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A contemporary perspective on the diagnosis and treatment of diffuse gliomas in adults

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Summary

Gliomas are intrinsic brain tumours, which are classified by the World Health Organization (WHO) into different grades of malignancy, with glioblastoma being the most frequent and most malignant subtype (WHO grade IV). Mutations in the isocitrate dehydrogenase (IDH) 1 or 2 genes are frequent in lower (WHO II/III) grade tumours but typically absent in classical glioblastoma. IDH mutations are associated with a better prognosis compared with IDH wild-type tumours of the same WHO grade. Following detection of a tumour mass by imaging, maximum safe surgery as feasible is commonly performed to reduce mass effect and to obtain tissue allowing histopathological diagnosis and molecular assessment. Radiotherapy has been the mainstay in the treatment of diffuse gliomas for several decades. It provides improved local control, but is not curative. Furthermore, several randomised trials have shown that the addition of alkylating chemotherapy, either temozolomide or nitrosourea-based regimens, to radiotherapy results in prolonged survival. Tumour-treating fields (TTFields) have emerged as an additional treatment option in combination with maintenance temozolomide treatment for patients with newly diagnosed glioblastoma. Treatment at recurrence is less standardised and depends on the patient's performance status, symptom burden and prior treatments. Bevacizumab prolongs progression-free survival in newly diagnosed and recurrent glioblastoma, but does not impact overall survival. However, in Switzerland and some other countries, it is still considered a valuable treatment option to reduce clinical symptom burden. Given the generally poor outcome for these patients, various novel treatment approaches are currently being explored within clinical trials including immunotherapeutic strategies such as immune checkpoint inhibition and the brain-penetrant proteasome inhibitor marizomib.

Keywords: *glioblastoma*, *glioma*, *surgery*, *radiotherapy*, *chemotherapy*, *temozolomide*, *bevacizumab*

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Introduction

The present manuscript results from two *ad hoc* meetings of Swiss neuro-oncologists that aimed to define current standards of clinical practice as well as challenges in the diagnosis and management of gliomas in adulthood, including specific considerations for Switzerland. The neuro-oncologists involved considered the European Association of Neuro-Oncology (EANO) recommendations [1] and, at single centres, NCCN guidelines valid for Switzerland, but there are country-specific challenges discussed herein, as well as several recent developments not covered in the currently available versions of these guidelines. This consensus paper addresses the clinical and scientific evidence, but does not seek to value interventions by relating efficacy and cost.

Classification of gliomas

Gliomas are intrinsic brain tumours that most likely develop from neuroglial progenitor cells. Traditionally, the diagnosis of gliomas was based on histopathological features alone according to the World Health Organization (WHO) classification of primary brain tumours. The most recent version of the WHO classification includes molecular markers, which allows for a more accurate diagnosis and prognosis. The vast majority of grade II gliomas and approximately 60–70% of all anaplastic gliomas (WHO grade III) harbour a mutation in the isocitrate dehydrogenase (IDH) 1 or 2 genes, whereas only a minority of glioblastomas, the most frequent and most malignant type

of glioma, are IDH mutant [2]. A co-deletion of chromosome arms 1p/19q, also referred to as loss of heterozygosity (LOH) 1p/19q, assigns the diagnosis of an oligodendroglial tumour [3]. Recently, mutations in the histone H3 gene (*H3K27M*) have been identified as a subgroup of midline gliomas. These tumours show an extremely poor prognosis and must be considered as high grade gliomas [4]. It can be assumed that additional molecular markers, such as the presence of telomerase reverse transcriptase (TERT) promoter mutations or homozygous deletion of CDKN2a, will allow for even more refined diagnoses and become part of an updated version of the WHO classification [5, 6]. In glioblastoma, and probably also other IDH wild-type gliomas, methylation of the promoter region of the O^6-methylguanine DNA methyltransferase (MGMT) gene is a predictive marker for benefit from alkylating agents. Recently, genome-wide DNA methylation profiling has been described as a valuable tool to classify primary brain tumours and may be integrated into routine diagnostics in the coming years [7].

Diagnosis and work-up

Gliomas may present with various neurological symptoms or signs, including seizures, focal deficits, cognitive alterations or any other focal neurological symptom or sign that triggers an imaging procedure. Magnetic resonance imaging (MRI) is the gold standard for the detection and monitoring of gliomas and evaluation should be according to RANO criteria [8]. Only patients who are unable to undergo MRI should be examined by computed tomography (CT). Amino acid positron emission tomography (PET) has become increasingly available and may be used in selected patients for various purposes including the delineation of tumour extension, the definition of appropriate biopsy spots in non-contrast-enhancing tumours and radiotherapy planning, as well as monitoring of tumour growth and response assessment (fig. 1) [9].

Once tumour tissue is available, a standard histopathological examination will be performed (fig. 2), which subsequently should be supplemented by molecular assessments. These include the determination of the IDH status, first by immunohistochemistry, which will reveal IDH R132H-mutant tumours, representing approximately 90% of all IDH-mutant gliomas. In patients younger than 60 years with negative immunohistochemistry, additional sequencing of the IDH genes is recommened to exclude less frequent IDH 1 as well as IDH 2 mutations. IDH-mutant tumours should be further assessed for the presence of a 1p/19q co-deletion [10]. Some sites prefer to determine the 1p/19q status only in tumours which are α-thalassaemia/mental-retardation-syndrome-X-linked gene (ATRX) wild-type by immunohistochemistry [11]. The determination of the MGMT promoter methylation status may guide clinical decision making, particularly in elderly glioblastoma patients (see below), but does not aid in diagnosis. TERT promoter mutations may help to increase the diagnostic accuracy because they are common in oligodendrogliomas and glioblastomas, but rare in lower grade astrocytomas. The search for potentially "actionable" molecular alterations, such mutations in the BRAF gene or NTRK gene fusions may be considered, particularly in younger patients [12]. Larger next generation sequencing (NGS) panels are used at different centres to identify such molecular alterations, which are rare overall.

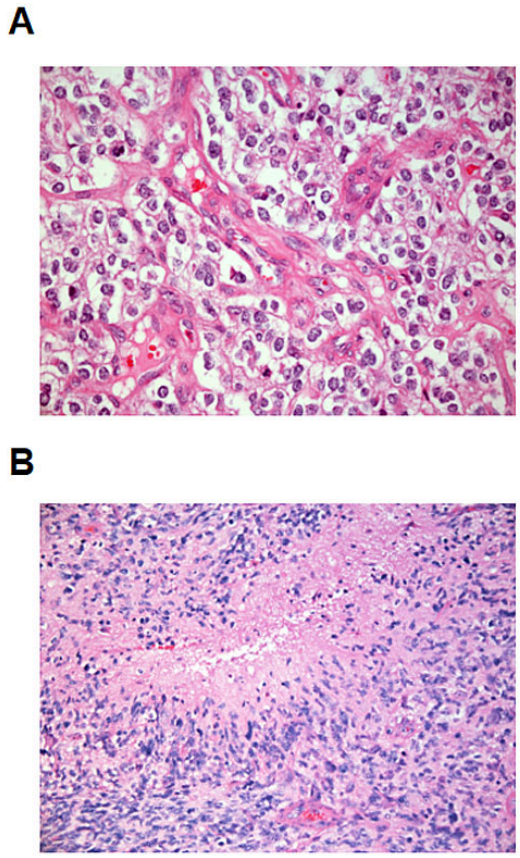
Following the diagnosis of a glioma, regular assessment of the Karnofsky performance status (KPS) and a clinical examination are required to monitor the occurrence or development of symptoms that may be related to the tumour or therapy. The Neurologic Assessment in Neuro-Oncology (NANO) scale provides a tool for a standardised clinical evaluation of glioma patients [13]. Glioblastoma patients are typically followed-up every 2–3 months, but longer intervals may be warranted in patients with lower grade tumours and those with prolonged stable disease.

Treatment

Surgery

Maximum safe surgical resection has been considered a standard of care despite lack of evidence from randomised clinical trials. In glioblastoma, 5-aminolevulinic acid-guided resection resulted in a higher rate of gross total resections and in prolonged progression-free survival (PFS) [14], but there was no effect on overall survival (OS) and this trial was conducted prior to the introduction of temozolomide. Similarly, the use of intraoperative MRI guidance increased the percentage of patients with gross total resection [15], but survival data were not reported. Thus,

Figure 2: Exemples of the histopathological features of gliomas. Haematoxylin and eosin staining of tumour tissue specimens. A. Anaplastic oligodendrogioma with typical cytoplasmatic halos ("fried eggs") which are the result of a fixation artifact (magnification 400×). B. Glioblastoma with pseudopalisading necrosis (magnification 200×). Images courtesy of G. Reifenberger, MD, Institute of Neuropathology, Düsseldorf.

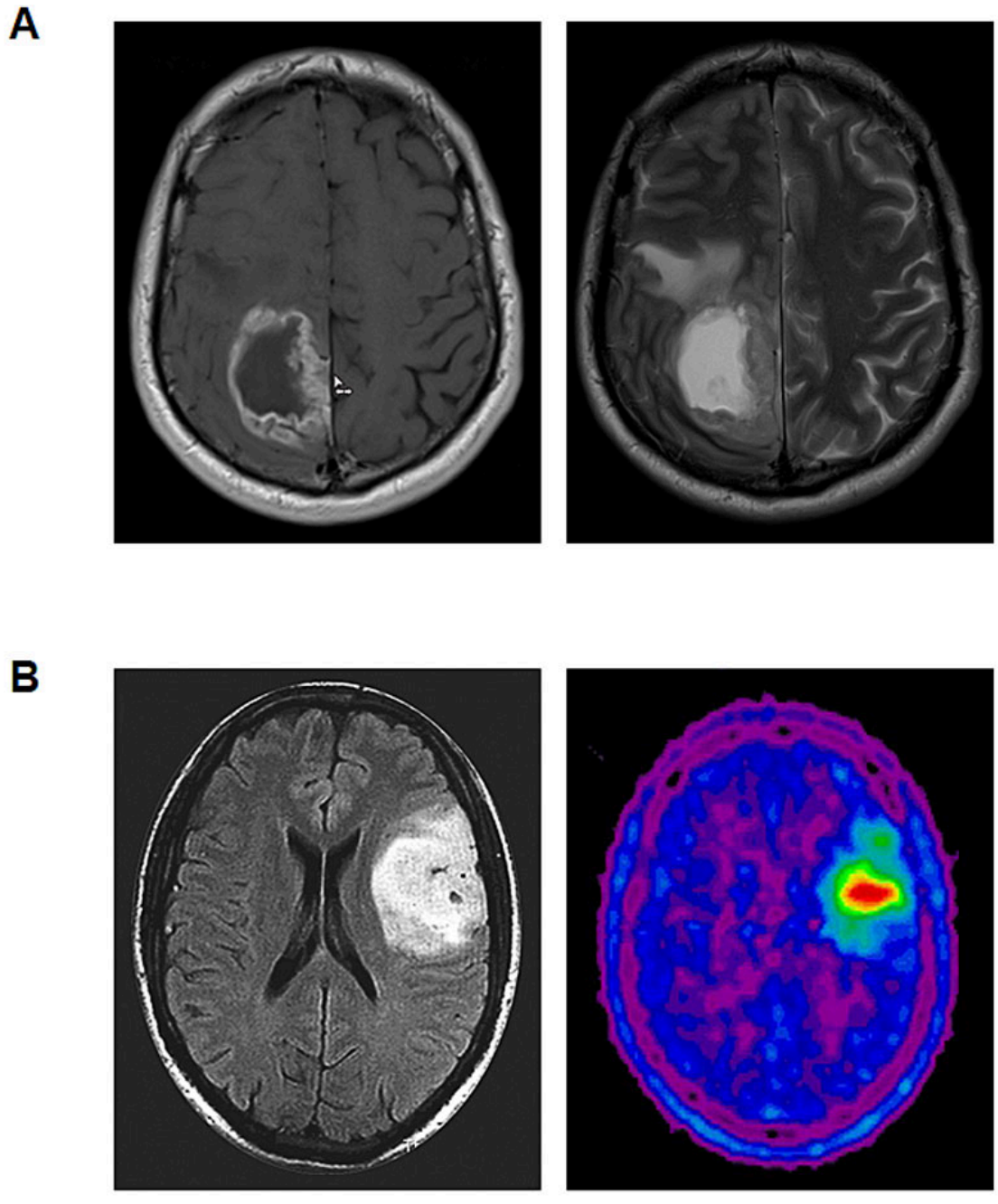


any impact of extent of resection and residual tumour on survival remains a matter of debate. The extent of resection should be determined by MRI within 24–72 hours after the intervention.

Radiotherapy

Radiotherapy has been used as a treatment for gliomas for several decades. It is typically administered in 1.8–2 Gy fractions up to a dose of 54–60 Gy. Prolongation of OS by radiotherapy was demonstrated in high-grade gliomas 40 years ago [16]. In contrast, radiotherapy prolonged PFS but not OS in patients with WHO grade II gliomas [17]. Particularly in elderly and frail patients affected by glioblastoma, hypofractionated radiotherapy with a dose of 40 Gy given in 15 fractions of 2.67 Gy has been established as a standard of care [18]. In glioblastoma patients, several studies failed to demonstrate an impact on survival by dose escalation or high precision techniques including brachytherapy, stereotactic boosts or hypofractionated schemes [19, 20]. However, techniques such as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) may improve safety via reduction of the dose to healthy tissue. Dose escalation also did not prolong OS in patients with low grade gliomas in two randomised trials [21, 22]. While the number of studies demonstrating superiority of combined radiochemotherapy compared to radiotherapy alone across various WHO grades has continuously increased (see below), it has remained unclear

Figure 1: Representative imaging findings in glioma patients. A. Glioblastoma. T1-weighted contrast-enhanced MRI (left) and T2-weighted MRI sequence (right). B. Oligodendroglioma WHO grade 2. T2/FLAIR-weighted MRI (left) and ^{18}F-fluoroethyl-tyrosine (FET)-PET (right).



whether irradiation may be safely deferred in subgroups of patients, particularly with WHO grade II and III tumours. This strategy has been partially integrated into standards of care in elderly patients with MGMT promoter-methylated glioblastoma who are not considered candidates for combined radiochemotherapy. These patients benefit from treatment with temozolomide alone and may receive radiotherapy as salvage therapy [23, 24].

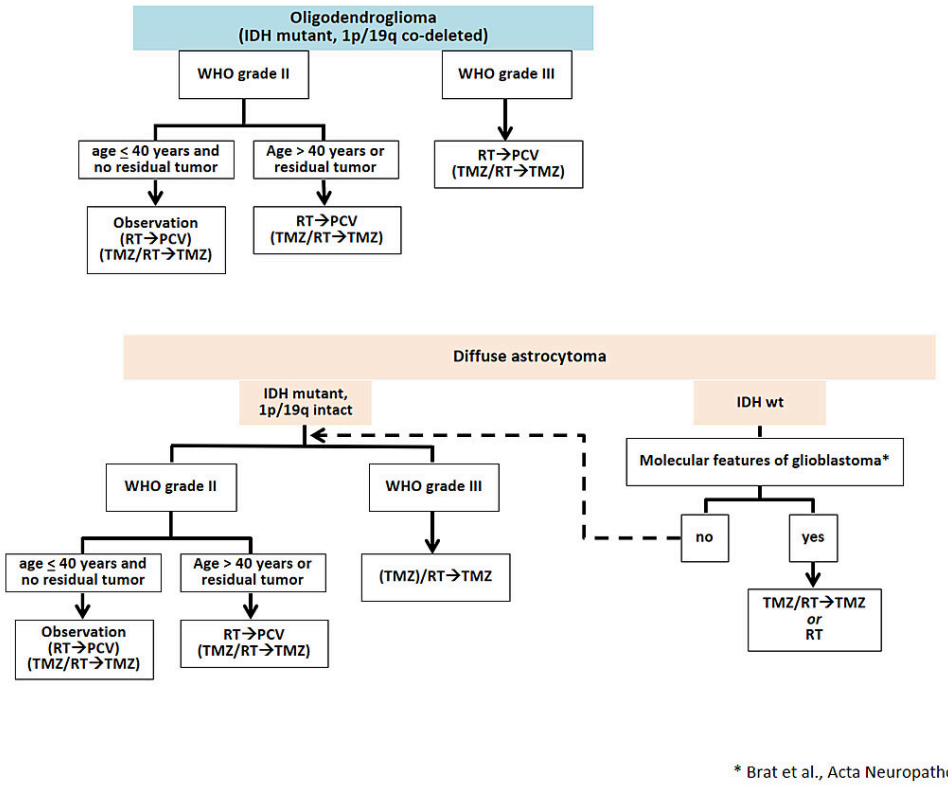
Systemic treatment

Data from several randomised trials have defined the role of systemic therapy in the treatment of diffuse gliomas [1]. A randomised trial enrolling patients with a diagnosis of a WHO grade II glioma considered to be at increased risk of further progression (age of 40 years or more, or residual tumour following resection) demonstrated that the addition of procarbazine, lomustine and vincristine (PCV) to radiotherapy prolongs PFS and OS compared with radiotherapy alone [25]. In the European Organisation for Research and Treatment of Cancer (EORTC) trial 22033-26033, temozolomide alone yielded similar results to radiotherapy alone [26]. Altogether, these data suggest that combined modality treatment is uniformly superior to either radiotherapy alone or alkylating agent chemotherapy alone. Several studies have also demonstrated a survival benefit upon addition of alkylating chemotherapy to radiotherapy in patients with anaplastic gliomas (fig. 3). Long-term analyses of two randomised trials showed that the combination of radiotherapy and PCV was superior to radiotherapy alone in patients with 1p/19q co-deleted anaplastic gliomas [27, 28]. In patients with 1p/19q intact anaplastic gliomas, radiotherapy followed by up to 12 cycles of maintenance treatment with temozolomide prolonged PFS and OS compared with radiotherapy alone [29]. Whether the addition of concomitant treatment with temozolomide to radiotherapy provides an additional benefit in subgroups of patients requires further analyses and longer follow-up of the EORTC 26053 trial (CATNON).

Temozolomide became part of the standard treatment for glioblastoma patients in 2005. Concomitant treatment during radiotherapy followed by maintenance treatment with temozolomide resulted in prolonged PFS and OS compared with radiotherapy alone, a finding that was also recently confirmed in elderly glioblastoma patients [30, 31]. Benefit from temozolomide is largely restricted to patients with glioblastoma with methylation of the MGMT promoter [32]. However, in the absence of convincing alternatives, such as within a clinical trial, and given the overall good tolerability, most neuro-oncological centres treat all glioblastoma patients with combined temozolomide-based radiochemotherapy up to approximately 70 years of age as long as the performance status is favourable (fig. 4). Based on the CeTeG trial, in younger patients with good performance status and MGMT promoter-methylated tumours, the addition of the combination of lomustine and temozolomide chemotherapy to and after radiotherapy may be considered [33].

The addition of the vascular endothelial growth factor (VEGF)-targeting agent bevacizumab to the standard of

Figure 3: Therapeutic options for patients with WHO grade II and III diffuse gliomas. Alternative treatment options which may considered on an invididual base are indicated in brackets. The dotted arrow indicates that for IDH wild-type tumours without molecular features of glioblastoma, the same therapeutic approach as for IDH mutant tumours should be considered.IDH = isocitrate dehydrogenase; WHO = World Health Organization; RT = radiotherapy; TMZ = temozolomide; PCV = procarbazine; CCNU = vincristine.



care in patients with newly diagnosed glioblastoma resulted in prolonged PFS but not OS [34–36] and was therefore not approved in this situation.

Tumour-treating fields

Tumour-treating fields (TTFields) have emerged as a new treatment modality for glioblastoma patients. TTFields are low-intensity, intermediate-frequency (200 kHz) alternating electrical fields, which are applied to the tumour region using specific transducer arrays. Administration of TTFields in patients with recurrent glioblastoma, most of them with multiple prior lines of therapy, did not result in superior outcome compared with the control arm, where the best available chemotherapy according to the treating physician's choice was allowed [37]. In contrast, the addition of TTFields to maintenance temozolomide in patients with newly diagnosed glioblastoma prolonged PFS and OS compared with standard treatment alone [38]. Treatment with TTFields is usually well tolerated except for skin reactions [39]. Subgroups of patients with preferential benefit from TTFields have not been identified. Controversies regarding this treatment within the neuro-oncology community concern the unclear mode of action *in vivo* and the discrepancy between efficacy in the front-line setting versus the recurrent setting.

Treatment at recurrence

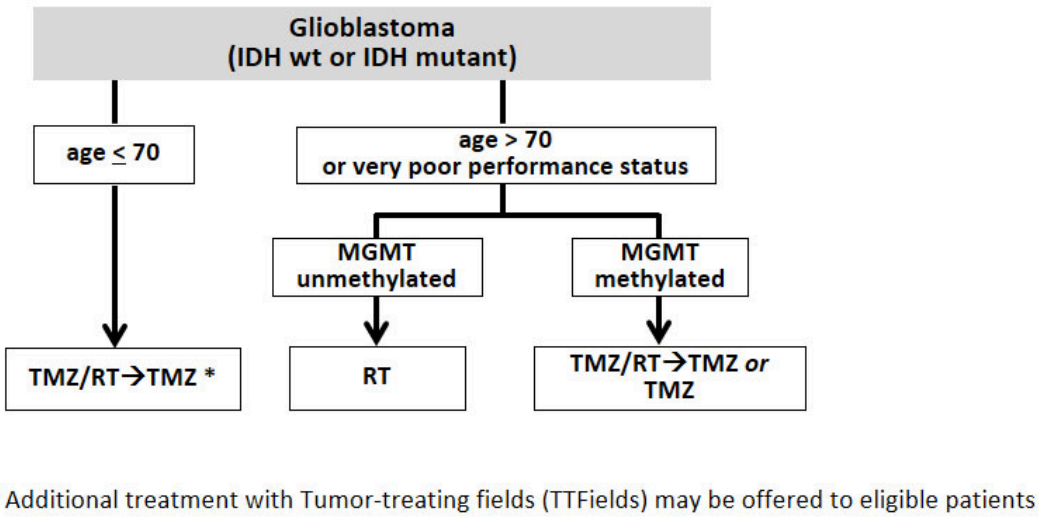
For patients with recurrent glioma, treatment is less standardised. The benefit of re-resection at recurrence remains contested because of the lack of evidence from prospective trials. It is most likely limited to patients with focal tumour recurrence who are candidates for a gross total resection. Re-irradiation may be administered in selected patients with small tumours, but its efficacy has not been assessed in a randomised trial. Furthermore, several systemic therapy options are available and in use [40]. Patients who initially only received radiotherapy or alkylating chemotherapy should be treated with the therapeutic modality not used so far. Although patients with lower-grade tumours typically present with a good performance status at recurrence, the situation may be different in glioblastoma where only a fraction of patients qualify for further treatment [41]. Systemic treatment options at recurrence comprise alkylating agents including primarily nitrosoureas such as lomustine, particularly in patients with MGMT-methylated tumours [42, 43]. However, access to lomustine has become more difficult as it is not licenced in Switzerland, in contrast to carmustine, an analogue nitrosourea formulation that is administered intravenously and less well studied in the context of glioblastoma. Re-exposure to temozolomide is less frequently used today than some years ago [44]. A positive trial compared temozolomide with procarbazine [45], but this trial predated the introduction of temozolomide into the first-line setting. Treatment options for patients with MGMT-unmethylated tumours thus remain limited.

Bevacizumab was approved in Switzerland for patients with recurrent glioblastoma in 2009. Similarly to the situation in the newly diagnosed setting, the addition of bevacizumab to lomustine in patients with recurrent glioblastoma prolonged PFS but not OS [43]. In line with these data, a Swiss population-based analysis did not reveal prolonged survival of glioblastoma patients after the introduction of bevacizumab [41]. However, the drug remains a useful option in patients with symptomatic tumours who experience a clinical benefit due to relief of the mass effect.

Supportive therapy

Glioma patients frequently suffer from clinical symptoms related to therapeutic interventions or directly to the tumour, such as surrounding oedema. Steroids such as dexamethasone or prednisone have been used for decades to reduce peritumoural oedema and thereby alleviate neurological symptoms. They should always be used at the lowest effective dose and tapering should be considered as soon as clinically justified [46]. Many glioma patients are

Figure 4: First-line therapy in patients with newly diagnosed glioblastoma. Patients older than 70 years with MGMT-methylated glioblastoma may receive combined temozolomide-based radiochemotherapy or monotherapy with temozolomide, depending on the performance status as considered appropriate by the treating physician.IDH = isocitrate dehydrogenase; RT = radiotherapy; TMZ = temozolomide; MGMT = O^6-methylguanine-DNA methyltransferase.



affected by seizures requiring treatment with anti-epileptic drugs. Drug interactions,such as with chemotherapeutic agents, should be considered. There is no indication for primary prophylactic antiseizure medication in patients with gliomas who never had a seizure [47]. Furthermore, glioma patients must be monitored for the occurrence of venous thromboembolic events, which should be adequately treated according to local guidelines as in other patients unless there are clear-cut contraindications. Supportive measures are the major therapeutic focus in patients who present in poor performance status, unable to undergo radiotherapy or chemotherapy [48].

Further developments and outlook

The role of re-resection in patients with recurrent glioblastoma shall be clarified in the ongoing ReSurge trial (NCT02394626). Furthermore, immunotherapy has been considered an attractive treatment option for glioma patients. However, so far, no immunotherapeutic agent has been shown to prolong the survival of glioma patients. This includes the EGFRvIII-targeting peptide vaccine rindopepimut, which was explored in patients with newly diagnosed glioblastoma and the PD-1 inhibitor nivolumab, which was assessed in patients with recurrent glioblastoma [49, 50]. Furthermore, the combination of nivolumab and radiotherapy was not superior to temozolomide-based radiotherapy in patients with newly diagnosed MGMT-unmethylated glioblastoma (CheckMate 498 [NCT02617589], press release). Nivolumab is currently also being explored in the CheckMate 548 trial (NCT02667587), in patients with newly diagnosed glioblastoma with MGMT promoter methylation. The antibody-drug conjugate depatuxizumab-mafodotin was assessed in patients with recurrent EGFR-amplified glioblastoma. Although the primary endpoint of the trial was not met, a long-term analysis suggested that the drug may be active [51]. Yet, according to a press release, the addition of depatuxizumab-mafodotin to the standard of care in patients with newly diagnosed glioblastoma harboring an EGFR amplification did not prolong overall survival (NCT02573324). Marizomib, a brain-penetrant pan-proteasome inhibitor is currently examined in patients with newly diagnosed glioblastoma in a randomised phase III trial (EORTC 1709, NCT03345095). Furthermore, molecular alterations such as $BRAF^{V600E}$ mutations, which are found in a subset of gliomas, will be used more frequently for targeted therapeutic strategies in the future [52, 53].

Potential competing interests

AH's institution received honoraria for advisory boards participation, research or travel grants from Roche, MSD, Abbvie and Novocure. TH has received honaria for advisory boards participation or travel grants from Roche, MSD, Novocure and Abbvie. HL has received research grants from BMS, and honoraria from MSD, Roche, and BMS. CM has received honoraria for advisory board participation or lectures from Abbvie, Böhringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, MSD, Novartis, Roche and Takeda. GP: Has received honoraria for advisory board participation from MSD, Roche, and Novocure. MR has received research and travel support from Novocure. PR has received research grants from MSD and Novocure and honoraria for advisory board participation or lectures from Bristol-Myers Squibb, Covagen, Debiopharm, Medac, MSD, Novartis, Novocure, QED, Roche and Virometix. MW has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, OGD2, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb, Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen. The other authors declare no conflict of interest.

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