and associated findings; however, in making the glioma diagnosis, CT scanning is not sensitive enough and may cause small tumors to be missed. Magnetic resonance imaging (MRI) is significantly more sensitive to the presence of tumor, as well as its proportion and location, which will help guide diagnostic interventions such as biopsy and treatment including surgery and radiation [46,47]. Positron emission tomography (PET) scanning is also a useful supporting method in the evaluation of gliomas, particularly for differential diagnosis. PET scanning with 18-fluorodeoxyglucose (FDG) is positive in cases of active tumor, which shows high metabolic activity and glucose utilization [48].

Surgical resection remains essential to the management of gliomas across all grades. Maximal safe resection should be attempted to protect patients' neurological functions [49]. Gross total resection is proposed as the result of its association with better clinical outcome [50]. Meanwhile, many tools are available to increase the extent of resection, while keeping the risk of new neurological deficits at a low level, including surgical navigation systems housing functional MRI datasets, intraoperative MRI, and intraoperative functional monitoring [51]. However, it is also recommended that biopsy, or partial resection, may all be considered as the initial management of gliomas depending on the condition of the patient, the size and location of the tumor, and so on [52]. Awake surgery may help neurosurgeon to remove tumors which are too close to the functional brain areas that control vision, language and body movements [53]. Furthermore, surgical resection could improve tumor related seizure control, particularly in patients with a long epileptic history [54,55].

A sufficient amount of tumor tissue should be obtained for histology and molecular analyses through resection or biopsy. The inclusion of molecular parameters in the WHO definition of brain tumors has been forwarded as the "ISN-Haarlem" consensus [56]. The "integrated" diagnosis was recommended based on histology and stepwise analysis with initial immunohistochemistry for ATRX and IDH1-R132H followed by 1p/19q status analysis and *IDH1* and

Table 1
Molecular biomarkers and their clinical relevance in gliomas.

Clinical importance		IDH1/2 mutation	1p/19q codeletion	MGMT promoter methylation	EGFR vIII	ATRX loss or mutation	TERT promoter mutation	miR-181d	Ki-67
Methods of assessment		IHC; pyrosequencing	FISH	MSP; bisulfite (pyro) sequencing	rtPCR; IHC; MLPA	IHC; Sanger sequencing	Sanger sequencing	qPCR, ISH	IHC
Frequency (%)	Diffuse astrocytoma	70–80	15	40–50	0	70	18	NA	5
	Oligoastrocytoma	50–70	30–60	60–80	0	50–60	31	NA	5
	Oligodendroglioma	70–80	30–60	60–80	0	14	68–79	NA	5
	Anaplastic astrocytoma	50–70	15	50	0	60–80	18	NA	35–48
	Anaplastic oligoastrocytoma	50–70	50–80	70	0	70–80	31	NA	35–48
	Anaplastic oligodendrogliomas	50–80	50–80	70	0	7	68–79	NA	35–48
	Glioblastoma	Pri:5–10; Sec:57	<5	35	25–30	Pri:4; Sec:57	50–74	50	64
Biological role		Increased concentrations of 2-hydroxyglutarate, association with G-CIMP phenotype	Unclear, link to candidate genes CIC and FUBP1	Silencing DNA damage repair, association with G-CIMP + in IDH1/2-mutated tumors	Constitutive activation of downstream pro-oncogenic pathways	Telomere dysfunction, genomic destabilization	Overexpression of TERT, maintain telomerase activity	Downregulate MGMT, K-ras, and Bcl-2 expression	A nuclear protein expressed during the G1, S, G2 and M phases of the cell cycle, used as a stable marker of cell proliferation
Diagnostic role		Differential diagnosis between diffuse glioma and gliosis	Oligodendroglial lineage	None	Association with glioblastoma	Astrocytic lineage	Association with primary glioblastoma or oligodendroglial lineage	None	None
Prognostic role		Favorable survival in IDH-mutated tumors	Favorable survival in 1p/19q codeletion tumors	Favorable survival in high grade astrocytic tumors	Unfavorable survival	Favorable survival in astrocytic tumors	Contradictory	Favorable survival in glioblastoma	Unfavorable survival
Predictive role		Absence of mutation suggests predictive role for MGMT promoter methylation	Patients for (anaplastic) oligodendrogliomas treated with early alkylating agents	Predictive for glioblastoma (elderly patients, without IDH mutation) treated with alkylating agents	Possible biomarker for vaccination	None	Potential biomarker for targeted therapy	Predictive for glioblastoma treated with alkylating agents	None

Abbreviations: IHC, immunohistochemistry; FISH, fluorescence in-situ hybridization; MSP, methylation-specific PCR; rtPCR, real-time PCR; MLPA, multiplex litigation-dependent probe amplification; Pri, primary; Sec, secondary. Table revised from refs [58], [78].

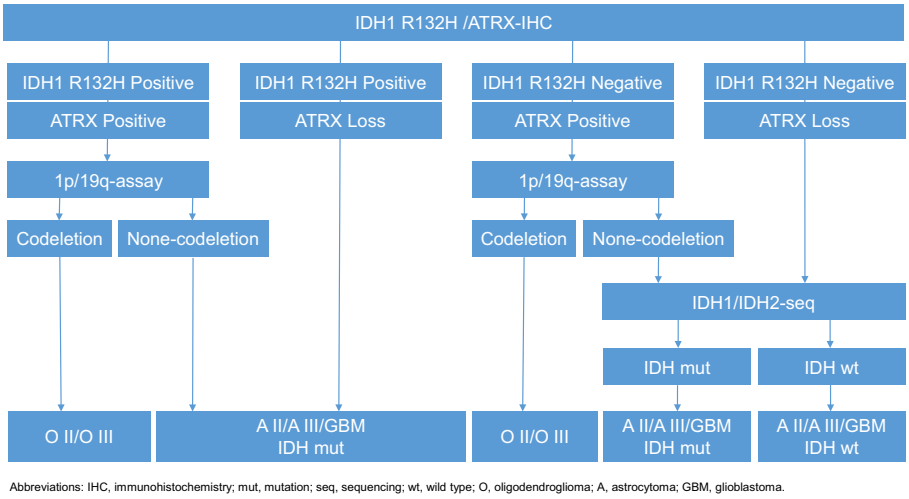

Fig. 1. Algorithm for the integrated diagnosis of astrocytomas, oligodendrogliomas and glioblastomas. Figure adapted from ref [57].

IDH2 sequencing (Fig. 1) [57]. Post-operative radiation therapy and chemotherapy should depend on the patients' clinical information, extent of resection, histology classification and molecular characteristics, and so on (Fig. 2). The assessment of *IDH* mutation, 1p and 19q codeletion, and *MGMT* promoter methylation status could be considered to establish a management algorithm for patients with anaplastic glioma and glioblastoma [58]. Additionally, the decision for specific treatments must consider several issues such as patient preference, tumor location, target volume of radiotherapy, and potential comorbidities that might increase the risk of toxicity from therapy.

Low grade gliomas (WHO II, LGG)

Although recent advances have been made in chemotherapy and radiation therapy for LGGs, surgical resection remains essential to its management. A growing body of literature supports the claim that a greater extent of resection leads to a significant survival benefit for LGGs [59–65]. The National Comprehensive Cancer Network (NCCN) guidelines for the management of low-grade infiltrative supratentorial astrocytoma/oligodendroglioma in adult patients recommend maximum safe resection of tumor tissue, if possible, with the caveat that serial observation may be appropriate for selected patients [66]. Observation may be reasonable in low-risk LGG patients (≤40 years old and receiving gross total resection) [67] with minimal or no symptoms [68], receiving MRI every 3–6 months for 5 years and then least annually. However, even in the low-risk cohort, patients with astrocytoma histology were found to have had increased rate of recurrence and death. Patients receiving early radiotherapy may have a statistically significant improvement in progression-free survival, although overall survival is usually equivalent. A total RT dose of 50.4–54 Gy in fractions of 1.8 Gy represents the current standard of radiotherapy for LGGs [69,70]. Seizures are also more likely to be controlled in the early radiotherapy group [71]. According to several randomized clinical trials (RTOG 9802, EORTC 22033 and RTOG 0424), patients with high-risk LGGs (>40 years old or none receiving gross total resection) could benefit from radiotherapy plus concurrent and adjuvant chemotherapy (or only adjuvant chemotherapy) [72–75]. Although temozolomide has been proved to be more tolerable than procarbazine, lomustine (CCNU), and vincristine (PCV regimen), which justified the use of temozolomide in the early setting as an alternative to PCV [74], the

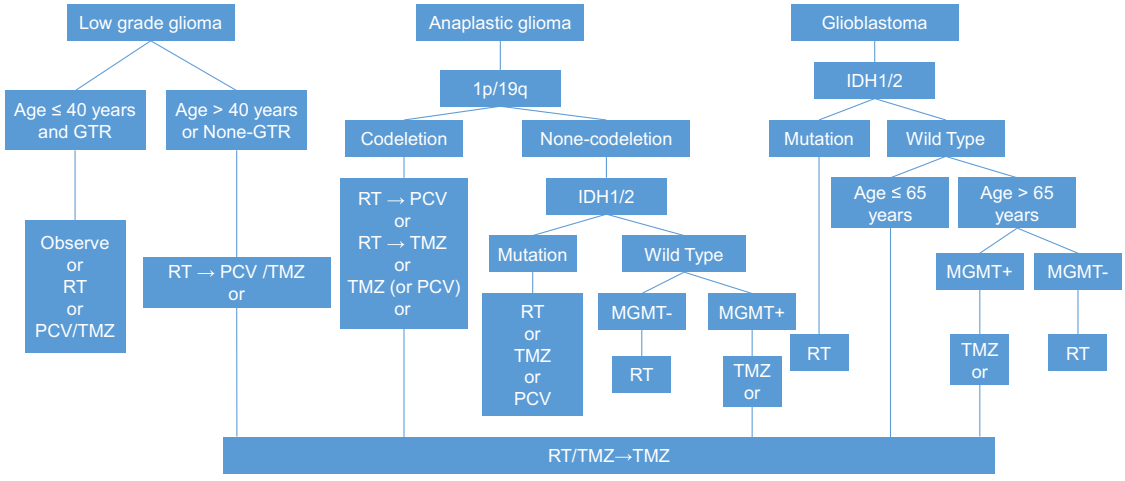

Fig. 2. Treatment approach for gliomas based on clinical and molecular information. Figure revised from refs [58], [66], [79].

benefits of TMZ should now be considered more carefully against its potentially adverse effects of hypermutation on the basis of the studies on paired gliomas with *IDH* mutations [76,77].

Anaplastic gliomas (WHO III, AG)

Anaplastic gliomas comprise three histological subtypes: anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA). Surgery by removing tumor mass and improving mass-related symptoms also allows the potential for functional improvement of the patients [55]. Standard therapy consists of adjuvant radiotherapy up to a total dose of 60 Gy after surgery [78]. Postoperative chemotherapy following initial surgery varies according to the histological type, molecular subtype and the clinical status of the patients. 1p/19q codeletion harbors the predictive value for the benefit from chemotherapy, in addition to characterize a prognostically more favorable subgroup of patients with anaplastic oligodendroglial tumors. Patients with 1p/19q-codeleted oligodendroglial tumors may benefit from radiotherapy plus PCV after surgery [79–81]. TMZ is widely considered as less toxic than PCV [14,18,81,82], and no difference in response rate or survival was identified [83]. The outcome of TMZ in anaplastic gliomas in several ongoing clinical trials is expected. CODEL trial was designed to address whether the addition of temozolomide to radiotherapy increased the survival of patients with codeleted tumors and answer the question whether progression-free survival of the combination of radiotherapy and temozolomide is not relevantly different from the combination of radiotherapy and PCV. Another phase III trial "CATNON" will show whether combined radiochemotherapy with temozolomide (concomitant and/or as an adjuvant maintenance treatment) is superior to radiotherapy alone [84]. In summary, 1p/19q codeleted AGs may have several therapeutic options varying in evidence-based recommendations: RT and adjuvant PCV, RT and adjuvant TMZ, RT plus concomitant and adjuvant TMZ, or chemotherapy only (TMZ or PCV) [79]. In a sub-study for anaplastic gliomas, MGMT promoter methylation was a predictive marker for response to alkylating chemotherapy in *IDH* wild-type tumors only and not in *IDH* mutated tumors [20,85]. On the other hand, patients with noncodeleted and nonmutated AO/AOA experienced no discernible benefit from the addition of PCV to RT. Combined radiochemotherapy has not been established as superior to RT only or chemotherapy only in newly diagnosed non-codeleted AGs [66,84,86,87]. The NCCN recommends treatment of newly diagnosed AAs by RT only followed by observation and chemotherapy at progression [66]. A retrospective study depicted that in patients with 1p/19q noncodeleted tumors with *IDH* mutations, those who were ATRX positive might have benefitted more than those who were negative from pre-RT PCV [88].

Glioblastoma (WHO IV, GBM)

The trial-EORTC 26981/NCIC CE3 was the first study to demonstrate unequivocally that addition of temozolomide to radiotherapy for the treatment of patients with newly diagnosed glioblastoma significantly improved survival. Radiotherapy plus concomitant and adjuvant TMZ chemotherapy is the current standard of care for patients less than 70 years old with GBM [18,89]. Radiation therapy, usually dosed as 60 Gy in 30 fractions, has been the cornerstone of glioblastoma therapy for decades [90]. The radiotherapy volume often contains the T1-enhanced region plus a 2–3 cm safety margin on the T2 or FLAIR abnormality [91]. TMZ is administered at 75 mg/m^2 daily (7 days a week) during radiotherapy and for six maintenance cycles on 5 out of 28 days at 150–200 mg/m^2 as maintenance (adjuvant) treatment after the end of radiation. Several clinical trials and cohort studies have shown that MGMT promoter methylation is associated with prolonged progression-free and overall survival in patients with glioblastoma receiving alkylating drug chemotherapy [19,89,92–95]. In 2012, two independent randomized trials in elderly patients with glioblastoma assessed radiotherapy alone versus temozolomide chemotherapy alone as initial treatment. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma. Subgroup analyses of both trials showed better outcome for chemotherapy in patients with *MGMT* promoter methylated tumors, but reduced survival in patients with unmethylated tumors [96,97]. On the basis of findings from the NOA-08 and Nordic trials, MGMT testing should be standard practice [21]. Recently, the CGGA project reported that patients with *IDH* wild-type glioblastoma who underwent RT + TMZ exhibited significantly longer survival times compared to the patients who were assigned to the RT alone treatment. However, among patients with *IDH* mutation tumors, the survival patterns of patients undergoing RT + TMZ or RT were comparable [98]. *IDH* mutations have been recognized as definitive diagnostic molecular markers of secondary glioblastoma, distinctive from *de novo* glioblastoma and more reliable and objective than clinical and/or pathological criteria [33]. These results strongly suggest that treatment strategies for elderly patients with glioblastoma should be individualized dependent on *IDH* and *MGMT* [58]. Two large-scale randomized trials have showed that patients with newly diagnosed glioblastoma, when receiving bevacizumab in addition to temozolomide chemoradiotherapy, could benefit in progression-free survival, but not in overall survival [99,100].

Tumor recurrence

Standards of care for patients with recurrent glioma are not well defined and clinical decision making is often based on histology classification, previous treatment, age, Karnofsky performance score, molecular information and patterns of relapse. At tumor progression, second surgery becomes the potential option, which should typically be considered when patients have large but circumscribed lesions causing neurological deficits and when the interval between surgeries is more than 6 months. However, there are no prospective data available on the impact of repeat surgery on OS. Retrospective analyses also failed to identify surgery for recurrent disease as a significant prognostic factor for prolonged survival [101,102]. For recurrent patients who have already received radiation, hypofractionated radiotherapy (e.g., with 25–30 Gy in five fractions of 5 or 6 Gy, or with 35 Gy in ten 3·5 Gy fractions) is feasible if relapses are circumscribed and chemotherapy is contraindicated. Alkylating agent chemotherapy is the treatment of choice for most tumors previously untreated with chemotherapy that relapse after receiving radiotherapy. In NCCN guidelines, the antiangiogenic therapy with bevacizumab is also recommended in the management of progressive malignant gliomas. Although patients cannot get overall survival benefit from bevacizumab [103–105], bevacizumab is universally accepted because of evident symptom relief effects, for example, reducing cerebral edema [106]. Randomized trials in recurrent glioblastoma have failed to demonstrate the significant anti-tumor efficacy of epidermal growth factor receptor (EGFR) inhibition (e.g. erlotinib) or platelet-derived growth factor receptor inhibition (e.g. imatinib) [107,108].

Supportive care

Corticosteroids (usually dexamethasone 8–16 mg/day) are often prescribed to patients for control of tumor-associated edema and improving clinical symptoms. Steroids are not necessary in patients without increased intracranial pressure or in the absence of edema-associated neurological deficits. There is no need for prolonged steroid therapy after tumor resection or for prophylaxis during radiotherapy in asymptomatic patients. Rapid tapering and

discontinuation of corticosteroids is recommended in order to avoid toxicity associated with prolonged exposure to steroids, e.g. lymphopenia and risk of infection, osteoporosis and Cushing syndrome.

Anti-epileptic therapy is indicated in patients presenting with seizures. If no further seizure occurs after surgery and the tumor seems to be controlled by treatment, tapering of anticonvulsants should be attempted within the first weeks or months after surgery. After tumor resection, the indication for anti-epileptic therapy should be revisited only if seizures occur [109,110].

Patients with gliomas are at increased risk of thromboembolic events throughout the course of disease due to many reasons, including neurological deficits, steroid use, radiotherapy, chemotherapy, and release of vasoactive molecules from glioma cells [111]. Prophylactic anticoagulation is not recommended; however, a low threshold for excluding deep vein thrombosis and pulmonary emboli is indicated when suspicious symptoms occur.

Response evaluation and follow-up

The Response Assessment in Neuro-Oncology (RANO) defines a set of criteria for assessing outcome in trials of adult gliomas [112,113], including specific guidelines for using tumor size and appearance on T2/FLAIR MRI sequences to define tumor response. The criteria take into account stability of corticosteroid dosing, neurological function, clinical status (Macdonald criteria) [114], and differentiation between new T2 or FLAIR abnormalities related to tumor spread in comparison with those attributable to radiation effects. MRI should be utilized to evaluate the efficacy of treatment or as surveillance imaging after completion of treatment at an interval of 3–6 months. Contrast enhancement and presumed tumor progression on imaging 4–8 weeks after the end of radiotherapy may be a reactive process following radiotherapy (pseudo-progression) [115] and should be re-evaluated 4 weeks later with a second MRI. Longer intervals might be considered for patients with lengthy disease control, notably young patients with 1p/19q-codeleted oligodendroglial tumors. Laboratory tests should also be indicated if the patient is receiving chemotherapy (blood counts), corticosteroids (glucose) or anti-epileptic drugs (blood count, liver function tests).

Note

The following electronic databases were searched: the Cochrane Library to date; Medline–Ovid (January 1966 to date); Medline–ProQuest; Medline-EIFL; Embase–Ovid (January 1990 to date); CancerNet; and Science Citation Index. We used specific and sensitive keywords, as well as combinations of keywords, and publications in any language of countries represented in the Task Force. The search was completed in June 2015.

The Panel covered all fields of expertise in neuro-oncology, i.e. neurosurgeons, neurologists, neuropathologists, neuroradiologists, radiation and medical oncologists and clinical trial experts. The scientific evidence of papers collected from the literature was evaluated and graded and recommendations were given accordingly. These are summarized in Table 2 with explanatory notes, and statements without grading were considered justified standard clinical practice by the expert authors and the CGCG faculty. The Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (March 2009) are shown in Table 3 and Table 4 [116].

Funding

This work was supported by grants from 1. The Research Special Fund For Public Welfare Industry of Heath (No. 201402008); 2. National Key Technology Research and Development Program of the Ministry of Science and Technology of China (No. 2013BAI09B03, No.2014BAI04B02); 3. National High Technology Research and Development Program (863) (No. 2012AA02A508); 4. Beijing Science and Technology Plan (No. Z131100006113018); 5. National Natural Science Foundation of China (No. 91229121, No. 81201993, No. 81572701, No. 81372700); and 6. International Science and Technology Cooperation Program (No. 2012DFA30470).

Authors' contributions

Tao Jiang, Ying Mao, Wenbin Ma, Qing Mao, Yongping You and Xuejun Yang take responsibility for the integrity and the accuracy of the guideline.

Table 2
Conclusion and recommendations.

	Level of evidence	Grade of recommendation
General recommendations		
Gliomas are diagnosed using morphological criteria according to WHO classification.	1a	A
Karnofsky performance score, neurological function, and age need to be considered in clinical decision making in neuro-oncology.	1b	A
Magnetic resonance imaging (MRI) can be used to detect the presence of tumor and guide managements such as biopsy, surgery and radiation.	2b	B
Maximal safe resection is the first option for all gliomas, while minimizing the postoperative morbidity.	2a	B
When surgery is not feasible, a biopsy should be performed to obtain a histological diagnosis.	4	C
MGMT promoter methylation, IDH mutations and 1p/19q codeletion are commonly determined depending on the histological and clinical contexts.	1b	A
Low grade gliomas (WHO grade II)		
Younger patients (≤40 years of age) with gross total resection can be observed after surgery, but close follow-up is needed.	1b	B
For patients with high risk (age >40 years or none receiving gross total resection), an adjuvant treatment is indicated at any time.	1b	B
Radiotherapy may be selected for high risk patients (age >40 years or gross total resection not received).	1b	A
Chemotherapy is an option as initial treatment for patients with large residual tumors after surgery or unresectable tumors, especially when 1p/19q loss is present.	1b	B
Anaplastic gliomas (WHO grade III)		
Patients with 1p/19q co-deleted anaplastic oligodendroglioma (oligoastrocytoma) should receive chemotherapy with alkylating agents with or without radiotherapy.	1b	B
MGMT promoter methylation could be a predictive marker for response to alkylating chemotherapy in IDH wild-type anaplastic gliomas.	2b	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy.	1b	A
Glioblastoma (WHO grade IV)		
Radiotherapy combined with temozolomide remains the standard of care for newly diagnosed glioblastoma.	1b	A
In elderly patients (>65 years) with IDH wild-type and MGMT promoter methylation, temozolomide chemotherapy may be considered, while radiotherapy is the treatment of choice for patients with an unmethylated gene promoter.	1b	B
Bevacizumab (±irinotecan) is an option for the management of recurrent glioblastoma.	1b	B

Table 3
Levels of evidence.

Level	Therapy/Prevention, etiology/Harm	Prognosis	Diagnosis
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of level 1 diagnostic studies; CDR† with 1b studies from different clinical centers
1b	Individual RCT (with narrow confidence interval)	Individual inception cohort study with >80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical center
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of level >2 diagnostic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases
2c	"Outcomes" research; ecological studies	"Outcomes" Research	
3a	SR (with homogeneity*) of case–control studies		SR (with homogeneity*) of 3b and better studies
3b	Individual case–control study		Non-consecutive study; or without consistently applied reference standards
4	Case-series (and poor quality cohort and case–control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case–control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* Homogeneity means a systematic review (SR) that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all SRs with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneities need be statistically significant.
† Clinical decision rule. (Algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
§ Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.
§§ Poor quality cohort study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow up of patients. Poor quality case–control study: one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§ Split sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
†† An "Absolute SpPin": a diagnostic finding whose specificity is so high that a positive result rules in the diagnosis. An "Absolute SnNout": a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis.
††† Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the "test" is included in the "reference", or where the "testing" affects the "reference") implies a level 4 study.
** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (for example, using a regression analysis) to find which factors are "significant."
*** Poor quality prognostic cohort study: one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors. Table adapted from ref [116].

Table 4
Grades of recommendation.

Grades	Description
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	Level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

Table adapted from ref [116].

Conceived and designed the guideline: Tao Jiang, Ying Mao, Wenbin Ma, Qing Mao, Yongping You and Xuejun Yang.

Acquisition of data: Jinquan Cai, Wei Zhang, Hongjun Wang, Lingchao Chen, Chuanbao Zhang, Pei Yang, Wei Yan, Huimin Hu, Jing Chen, Yuqing Liu, Yuan Yang, Zheng Wang, Zhiliang Wang, Yongzhi Wang, Gan You, Lei Han, Zhaoshi Bao, Yanwei Liu, Yinyan Wang, Xing Fan, Shuai Liu, Xing Liu, Yu Wang, Kun Yao and Qixue Wang.

Analysis and interpretation of data: Jinquan Cai, Wei Zhang, Hongjun Wang, Lingchao Chen, Chuanbao Zhang, Pei Yang, Wei Yan, Zhixiong Liu, Huimin Hu, Jing Chen, Yuqing Liu, Yuan Yang, Zheng Wang, Zhiliang Wang, Yongzhi Wang, Gan You, Lei Han, Zhaoshi Bao, Yanwei Liu, Yinyan Wang, Xing Fan, Shuai Liu, Xing Liu, Yu Wang, Kun Yao and Qixue Wang.

Drafting of the manuscript: Tao Jiang, Ying Mao, Wenbin Ma, Qing Mao, Yongping You, Xuejun Yang, Chuanlu Jiang, Chunsheng Kang, Xuejun Li, Ling Chen, Xiaoguang Qiu, Weimin Wang, Wenbin Li, Yu Yao, Shaowu, Li, Shouwei Li, Anhua Wu, Ke Sai, Hongmin Bai and Guilin Li.

Critical revision of the manuscript for important intellectual content: Tao Jiang, Ying Mao, Wenbin Ma, Qing Mao, Yongping You, Xuejun Yang, Chuanlu Jiang, Chunsheng Kang, Xuejun Li, Ling Chen, Xiaoguang Qiu, Weimin Wang, Wenbin Li, Shaowu, Li, Shouwei Li, Anhua Wu, Ke Sai, Hongmin Bai, Guilin Li, Xin Sun, Xinting Wei, Xianzhi Liu, Zhiwen Zhang, Yiwu Dai, Shengqing Lv, Liang Wang, Zhixiong Lin, Jun Dong, Guozheng Xu.

Supervision: Tao Jiang, Ying Mao, Wenbin Ma, Qing Mao, Yongping You and Xuejun Yang.

Acknowledgements

The Expert Panel wishes to express its gratitude to Liangfu Zhou (Department of Neurosurgery, Huashan Hospital, Fudan University), Jizong Zhao (Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University), Renzhi Wang (Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College), and Zhongping Chen (Department of Neurosurgery, Sun Yat-Sen University Cancer Center) for their help with guideline preparation and their thoughtful review of earlier versions of the guidelines.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

[1] T. Jiang, G.F. Tang, Y. Lin, X.X. Peng, X. Zhang, X.W. Zhai, et al., Prevalence estimates for primary brain tumors in China: a multi-center cross-sectional study, Chin. Med. J. 124 (17) (2011) 2578–2583 PubMed PMID: 22040406.

[2] D.N. Louis, H. Ohgaki, O.D. Wiestler, W.K. Cavenee, P.C. Burger, A. Jouvet, et al., The 2007 WHO classification of tumours of the central nervous system, Acta Neuropathol. 114 (2) (2007) 97–109, doi:10.1007/s00401-007-0243-4 PubMed PMID: 17618441.

[3] F. Shen, C.X. Wu, Y. Yao, P. Peng, Z.Y. Qin, Y. Wang, et al., Transition over 35 years in the incidence rates of primary central nervous system tumors in Shanghai, China and histological subtyping based on a single center experience spanning 60 years, Asian Pac. J. Cancer Prev. 14 (12) (2013) 7385–7393 PubMed PMID: 24460308.

[4] P. Yang, Y. Wang, X. Peng, G. You, W. Zhang, W. Yan, et al., Management and survival rates in patients with glioma in China (2004–2010): a retrospective study from a single-institution, J. Neurooncol. 113 (2) (2013) 259–266, doi:10.1007/s11060-013-1103-9 PubMed PMID: 23483435. Epub 2013/03/14.

[5] K. Ichimura, D.M. Pearson, S. Kocialkowski, L.M. Backlund, R. Chan, D.T. Jones, et al., IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas, Neuro Oncol. 11 (4) (2009) 341–347, doi:10.1215/15228517-2009-025 PubMed PMID: 19435942. PubMed Central PMCID: PMC2743214.

[6] H. Yan, D.W. Parsons, G.L. Jin, R. McLendon, B.A. Rasheed, W.S. Yuan, et al., IDH1 and IDH2 Mutations in Gliomas, NEJM 360 (8) (2009) 765–773 PubMed PMID: WOS:000263411300006.

[7] C.B. Zhang, Z.S. Bao, H.J. Wang, W. Yan, Y.W. Liu, M.Y. Li, et al., Correlation of IDH1/2 mutation with clinicopathologic factors and prognosis in anaplastic gliomas: a report of 203 patients from China, J. Cancer Res. Clin. Oncol. 140 (1) (2014) 45–51, doi:10.1007/s00432-013-1519-9 PubMed PMID: 24149775.

[8] W. Yan, W. Zhang, G. You, Z. Bao, Y. Wang, Y. Liu, et al., Correlation of IDH1 mutation with clinicopathologic factors and prognosis in primary glioblastoma: a report of 118 patients from China, PLoS ONE 7 (1) (2012) e30339, doi:10.1371/journal.pone.0030339 PubMed PMID: 22291938. Epub 2012/02/01, PubMed Central PMCID: PMC3264567.

[9] J. Cai, P. Yang, C. Zhang, W. Zhang, Y. Liu, Z. Bao, et al., ATRX mRNA expression combined with IDH1/2 mutational status and Ki-67 expression refines the molecular classification of astrocytic tumors: evidence from the whole transcriptome sequencing of 169 samples, Oncotarget 5 (9) (2014) 2551–2561, doi:dx.doi.org/10.18632/oncotarget.1838 PubMed PMID: 24810474.

[10] M.Y. Li, Y.Y. Wang, J.Q. Cai, C.B. Zhang, K.Y. Wang, W. Cheng, et al., Isocitrate dehydrogenase 1 gene mutation is associated with prognosis in clinical low-grade gliomas, PLoS ONE 10 (6) (2015) e0130872, doi:10.1371/journal.pone.0130872 PubMed PMID: 26115094. PubMed Central PMCID: PMC4482584.

[11] R.B. Jenkins, H. Blair, K.V. Ballman, C. Giannini, R.M. Arusell, M. Law, et al., A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma, Cancer Res. 66 (20) (2006) 9852–9861, doi:10.1158/0008-5472.CAN-06-1796 PubMed PMID: 17047046.

[12] S. Li, C. Yan, L. Huang, X. Qiu, Z. Wang, T. Jiang, Molecular prognostic factors of anaplastic oligodendroglial tumors and its relationship: a single institutional review of 77 patients from China, Neuro Oncol. 14 (1) (2012) 109–116, doi:10.1093/neuonc/nor185 PubMed PMID: 22039037.

[13] M. Kujas, J. Lejeune, A. Benouaich-Amiel, E. Criniere, F. Laigle-Donadey, Y. Marie, et al., Chromosome 1p loss: a favorable prognostic factor in low-grade gliomas, Ann. Neurol. 58 (2) (2005) 322–326, doi:10.1002/ana.20543 PubMed PMID: 16049942.

[14] W. Wick, C. Hartmann, C. Engel, M. Stoffels, J. Felsberg, F. Stockhammer, et al., NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide, J. Clin. Oncol. 27 (35) (2009) 5874–5880, doi:10.1200/JCO.2009.23.6497 PubMed PMID: 19901110.

[15] Y. Jiao, P.J. Killela, Z.J. Reitman, A.B. Rasheed, C.M. Heaphy, R.F. de Wilde, et al., Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas, Oncotarget 3 (7) (2012) 709–722 PubMed PMID: 22869205. PubMed Central PMCID: PMC3443254.

[16] C. Bettegowda, N. Agrawal, Y. Jiao, M. Sausen, L.D. Wood, R.H. Hruban, et al., Mutations in CIC and FUBP1 contribute to human oligodendroglioma, Science 333 (6048) (2011) 1453–1455, doi:10.1126/science.1210557 PubMed PMID: 21817013. PubMed Central PMCID: PMC3170506.

[17] A.K. Chan, J.C. Pang, N.Y. Chung, K.K. Li, W.S. Poon, D.T. Chan, et al., Loss of CIC and FUBP1 expressions are potential markers of shorter time to recurrence in oligodendroglial tumors, Mod. Pathol. 27 (3) (2014) 332–342, doi:10.1038/modpathol.2013.165 PubMed PMID: 24030748.

[18] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. 352 (10) (2005) 987–996, doi:10.1056/NEJMoa043330 PubMed PMID: 15758009.

[19] M.E. Hegi, A.C. Diserens, T. Gorlia, M.F. Hamou, N. de Tribolet, M. Weller, et al., MGMT gene silencing and benefit from temozolomide in glioblastoma, N. Engl. J. Med. 352 (10) (2005) 997–1003, doi:10.1056/NEJMoa043331 PubMed PMID: 15758010.

[20] M.C. Chamberlain, Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation, Neurology 82 (23) (2014) 2147–2148, doi:10.1212/01.wnl.0000451452.30826.6b PubMed PMID: 24912510.

[21] W. Wick, M. Weller, M. van den Bent, M. Sanson, M. Weiler, A. von Deimling, et al., MGMT testing-the challenges for biomarker-based glioma treatment, Nat. Rev. Neurol. 10 (7) (2014) 372–385, doi:10.1038/nrneurol.2014.100 PubMed PMID: 24912512.

[22] S. Kreth, E. Limbeck, L.C. Hinske, S.V. Schutz, N. Thon, K. Hoefig, et al., In human glioblastomas transcript elongation by alternative polyadenylation and miRNA targeting is a potent mechanism of MGMT silencing, Acta Neuropathol. 125 (5) (2013) 671–681, doi:10.1007/s00401-013-1081-1 PubMed PMID: 23340988.

[23] W. Zhang, J. Zhang, K. Hoadley, D. Kushwaha, V. Ramakrishnan, S. Li, et al., miR-181d: a predictive glioblastoma biomarker that downregulates MGMT expression, Neuro Oncol. 14 (6) (2012) 712–719, doi:10.1093/neuonc/nos089 PubMed PMID: 22570426. Epub 2012/05/10, PubMed Central PMCID: PMC3367855.

[24] A.B. Heimberger, R. Hlatky, D. Suki, D. Yang, J. Weinberg, M. Gilbert, et al., Prognostic effect of epidermal growth factor receptor and EGFRvIII in glioblastoma multiforme patients, Clin. Cancer Res. 11 (4) (2005) 1462–1466, doi:10.1158/1078-0432.ccr-04-1737 PubMed PMID: 15746047.

[25] Q.W. Fan, C.K. Cheng, W.C. Gustafson, E. Charron, P. Zipper, R.A. Wong, et al., EGFR phosphorylates tumor-derived EGFRvIII driving STAT3/5 and progression in glioblastoma, Cancer Cell 24 (4) (2013) 438–449, doi:10.1016/j.ccr.2013.09.004 PubMed PMID: 24135280. Epub 2013/10/19.

[26] J.H. Sampson, A.B. Heimberger, G.E. Archer, K.D. Aldape, A.H. Friedman, H.S. Friedman, et al., Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma, J. Clin. Oncol. 28 (31) (2010) 4722–4729, doi:10.1200/JCO.2010.28.6963 PubMed PMID: 20921459. PubMed Central PMCID: PMC3020702.

[27] B. Wiestler, D. Capper, T. Holland-Letz, A. Korshunov, A. von Deimling, S.M. Pfister, et al., ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis, Acta Neuropathol. 126 (3) (2013) 443–451, doi:10.1007/s00401-013-1156-z PubMed PMID: 23904111.

[28] C.M. Heaphy, R.F. de Wilde, Y. Jiao, A.P. Klein, B.H. Edil, C. Shi, et al., Altered telomeres in tumors with ATRX and DAXX mutations, Science 333 (6041) (2011) 425, doi:10.1126/science.1207313 PubMed PMID: 21719641. PubMed Central PMCID: PMC3174141.

[29] Y. Jiao, C. Shi, B.H. Edil, R.F. de Wilde, D.S. Klimstra, A. Maitra, et al., DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors, Science 331 (6021) (2011) 1199–1203, doi:10.1126/science.1200609 PubMed PMID: 21252315. PubMed Central PMCID: PMC3144496.

[30] J. Schwartzentruber, A. Korshunov, X.Y. Liu, D.T. Jones, E. Pfaff, K. Jacob, et al., Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma, Nature 482 (7384) (2012) 226–231, doi:10.1038/nature10833 PubMed PMID: 22286061.

[31] J. Cai, J. Chen, W. Zhang, P. Yang, C. Zhang, M. Li, et al., Loss of ATRX, associated with DNA methylation pattern of chromosome end, impacted biological behaviors of astrocytic tumors, Oncotarget 6 (20) (2015) 18105–18115.

[32] P.J. Killela, Z.J. Reitman, Y.C. Jiao, C. Bettegowda, N. Agrawal, L.A. Diaz, et al., TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal, Proc. Natl. Acad. Sci. U.S.A. 110 (15) (2013) 6021–6026, doi:10.1073/pnas.1303607110 PubMed PMID: WOS:000317537900058.

[33] N. Nonoguchi, T. Ohta, J.E. Oh, Y.H. Kim, P. Kleihues, H. Ohgaki, TERT promoter mutations in primary and secondary glioblastomas, Acta Neuropathol. 126 (6) (2013) 931–937, doi:10.1007/s00401-013-1163-0 PubMed PMID: 23955565. Epub 2013/08/21.

[34] M. Labussiere, B. Boisselier, K. Mokhtari, A.L. Di Stefano, A. Rahimian, M. Rossetto, et al., Combined analysis of TERT, EGFR, and IDH status defines distinct prognostic glioblastoma classes, Neurology (2014), doi:10.1212/wnl.0000000000000814 PubMed PMID: 25150284.

[35] J.E. Eckel-Passow, D.H. Lachance, A.M. Molinaro, K.M. Walsh, P.A. Decker, H. Sicotte, et al., Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors, N. Engl. J. Med. 372 (26) (2015) 2499–2508, doi:10.1056/NEJMoa1407279 PubMed PMID: 26061753.

[36] M. Labussiere, A.L. Di Stefano, V. Gleize, B. Boisselier, M. Giry, S. Mangesius, et al., TERT promoter mutations in gliomas, genetic associations and clinico-pathological correlations, Br. J. Cancer 111 (10) (2014) 2024–2032, doi:10.1038/bjc.2014.538 PubMed PMID: 25314060.

[37] A.K. Chan, Y. Yao, Z. Zhang, N.Y. Chung, J.S. Liu, K.K. Li, et al., TERT promoter mutations contribute to subset prognostication of lower-grade gliomas, Mod. Pathol. 28 (2) (2015) 177–186, doi:10.1038/modpathol.2014.94 PubMed PMID: 25081751.

[38] Z.Y. Zhang, A.K. Chan, X.J. Ding, Z.Y. Qin, C.S. Hong, L.C. Chen, et al., TERT promoter mutations contribute to IDH mutations in predicting differential responses to adjuvant therapies in WHO grade II and III diffuse gliomas,

Oncotarget 6 (28) (2015) 24871–24883, doi:10.18632/oncotarget.4549 PubMed PMID: 26314843. Epub 2015/09/01.
[39] Q. Jin, W. Zhang, X. Qiu, W. Yan, G. You, Y. Liu, et al., Gene expression profiling reveals Ki-67 associated proliferation signature in human glioblastoma, Chin. Med. J. 124 (17) (2011) 2584–2588, doi:10.3760/cma.j.issn.0366-6999.2011.17.004 PubMed PMID: 22040407.
[40] Cancer Genome Atlas Research N, Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas, N. Engl. J. Med. 372 (26) (2015) 2481–2498, doi:10.1056/NEJMoa1402121 PubMed PMID: 26061751.
[41] H. Bai, A.S. Harmanci, E.Z. Erson-Omay, J. Li, S. Coskun, M. Simon, et al., Integrated genomic characterization of IDH1-mutant glioma malignant progression, Nat. Genet. 48 (1) (2015) 59–66, doi:10.1038/ng.3457 PubMed PMID: 26618343.
[42] H. Suzuki, K. Aoki, K. Chiba, Y. Sato, Y. Shiozawa, Y. Shiraishi, et al., Mutational landscape and clonal architecture in grade II and III gliomas, Nat. Genet. 47 (5) (2015) 458–468, doi:10.1038/ng.3273 PubMed PMID: 25848751. Epub 2015/04/08.
[43] J.T. Huse, E.L. Diamond, L. Wang, M.K. Rosenblum, Mixed glioma with molecular features of composite oligodendroglioma and astrocytoma: a true "oligoastrocytoma, Acta Neuropathol. 129 (1) (2015) 151–153, doi:10.1007/s00401-014-1359-y PubMed PMID: 25359109.
[44] F. Sahm, D. Reuss, C. Koelsche, D. Capper, J. Schittenhelm, S. Heim, et al., Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma, Acta Neuropathol. 128 (4) (2014) 551–559, doi:10.1007/s00401-014-1326-7 PubMed PMID: 25143301.
[45] C. la Fougere, B. Suchorska, P. Bartenstein, F.W. Kreth, J.C. Tonn, Molecular imaging of gliomas with PET: opportunities and limitations, Neuro Oncol. 13 (8) (2011) 806–819, doi:10.1093/neuonc/nor054 PubMed PMID: 21757446. PubMed Central PMCID: PMC3145468.
[46] C. Chung, U. Metser, C. Menard, Advances in magnetic resonance imaging and positron emission tomography imaging for grading and molecular characterization of glioma, Semin. Radiat. Oncol. 25 (3) (2015) 164–171, doi:10.1016/j.semradonc.2015.02.002 PubMed PMID: 26050586.
[47] S. Cha, J.M. Lupo, M.H. Chen, K.R. Lamborn, M.W. McDermott, M.S. Berger, et al., Differentiation of glioblastoma multiforme and single brain metastasis by peak height and percentage of signal intensity recovery derived from dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging, AJNR Am. J. Neuroradiol. 28 (6) (2007) 1078–1084, doi:10.3174/ajnr.A0484 PubMed PMID: 17569962.
[48] K. Yamashita, T. Yoshiura, A. Hiwatashi, O. Togao, K. Yoshimoto, S.O. Suzuki, et al., Differentiating primary CNS lymphoma from glioblastoma multiforme: assessment using arterial spin labeling, diffusion-weighted imaging, and (1)(8)F-fluorodeoxyglucose positron emission tomography, Neuroradiology 55 (2) (2013) 135–143, doi:10.1007/s00234-012-1089-6 PubMed PMID: 22961074.
[49] M. Lacroix, D. Abi-Said, D.R. Fourney, Z.L. Gokaslan, W. Shi, F. DeMonte, et al., A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival, J. Neurosurg. 95 (2) (2001) 190–198, doi:10.3171/jns.2001.95.2.0190 PubMed PMID: 11780887.
[50] F.W. Kreth, N. Thon, M. Simon, M. Westphal, G. Schackert, G. Nikkhah, et al., Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy, Ann. Oncol. 24 (12) (2013) 3117–3123, doi:10.1093/annonc/mdt388 PubMed PMID: 24130262. Epub 2013/10/17.
[51] M. Weller, M. van den Bent, K. Hopkins, J.C. Tonn, R. Stupp, A. Falini, et al., EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma, Lancet Oncol. 15 (9) (2014) e395–e403, doi:10.1016/s1470-2045(14)70011-7.
[52] T.C. Ryken, B. Frankel, T. Julien, J.J. Olson, Surgical management of newly diagnosed glioblastoma in adults: role of cytoreductive surgery, J. Neurooncol. 89 (3) (2008) 271–286, doi:10.1007/s11060-008-9614-5 PubMed PMID: 18712281.
[53] H. Duffau, Surgery of low-grade gliomas: towards a 'functional neurooncology', Curr. Opin. Oncol. 21 (6) (2009) 543–549, doi:10.1097/CCO.0b013e3283305996 PubMed PMID: 19606033.
[54] D.J. Englot, S.J. Han, M.S. Berger, N.M. Barbaro, E.F. Chang, Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors, Neurosurgery 70 (4) (2012) 921–928, discussion 8, doi:10.1227/NEU.0b013e31823c3a30 PubMed PMID: 21997540.
[55] E.F. Chang, M.B. Potts, G.E. Keles, K.R. Lamborn, S.M. Chang, N.M. Barbaro, et al., Seizure characteristics and control following resection in 332 patients with low-grade gliomas, J. Neurosurg. 108 (2) (2008) 227–235, doi:10.3171/JNS/2008/108/2/0227 PubMed PMID: 18240916.
[56] D.N. Louis, A. Perry, P. Burger, D.W. Ellison, G. Reifenberger, A. von Deimling, et al., International society of neuropathology – Haarlem consensus guidelines for nervous system tumor classification and grading, Brain Pathol. 24 (5) (2014) 429–435, doi:10.1111/bpa.12171 PubMed PMID: 24990071.
[57] D.E. Reuss, F. Sahm, D. Schrimpf, B. Wiestler, D. Capper, C. Koelsche, et al., ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma, Acta Neuropathol. 129 (1) (2015) 133–146, doi:10.1007/s00401-014-1370-3 PubMed PMID: 25427834. Epub 2014/11/28.
[58] M. Weller, S.M. Pfister, W. Wick, M.E. Hegi, G. Reifenberger, R. Stupp, Molecular neuro-oncology in clinical practice: a new horizon, Lancet Oncol. 14 (9) (2013) e370–e379, doi:10.1016/s1470-2045(13)70168-2 PubMed PMID: 23896276.
[59] T. Hollon, S.L. Hervey-Jumper, O. Sagher, D.A. Orringer, Advances in the surgical management of low-grade glioma, Semin. Radiat. Oncol. 25 (3) (2015) 181–188, doi:10.1016/j.semradonc.2015.02.007 PubMed PMID: 26050588. PubMed Central PMCID: PMC4460567.
[60] E.B. Claus, A. Horlacher, L. Hsu, R.B. Schwartz, D. Dello-Iacono, F. Talos, et al., Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance, Cancer 103 (6) (2005) 1227–1233, doi:10.1002/cncr.20867 PubMed PMID: 15690327.
[61] T. Ius, M. Isola, R. Budai, G. Pauletto, B. Tomasino, L. Fadiga, et al., Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients: clinical article, J. Neurosurg. 117 (6) (2012) 1039–1052, doi:10.3171/2012.8.JNS12393 PubMed PMID: 23039150.
[62] A.S. Jakola, K.S. Myrmel, R. Kloster, S.H. Torp, S. Lindal, G. Unsgard, et al., Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas, JAMA 308 (18) (2012) 1881–1888, doi:10.1001/jama.2012.12807 PubMed PMID: 23099483.
[63] C. Leighton, B. Fisher, G. Bauman, S. Depiero, L. Stitt, D. MacDonald, et al., Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation, J. Clin. Oncol. 15 (4) (1997) 1294–1301 PubMed PMID: 9193320.
[64] J.S. Smith, E.F. Chang, K.R. Lamborn, S.M. Chang, M.D. Prados, S. Cha, et al., Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas, J. Clin. Oncol. 26 (8) (2008) 1338–1345, doi:10.1200/JCO.2007.13.9337 PubMed PMID: 18323558.
[65] E. Shaw, R. Arusell, B. Scheithauer, J. O'Fallon, B. O'Neill, R. Dinapoli, 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. 20 (9) (2002) 2267–2276 PubMed PMID: 11980997.
[66] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Central Nervous System Cancers. Version 1. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp, 2015.
[67] F. Pignatti, M. van den Bent, D. Curran, C. Debruyne, R. Sylvester, P. Therasse, et al., Prognostic factors for survival in adult patients with cerebral low-grade glioma, J. Clin. Oncol. 20 (8) (2002) 2076–2084 PubMed PMID: 11956268. Epub 2002/04/17.
[68] N. Pouratian, A. Asthagiri, J. Jagannathan, M.E. Shaffrey, D. Schiff, Surgery insight: the role of surgery in the management of low-grade gliomas, Nat. Clin. Pract. Neurol. 3 (11) (2007) 628–639, doi:10.1038/ncpneuro0634 PubMed PMID: 17982433.
[69] R. Soffietti, B.G. Baumert, L. Bello, A. von Deimling, H. Duffau, M. Frenay, et al., Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force, Eur. J. Neurol. 17 (9) (2010) 1124–1133, doi:10.1111/j.1468-1331.2010.03151.x PubMed PMID: 20718851.
[70] D.A. Forst, B.V. Nahed, J.S. Loeffler, T.T. Batchelor, Low-grade gliomas, Oncologist 19 (4) (2014) 403–413, doi:10.1634/theoncologist.2013-0345 PubMed PMID: 24664484. PubMed Central PMCID: PMC3983820.
[71] E.G. Shaw, B. Berkey, S.W. Coons, D. Bullard, D. Brachman, J.C. Buckner, et al., Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial, J. Neurosurg. 109 (5) (2008) 835–841, doi:10.3171/JNS/2008/109/11/0835 PubMed PMID: 18976072. PubMed Central PMCID: PMC3833272.
[72] M.D. Chan, Recent technical advances and indications for radiation therapy in low-grade glioma, Semin. Radiat. Oncol. 25 (3) (2015) 189–196, doi:10.1016/j.semradonc.2015.02.001 PubMed PMID: 26050589.
[73] E.G. Shaw, M. Wang, S.W. Coons, D.G. Brachman, J.C. Buckner, K.J. Stelzer, et al., Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802, J. Clin. Oncol. 30 (25) (2012) 3065–3070, doi:10.1200/JCO.2011.35.8598 PubMed PMID: 22851558. PubMed Central PMCID: PMC3732006.
[74] B.J. Fisher, J. Lui, D.R. Macdonald, G.J. Lesser, S. Coons, D. Brachman, et al., Eds. A phase II study of a temozolomide-based chemoradiotherapy regimen for high-risk low-grade gliomas: Preliminary results of RTOG 0424. ASCO Annual Meeting Proceedings, 2013.
[75] J. Buckner, S. Pugh, E. Shaw, M. Gilbert, G. Barger, S. Coons, et al., Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG, J. Clin. Oncol. 32 (15 Suppl.) (2014).
[76] J. Kim, I.H. Lee, H.J. Cho, C.K. Park, Y.S. Jung, Y. Kim, et al., Spatiotemporal evolution of the primary glioblastoma genome, Cancer Cell 28 (3) (2015) 318–328, doi:10.1016/j.ccell.2015.07.013 PubMed PMID: 26373279.
[77] B.E. Johnson, T. Mazor, C. Hong, M. Barnes, K. Aihara, C.Y. McLean, et al., Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma, Science 343 (6167) (2014) 189–193, doi:10.1126/science.1239947.
[78] R. Stupp, M. Brada, M.J. van den Bent, J.C. Tonn, G. Pentheroudakis, High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 25 (Suppl. 3) (2014) iii93-101, doi:10.1093/annonc/mdu050 PubMed PMID: 24782454. Epub 2014/05/02.
[79] E. Le Rhun, S. Taillibert, M.C. Chamberlain, Anaplastic glioma: current treatment and management, Expert Rev. Neurother. 15 (6) (2015) 601–620, doi:10.1586/14737175.2015.1042455 PubMed PMID: 25936680.
[80] G. Cairncross, M. Wang, E. Shaw, R. Jenkins, D. Brachman, J. Buckner, et al., Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma:

long-term results of RTOG 9402, J. Clin. Oncol. 31 (3) (2013) 337–343, doi:10.1200/JCO.2012.43.2674 PubMed PMID: 23071247. PubMed Central PMCID: PMC3732012.
[81] M.J. van den Bent, A.A. Brandes, M.J. Taphoorn, J.M. Kros, M.C. Kouwenhoven, J.Y. Delattre, et al., Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951, J. Clin. Oncol. 31 (3) (2013) 344–350, doi:10.1200/JCO.2012.43.2229 PubMed PMID: 23071237.
[82] M.J. van den Bent, A.F. Carpentier, A.A. Brandes, M. Sanson, M.J. Taphoorn, H.J. Bernsen, et al., Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial, J. Clin. Oncol. 24 (18) (2006) 2715–2722, doi:10.1200/JCO.2005.04.6078 PubMed PMID: 16782911.
[83] M. Brada, S. Stenning, R. Gabe, L.C. Thompson, D. Levy, R. Rampling, et al., Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma, J. Clin. Oncol. 28 (30) (2010) 4601–4608, doi:10.1200/JCO.2009.27.1932 PubMed PMID: 20855843.
[84] W. Wick, B. Wiestler, M. Platten, Treatment of anaplastic glioma, Cancer Treat. Res. 163 (2015) 89–101, doi:10.1007/978-3-319-12048-5_6 PubMed PMID: 25468227.
[85] B. Wiestler, D. Capper, V. Hovestadt, M. Sill, D.T. Jones, C. Hartmann, et al., Assessing CpG island methylator phenotype, 1p/19q codeletion, and MGMT promoter methylation from epigenome-wide data in the biomarker cohort of the NOA-04 trial, Neuro Oncol. 16 (12) (2014) 1630–1638, doi:10.1093/neuonc/nou138 PubMed PMID: 25028501. PubMed Central PMCID: PMC4232086.
[86] M.C. Chamberlain, Salvage therapy with lomustine for temozolomide refractory recurrent anaplastic astrocytoma: a retrospective study, J. Neurooncol. 122 (2) (2015) 329–338, doi:10.1007/s11060-014-1714-9 PubMed PMID: 25563816.
[87] D.R. Johnson, E. Galanis, Medical management of high-grade astrocytoma: current and emerging therapies, Semin. Oncol. 41 (4) (2014) 511–522, doi:10.1053/j.seminoncol.2014.06.010 PubMed PMID: 25173143.
[88] J.G. Cairncross, M. Wang, R.B. Jenkins, E.G. Shaw, C. Giannini, D.G. Brachman, et al., Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH, J. Clin. Oncol. 32 (8) (2014) 783–790, doi:10.1200/JCO.2013.49.3726 PubMed PMID: 24516018. PubMed Central PMCID: PMC3940537.
[89] R. Stupp, M.E. Hegi, W.P. Mason, M.J. van den Bent, M.J. Taphoorn, R.C. Janzer, et al., Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial, Lancet Oncol. 10 (5) (2009) 459–466, doi:10.1016/s1470-2045(09)70025-7 PubMed PMID: 19269895. Epub 2009/03/10.
[90] M.D. Walker, S.B. Green, D.P. Byar, E. Alexander Jr., U. Batzdorf, W.H. Brooks, et al., Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery, N. Engl. J. Med. 303 (23) (1980) 1323–1329, doi:10.1056/NEJM198012043032303 PubMed PMID: 7001230.
[91] N. Laperriere, L. Zuraw, G. Cairncross, Cancer care Ontario practice guidelines initiative neuro-oncology disease site G. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review, Radiother. Oncol. 64 (3) (2002) 259–273 PubMed PMID: 12242114.
[92] M.E. Hegi, A.C. Diserens, S. Godard, P.Y. Dietrich, L. Regli, S. Ostermann, et al., Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide, Clin. Cancer Res. 10 (6) (2004) 1871–1874 PubMed PMID: 15041700.
[93] M. Esteller, J. Garcia-Foncillas, E. Andion, S.N. Goodman, O.F. Hidalgo, V. Vanaclocha, et al., Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents, N. Engl. J. Med. 343 (19) (2000) 1350–1354, doi:10.1056/NEJM200011093431901 PubMed PMID: 11070098.
[94] U. Herrlinger, J. Rieger, D. Koch, S. Loeser, B. Blaschke, R.D. Kortmann, et al., Phase II trial of lomustine plus temozolomide chemotherapy in addition to radiotherapy in newly diagnosed glioblastoma: UKT-03, J. Clin. Oncol. 24 (27) (2006) 4412–4417, doi:10.1200/JCO.2006.06.9104 PubMed PMID: 16983109.
[95] M. Weller, J. Felsberg, C. Hartmann, H. Berger, J.P. Steinbach, J. Schramm, 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. 27 (34) (2009) 5743–5750, doi:10.1200/JCO.2009.23.0805 PubMed PMID: 19805672.
[96] W. Wick, M. Platten, C. Meisner, J. Felsberg, G. Tabatabai, M. Simon, et al., Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial, Lancet Oncol. 13 (7) (2012) 707–715, doi:10.1016/S1470-2045(12)70164-X PubMed PMID: 22578793.
[97] A. Malmström, B.H. Grønberg, C. Marosi, R. Stupp, D. Frappaz, H. Schultz, et al., Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial, Lancet Oncol. 13 (9) (2012) 916–926, doi:10.1016/s1470-2045(12)70265-6 PubMed PMID: 22877848.
[98] P. Yang, W. Zhang, Y. Wang, X. Peng, B. Chen, X. Qiu, et al., IDH mutation and MGMT promoter methylation in glioblastoma: results of a prospective registry, Oncotarget 6 (38) (2015) 40896–40906, doi:10.18632/oncotarget.5683 PubMed PMID: 26503470.
[99] O.L. Chinot, W. Wick, W. Mason, R. Henriksson, F. Saran, R. Nishikawa, et al., Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (8) (2014) 709–722, doi:10.1056/NEJMoa1308345 PubMed PMID: 24552318.
[100] A. Lai, A. Tran, P.L. Nghiemphu, W.B. Pope, O.E. Solis, M. Selch, et al., Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme, J. Clin. Oncol. 29 (2) (2011) 142–148, doi:10.1200/JCO.2010.30.2729 PubMed PMID: 21135282. PubMed Central PMCID: PMC3058273.
[101] T. Gorlia, R. Stupp, A.A. Brandes, R.R. Rampling, P. Fumoleau, C. Dittrich, et al., New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: a pooled analysis of EORTC brain tumour group phase I and II clinical trials, Eur. J. Cancer 48 (8) (2012) 1176–1184, doi:10.1016/j.ejca.2012.02.004 PubMed PMID: 22464345.
[102] J.L. Clarke, M.M. Ennis, W.K. Yung, S.M. Chang, P.Y. Wen, T.F. Cloughesy, et al., Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma?, Neuro Oncol. 13 (10) (2011) 1118–1124, doi:10.1093/neuonc/nor110 PubMed PMID: 21813511. Epub 2011/08/05, PubMed Central PMCID: PMCPmc3177665.
[103] H.S. Friedman, M.D. Prados, P.Y. Wen, T. Mikkelsen, D. Schiff, L.E. Abrey, et al., Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma, J. Clin. Oncol. 27 (28) (2009) 4733–4740, doi:10.1200/JCO.2008.19.8721 PubMed PMID: 19720927.
[104] T.N. Kreisl, L. Kim, K. Moore, P. Duic, C. Royce, I. Stroud, et al., Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma, J. Clin. Oncol. 27 (5) (2009) 740–745, doi:10.1200/JCO.2008.16.3055 PubMed PMID: 19114704. PubMed Central PMCID: PMC2645088.
[105] W. Zhang, X.G. Qiu, B.S. Chen, S.W. Li, Y. Cui, H. Ren, et al., Antiangiogenic therapy with bevacizumab in recurrent malignant gliomas: analysis of the response and core pathway aberrations, Chin. Med. J. 122 (11) (2009) 1250–1254 PubMed PMID: 19567132.
[106] S. Ananthnarayan, J. Bahng, J. Roring, P. Nghiemphu, A. Lai, T. Cloughesy, et al., Time course of imaging changes of GBM during extended bevacizumab treatment, J. Neurooncol. 88 (3) (2008) 339–347, doi:10.1007/s11060-008-9573-x PubMed PMID: 18389177.
[107] M.J. van den Bent, A.A. Brandes, R. Rampling, M.C. Kouwenhoven, J.M. Kros, A.F. Carpentier, et al., Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034, J. Clin. Oncol. 27 (8) (2009) 1268–1274, doi:10.1200/JCO.2008.17.5984 PubMed PMID: 19204207. PubMed Central PMCID: PMC2667826.
[108] G. Dresemann, M. Weller, M.A. Rosenthal, U. Wedding, W. Wagner, E. Engel, et al., Imatinib in combination with hydroxyurea versus hydroxyurea alone as oral therapy in patients with progressive pretreated glioblastoma resistant to standard dose temozolomide, J. Neurooncol. 96 (3) (2010) 393–402, doi:10.1007/s11060-009-9976-3 PubMed PMID: 19688297. Epub 2009/08/19.
[109] M. Weller, R. Stupp, W. Wick, Epilepsy meets cancer: when, why, and what to do about it?, Lancet Oncol. 13 (9) (2012) e375–e382, doi:10.1016/S1470-2045(12)70266-8 PubMed PMID: 22935237.
[110] A.O. Rossetti, R. Stupp, Epilepsy in brain tumor patients, Curr. Opin. Neurol. 23 (6) (2010) 603–609, doi:10.1097/WCO.0b013e32833e996c PubMed PMID: 20733482.
[111] J.R. Perry, Thromboembolic disease in patients with high-grade glioma, Neuro Oncol. 14 (Suppl. 4) (2012) iv73–iv80, doi:10.1093/neuonc/nos197 PubMed PMID: 23095833. PubMed Central PMCID: PMC3480243.
[112] M.J. van den Bent, J.S. Wefel, D. Schiff, M.J. Taphoorn, K. Jaeckle, L. Junck, et al., Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas, Lancet Oncol. 12 (6) (2011) 583–593, doi:10.1016/S1470-2045(11)70057-2 PubMed PMID: 21474379.
[113] P.Y. Wen, D.R. Macdonald, D.A. Reardon, T.F. Cloughesy, A.G. Sorensen, E. Galanis, et al., Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group, J. Clin. Oncol. 28 (11) (2010) 1963–1972, doi:10.1200/JCO.2009.26.3541 PubMed PMID: 20231676.
[114] D.R. Macdonald, T.L. Cascino, S.C. Schold Jr., J.G. Cairncross, Response criteria for phase II studies of supratentorial malignant glioma, J. Clin. Oncol. 8 (7) (1990) 1277–1280 PubMed PMID: 2358840.
[115] D. Brandsma, L. Stalpers, W. Taal, P. Sminia, M.J. van den Bent, Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas, Lancet Oncol. 9 (5) (2008) 453–461, doi:10.1016/S1470-2045(08)70125-6 PubMed PMID: 18452856.
[116] B. Phillips, C. Ball, D. Sackett, D. Badenoch, S. Straus, B. Haynes, et al. Oxford centre for evidence-based medicine–levels of evidence, http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/, 2009.