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Current Considerations in the Treatment of Grade 3 Gliomas

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Opinion statement

Treatment recommendations for grade 3 gliomas are guided by their histopathologic and molecular phenotype. In the 2021 WHO classification, these tumors are categorized into two types, grade 3 IDH mutant (IDHmt), 1p/19q codeleted oligodendroglioma and IDH mutant astrocytoma. Treatment consists of maximal safe surgery, followed by radiation therapy (RT) and alkylating agent–based chemotherapy. Based on the updated CATNON result, RT followed by temozolomide improves outcome in patients with non-codeleted grade 3 IDHmt astrocytoma. In patients with IDHmt, codeleted oligodendroglioma, the addition of procarbazine, CCNU, and vincristine regimen is the recommended treatment, based on large randomized controlled trials. These current treatments prolong the overall survival to up to 10 years in patients with grade 3 IDHmt astrocytoma and 14 years in grade 3 IDHmt codeleted oligodendroglioma. Treatment options at recurrence include re-resection, re-irradiation, and other cytotoxic chemotherapy; however, these are of limited benefit. Novel agents targeting IDH mutation and its metabolic effects are currently under investigation to improve the outcome of these patients.

Introduction

Evolving molecular data have led to a paradigm shift in the classification and treatment of gliomas. Mutations in isocitrate dehydrogenase (*IDH*) genes, IDH1and IDH2, represent an early event in gliomagenesis, occurring in

more than 70% of WHO grades 2 and 3 astrocytoma and oligodendroglioma [1•, 2]. The presence of IDH mutation is a strong determinant of prognosis and is associated with improved overall survival [3]. In the 2021 World Health Organization (WHO) classification of central nervous system tumors, diffuse gliomas are divided mainly into IDH-mutant (IDHmt) astrocytoma (WHO grades 2, 3, or 4), IDHmt and 1p/19q codeleted oligodendroglioma (WHO grades 2 or 3), and IDH-wild type (IDHwt) glioblastoma (WHO grade 4) [4••]. Several molecular markers provide robust prognostic information and have been added as biomarkers of grading and prognosis. The presence of *CDKN2A/B* homozygous deletion has been associated with shorter survival and its presence in IDHmt astrocytoma would qualify the tumor as a WHO grade 4 IDHmt astrocytoma. Additionally, in patients with histologically appearing grades 2 or 3 IDHwt astrocytoma, the presence of either *TERT* promoter mutation, *EGFR* amplification, or combined whole chromosome 7 gain and chromosome 10 loss would be assigned WHO grade 4 glioblastoma [4••]. The current classification has omitted the modifier term "anaplastic" to refer to grade 3 astrocytoma and oligodendroglioma.

Integration of molecular data is mandatory for both diagnosis and treatment of grade 3 IDHmt gliomas. Recent long-term analysis of randomized controlled trials (RCTs) demonstrated survival benefit with the addition of chemotherapy to radiation therapy (RT) in both grade 3 astrocytoma and oligodendroglioma [5••, 6••]. Focusing on grade 3 IDHmt and 1p/19q codeleted oligodendroglioma and grade 3 IDHmt astrocytoma, this manuscript will review the recent updates and treatment recommendations for these gliomas.

Oligodendroglioma, WHO grade 3, IDH mutated, 1p/19q codeleted

Surgery

Gross total resection (GTR) is associated with significant survival benefit in patients with diffuse glioma [7•]. However, recent evidence suggests diminished prognostic benefit of extensive resection once molecular profile is taken into account [8–10]. In a large retrospective study of patients with grades 2 and 3 glioma, including 269 with IDHmt 1p/19q codeleted and 363 with IDHmt non-codeleted tumors, extensive resection did not significantly improve PFS (HR 1.47; 95% CI 0.92–2.34; p=0.11) nor OS (HR 1.54; 95% CI 0.78–3.05; p=0.21) in patients with IDHmt, 1p/19q codeleted tumors [9]. This is in contrast to patients with IDHmt noncodeleted grades 2 and 3 gliomas where subtotal resection was significantly associated with increased hazard radio for both PFS and OS [9]. A smaller retrospective study similarly did not observe survival advantage among patients with 1p/19q codeletion who underwent GTR versus non-GTR (p=0.14) [8]. In the latter study, GTR was defined as no residual enhanced tumor or no residual T2-weighted hyperintense tumor in patients with pre-operative enhancing or those with partially or non-enhanced grade 3 gliomas, respectively [8]. In 122 patients with grade 3 gliomas who underwent resection of both non-enhancing and enhancing disease, a significant survival advantage was seen in patients with grade 3 astrocytoma and mixed oligoastrocytoma, but not in oligodendroglioma [11]. Although IDH mutation was shown to be predictive of survival in grade 3 astrocytoma and mixed oligoastrocytoma, analysis based on molecular subgroups was not performed in this study [11]. In contrast, supratotal resection (defined as complete removal of any signal abnormalities, with the volume of the postoperative cavity larger than preoperative tumor volume) of IDHmt grades 2 and 3 glioma was associated with prolongation of PFS, malignant PFS and OS regardless of

the molecular subtypes and grading [12]. These data suggest that GTR may have less impact in grade 3 oligodendroglioma than in grade 3 astrocytoma possibly due to its high sensitivity to RT and chemotherapy [9], as evidenced by the prolonged survival seen in those who received both RT and procarbazine, lomustine/CCNU, and vincristine (PCV) chemotherapy regimen in large RCTs [5••, 6••]. Further studies are needed to validate the effect of extensive resection in patients with IDHmt 1p/19q codeleted oligodendroglioma.

Currently, maximum safe resection remains the favored initial treatment in diffuse gliomas [7•]. However, in patients with grade 3 IDHmt, 1p/19q codeleted oligodendroglioma located in eloquent regions, aggressive surgery with high risk for neurologic morbidity may be unwarranted.

Radiation therapy and chemotherapy

Based on the results of two large phase III trials (RTOG 9402 and EORTC 26951) that demonstrated an almost twofold improvement of OS, the addition of PCV either prior to or after RT in patients with grade 3 IDHmt, 1p/19q codeleted oligodendroglioma has become the standard treatment [5••, 6••, 13•]. In RTOG 9402, long-term analyses after a median follow up of 16.4 years demonstrated significant prolongation of both PFS (9.8 versus 2.9 years, HR 0.46, 95% CI 0.3–0.7, $p<0.001$) and OS (13.2 versus 7.3 years, HR 0.61, 95% CI 0.40–0.94; $p=0.02$) with RT and PCV in grade 3 IDHmt, 1p/19q codeleted oligodendroglioma. In patients with IDH mutation without 1p/19q codeletion, the addition of PCV resulted in significant improvement of PFS (2.8 vs 1.9 years, HR 0.58, 95% CI 0.34–0.99, $p=0.046$) and a trend for prolonged OS (5.5 years vs 3.3 years, HR 0.6, 95% CI 0.34–1.03, $p=0.06$) [5••]. After a median follow up of 18.4 years, the EORTC 26951 study reported a similar trend of improved median OS with RT followed by PCV compared to RT alone (3.5 versus 2.6 years; HR 0.75, 95% CI 0.63–0.98, adjusted $p=0.06$). In 80 patients with 1p/19q codeletion, there was an impressive prolongation of OS and 20-year survival after RT and PCV versus RT alone (14 years and 37.1% versus 9.3 years and 13.6% (HR 0.60, 95% CI 0.35–1.03, unadjusted $p=0.06$), respectively); the 20-year PFS was 31.3% versus 10.8%, respectively (HR 0.49, 95% CI 0.29–0.83, unadjusted $p=0.007$) [6••]. Table 1 summarizes the results of clinical studies in grade 3 gliomas.

Despite the relative efficacy of temozolomide in the treatment of IDHmt codeleted oligodendroglioma, temozolomide is often the preferred first-line chemotherapy over PCV due to its favorable toxicity profile and ease of administration. In a large retrospective study including over 1000 adults with grade 3 oligodendroglioma, patients with 1p/19q codeletion demonstrated prolonged time-to-progression (TTP) of 7.2 years after combination of RT and chemotherapy either with PCV or temozolomide compared to 3.9 years with chemotherapy alone ($P=0.003$) and 2.5 years with RT alone ($P<0.001$) [14]. PCV appeared to offer a longer disease control than temozolomide, but without clear benefit in OS in patients with grade 3 oligodendroglioma with 1p/19q codeletion [14]. In RTOG 9813, no significant difference was noted in PFS, TTP, and OS in patients with grade 3 gliomas who received RT plus adjuvant temozolomide compared to RT plus adjuvant nitrosoureas [15]. Patients who received RT and nitrosourea experienced more ≥ grade 3 toxicity than those who received temozolomide [15]. In practice, vincristine is often omitted in the PCV regimen due to its uncertain

Table 1. Clinical studies in WHO grade 3 gliomas

Study	Population	Treatment	Outcomes
RTOG 9402 [5••]	N= 289 AO and AOA	PCV q6 weeks x 4 cycles followed by RT versus RT alone	**IDHmt, 1p/19q codeleted:** PCV+RT vs RT - PFS: 9.8 yrs vs 2.9 yrs (HR 0.46, 95% CI 0.3 0.7, p< 0.001) - OS: 13.2 vs 7.3 yrs (HR 0.61, 95% CI 0.40-0.94; p=0.02)
EORTC 26951 [6••]	N=368 AO and AOA	RT followed by PCV q6 weeks x 6 cycles versus RT alone	- Median PFS: RT+PCV 24.3 mos (2yrs) vs RT 13.2 mos. (1.1 yrs) (HR 0.66, 95% CI 0.52- 0.83) - Median OS: RT+PCV 42.3 mos (3.5 yrs) vs RT 30.6 mos (2.6 yrs) (HR 0.75, 95% CI 0.63-0.98, adjusted p=0.06) - 20-yr survival: 16.8% versus 10% (HR 0.78, 95% CI 0.63-0.98; adjusted p=0.06) (2019 report) **IDHmt, 1p/19q codeleted** (n=80): PCV+RT vs RT - OS: 14.2 yrs vs 9.3 yrs - PFS: 13.1 yrs vs 4.2 yrs - 20-yr OS: 37.1% vs 13.6% - 20-yr PFS: 31.3% vs 10.8% (p=0.007)
Lassman, et al. (2011) [14]	N=1013 AO and AOA	PCV alone vs TMZ alone; RT/PCV vs RT/TMZ	- Median OS: 6.3 years - TTP: 3.1 years **1p/19q codeleted:** CT+RT vs CT vs RT - TTP: 7.2 yrs vs 3.9 yrs (p=0.003) vs 2.5 yrs (p<0.001) - OS: 8.4 yrs vs 10.5 yrs vs 8.7 yrs (NS) - TTP: PCV alone 7.6 yrs vs TMZ alone 3.3 yrs (P=0.019) **1p/19q non-codeleted:** CT+RT vs CT vs RT - TTP: 3.1 yrs vs 0.9 yrs (p=0.0124) vs 1.1 yrs (p<.0001) - OS: 5 yrs vs 2.2 yrs (p=0.02) vs 1.9 yrs (P<.0001)
RTOG 9813 [15]	N=196 Grade 3 gliomas	Treatment: RT plus TMZ (RT/TMZ) versus RT plus NU (RT/NU)	- OS: RT/TMZ 3.9 years vs RT/NU 3.8 years (HR 0.94; 95% CI 3.0-7.0; p=0.36) - PFS: RT/TMZ vs RT/NU was not significant (HR 0.85, 95% CI 0.61-1.17, p=0.31) - TTP: RT/TMZ vs RT/NU was not significant (HR 0.80, 95% CI 0.55-1.16, p=.24) **Based on IDH status**: (IDHmt=49, IDHwt=44) - OS: IDHmt 7.9 years versus IDHwt 2.8 years (HR 0.50, 95% CI 0.31-0.81; p=0.004)
NOA-04 [16]	N=318 Grade 3 gliomas	Treatment: RT with chemotherapy (PCV or TMZ) deferred until progression versus Chemotherapy (PCV or TMZ) with RT deferred until progression Arms: A=RT →chemotherapy B1=PCV →RT B2=TMZ→RT	- TTF: Arm A 4.6 yr vs B1/B2 4.4 yrs (NS) - PFS: Arm A 2.5 yrs. (CI 1.4-3.4) vs B1/B2 2.7 yrs. (CI 1.9-3.2) (NS) - OS: 8 yrs (CI 5.5-10.3) vs 6.5 yrs. (CI 5.4-8.3) (NS) **IDHmt, 1p/19q codeleted:** - TTF: 9.8 years - PFS: PCV 9.4 yrs vs TMZ 4.5 yrs, vs RT 8.7 yrs - OS: PCV not reached, TMZ 8.1 yrs. **IDHmt, 1p/19q non-codeleted** - TTF: 4.5 yrs - Median PFS and OS not reported

Table 1. (Continued)

Study	Population	Treatment	Outcomes
CATNON [19••]	N=751 1p/19q noncodeleted grade 3 gliomas	Treatments: RT vs RT with concurrent daily TMZ (75 mg/m2) vs RT followed by adjuvant TMZ (150-200 mg/m2) x12 cycles vs RT with concurrent and adjuvant TMZ x12 cycles	**RT with versus without adjuvant TMZ** - OS: 82.3 mos or 6.86 yrs vs 46.9 mos or 3.9 yrs (HR 0.64; 95% CI 0.52-0.79; p<0.0001) - PFS: 19.1 mos or 1.6 yrs vs 42.8 mos or 3.6 yrs (p<0.0001) **RT with versus without concurrent TMZ** - OS: 66.9 mos or 5.57 yrs vs 60.4 mos or 5.03 yrs (HR 0.97, 99.1% CI 0.73-1.28; p=0.76) - PFS: 33 mos 2.75 yrs vs 20.9 mos or 1.74 yrs (p=0.045) **IDH mutant** (444/660 patients; 67%) - RT with adjuvant TMZ vs RT with concurrent/adjuvant TMZ: 5-yr OS 80.5% vs 82.8% (HR 0.82; 95% CI 0.49-1.36; p=0.44) - RT with concurrent TMZ vs RT with concurrent/adjuvant TMZ: 5-yr OS 64.8% vs 82.8% (HR 0.49; 95% CI 0.30-0.81; p=0.0050) - Any TMZ versus RT alone: OS: 114.4 mos or 9.5 yrs vs 68.2 mos or 5.7 yrs (HR 0.53; 95% CI 0.38-0.74; p<0.0001) PFS: 77 mos or 6.4 yrs vs 34.2 mos or 2.85 yrs (HR 0.48; 95% CI 0.37-0.63; p<0.0001)

AO: Anaplastic oligodendroglioma grade 3; AOA: Anaplastic oligoastrocytoma grade 3; PCV: procarbazine, CCNU and vincristine; RT: Radiation therapy; CT: Chemotherapy; NU: Nitrosurea; TMZ: temozolomide; PFS: Progression free survival; OS: Overall survival; TTP: Time-to-tumor progression; TTF: Time-to-failure; HR: Hazard ratio; NS: not significant; IDHmt: Isocitrate dehydrogenase mutated

blood-brain barrier penetration [7•]. The ongoing modified randomized phase III CODEL trial (NCT00887146) will compare the efficacy, safety, and quality of life of RT followed by PCV versus RT with concomitant and adjuvant temozolomide in 1p/19q codeleted grades 2 and 3 oligodendroglioma.

Given the chemosensitivity of oligodendroglioma and the delayed RT-induced neurotoxicity, a treatment approach of administering chemotherapy alone and delaying RT until tumor progression may also be considered. The NOA-04 trial randomized 318 patients with grade 3 gliomas to RT (arm A) or chemotherapy with either PCV (arm B1) or temozolomide (arm B2) as initial therapy [16]. The study primary endpoint was median time-to-treatment-failure (TTF), defined as progression after two lines of therapy or any time before, no further treatment was administered. The median TTF was similar when RT was given upfront with chemotherapy at progression (4.6 years) versus chemotherapy followed by RT at recurrence (4.4 years). The median PFS was also similar between the two groups (arm A: 2.5 versus B1/2: 2.7 years). The TTF was 9.8 years in patients with codeletion and 4.5 years in patients with IDHmt/non-codeletion. A French trial randomizing patients with low grade oligodendroglioma to PCV alone versus RT followed by PCV (NCT04702581) is ongoing to address this issue.

Astrocytoma, WHO grade 3, IDH mutated

Surgery

Maximum safe resection, if feasible is the recommended initial treatment in grade 3 IDHmt astrocytoma [13•]. GTR of enhancing disease is associated with improved survival [17]. However, grade 3 gliomas are a radiographically heterogenous disease, with up to 30% having no contrast enhancement evident on presentation [18]. For IDHmt grade 3 astrocytoma, resection of both FLAIR/T2-weighted hyperintense non-enhancing and enhancing tumor has been shown to provide a significant survival benefit [11, 18]. In comparison, complete resection of enhancing disease demonstrated improved survival, but no additional benefit with resection of non-enhancing tumor volume in patients with IDHwt gliomas [18]. Recent data have demonstrated supratotal resection is associated with prolongation of PFS, reduced rate of malignant transformation, and a longer OS in IDHmt grades 2 and grade 3 gliomas [12]. This interesting surgical approach requires further validation.

Radiation therapy and chemotherapy

Recent data from RCTs have defined the role of chemotherapy in patients with grade 3 IDHmt non-codeleted astrocytoma. The phase III CATNON trial randomized 751 patients with non-codeleted grade 3 glioma to receive RT alone or followed by adjuvant temozolomide for 12 cycles, or RT with concurrent temozolomide with or without adjuvant temozolomide. After a median follow up of 55.7 months, the second interim results demonstrated no survival benefit with concurrent temozolomide in the entire study cohort. The median OS was 66.9 months with concurrent versus 60.4 months without concurrent temozolomide (HR 0.97, 99.1% CI 0.73–1.28, p=0.76). In contrast, adjuvant temozolomide significantly improved OS compared to patients who did not receive adjuvant temozolomide (median OS 82.3 months versus 46.9 months; HR 0.64, 95% CI 0.52–0.79, p<0.0001) [19••]. Among the 67% of patients with IDH mutation, survival benefit was similarly observed with adjuvant temozolomide, but not with concurrent temozolomide. In addition, patients who received any temozolomide experienced a significantly prolonged median PFS (77 months versus 34.2 months; HR 0.48, 95% CI 0.37–0.63, p<0.0001) and OS (114.4 months versus 68.2 months; HR 0.53, 95% CI 0.38–0.74, p<0.0001) than those who received RT alone [19••]. Based on the CATNON trial, RT followed by 12 cycles of adjuvant temozolomide is the current recommended treatment. Table 1 summarizes the results of clinical studies in grade 3 gliomas.

Adjuvant treatment is generally recommended for grade 3 gliomas, although the optimal timing is still not well-established [10]. In a retrospective study of 44 patients with diffuse low-grade glioma with at least one focus of high-grade (grade 3 or 4) features within the whole tumor (including 88% patients with IDH mutation and 59% 1p/19q non-codeletion), postponing adjuvant treatment with the aim to preserve cognitive function and quality of life seems reasonable, without negatively affecting OS [20]. The median interval time between surgery and initiation of either RT or chemotherapy was 3.4 years, and the median interval to RT was 9.5 years among 19 patients. The ongoing

EORTC 1635 I-WOT trial (NCT03763422) will assess whether early adjuvant RT and temozolomide will improve outcome and outweigh potential side effects in clinically favorable patients with grades 2 and 3 IDHmt astrocytoma. Due to the potentially reduced late toxicities with protons, the ongoing NRG-BN005 (NCT03180502) randomizes patients with grades 2 and 3 gliomas to proton versus photon RT, to determine whether proton therapy preserves cognitive outcomes over time.

Recurrent grade 3 gliomas

Treatment approach at progression depends on the response and tolerability to the first-line therapy. At recurrence, treatment options include re-resection, re-irradiation, systemic therapies, or experimental therapies [13•].

Reoperation should be considered on all patients with recurrent grade 3 gliomas [13•]. In a retrospective analysis of 78 patients with recurrent grades 3 and 4 gliomas, the median PFS of 12 patients with grade 3 astrocytoma was 52 weeks, 6-month PFS was 75%, median OS was 62 weeks, and 2-year OS was 58.3% after second surgery [21]. A systematic review demonstrated a survival benefit of reoperation in patients with recurrent grades 3 and 4 gliomas who underwent GTR [22]. IDHmt and 1p/19q codeletion were associated with longer survival after reoperation [23, 24].

A few retrospective studies have assessed the feasibility and safety of re-irradiation. In a large study including 300 patients with recurrent glioma, reirradiation was found to be safe and feasible with limited rate of toxicity [25]. The median interval time between first RT and reirradiation was 16 months, and the median biological effective dose was 43 Gy. Among 77 patients with grade 3 glioma, the median OS was 12.2 months, and 2-year OS was 34.4% after reirradiation. Longer survival was noted in patients with IDH mutation (18.5 months) and 1p/19q codeletion (14.7 months). Younger age, good performance status, prior low-grade histology, longer interval time (>12 months) between primary RT, and reirradiation were identified as factors affecting survival [25]. In 172 patients with recurrent gliomas (including 42 patients with grade 3 gliomas), fractionated stereotactic reirradiation with a median dose of 36 Gy was likewise well tolerated [26]. The median time between first and second RT was 32 months in patients with recurrent grade 3 gliomas, with a median OS of 16 months and PFS of 8 months after reirradiation [26]. In patients whose tumor recurred more than 1–2 years from initial RT, those with limited systemic treatment option, or if tumor has progressed to a higher grade, reirradiation can be considered [7•, 13•]. Moreover, reirradiation is generally recommended if the recurrence is outside the previous RT field [7•].

Chemotherapeutic options for recurrent grade 3 glioma are limited, consisting mainly of temozolomide or nitrosoureas [27–29]. Temozolomide is considered if patients relapse after PCV and vice versa [7•, 13•, 30]. Both temozolomide and PCV are equally effective in this setting, with a median OS of 7.2 months and 6.7 months, and median PFS of 4.7 months and 3.6 months, respectively [28]. Single agent CCNU comparably demonstrated a modest activity in patients with grade 3 astrocytoma refractory to temozolomide with a median PFS of 4.5 months, 6-month PFS 40%, median OS of 9.5 months, and

1-year OS of 11.4% [29]. In the randomized phase III TAVAREC study, the addition of bevacizumab to temozolomide did not improve PFS, OS, or cognitive function after first contrast-enhancing recurrence in patients with IDHmt, 1p/19q non-codeleted grades 2 and 3 gliomas [31•]. Thus, the role of bevacizumab in this setting is mainly for palliation of symptoms from vasogenic edema [7•, 13•].

Investigational agents

Despite unequivocal efficacy of RT and alkylating agents for the treatment of IDHmt grade 3 gliomas, standard initial therapy is non-curative; IDHmt tumors almost inevitably recur and progress. As noted earlier, IDH mutation is an important early event in the tumorigenesis of IDHmt gliomas [1•, 32, 33]. IDH1 and IDH2 are homodimeric isoenzymes that play a key role in the Krebs cycle. IDH mutation transform α-ketoglutarate into 2-hydroxyglutarate (2-HG), an oncometabolite that inhibits several cellular processes resulting in increased hypoxia-inducible factor activity, widespread DNA and histone methylation, and a stem-like cell differentiation block [33–35]. Thus, several potential therapeutic strategies targeting IDH mutation have been actively investigated.

IDH inhibitors target the production of 2-HG and have been approved for adult patients with acute myeloid leukemia. Ivosidenib (AG-120), a small molecule, orally available IDH1 inhibitor, has been associated with a favorable safety profile and putative disease control in non-enhancing IDHmt gliomas in a phase I study for treatment of IDHmt solid tumors, including 66 patients with advanced gliomas [36, 37]. Thirty of 35 (87.5%) patients with non-enhancing IDHmt glioma achieved stable disease compared to 14 of 31 (45.2%) with enhancing glioma. The median PFS was 13.6 months (95% CI, 9.2 to 33.2 months) and 1.4 months (95% CI, 1 to 1.9 months) for the non-enhancing and enhancing glioma cohorts, respectively [37]. These findings suggest that ivosidenib has better anti-tumor activity in non-enhancing glioma, hypothesized to represent early tumor stage where the role of IDH mutation for tumor maintenance is most important, before additional genetic alterations are acquired in higher tumor grades [34]. Vorasidenib (AG-881), an oral pan inhibitor of both mutant IDH1 and IDH2, was well tolerated in a phase 1 trial in recurrent or progressive IDHmt gliomas (NCT02481154) [38]. Updated data in patients with non-enhancing gliomas showed encouraging activity of vorasidenib, with an objective response rate of 13.6%, stable disease in 77.3% of patients and PFS duration extending to 24 months or longer in 60% of patients [39]. Both ivosidenib and vorasidenib demonstrated brain penetrance and lowered 2-HG levels in a phase I perioperative study in patients with recurrent, non-enhancing grade 2 or 3 IDHmt glioma (NCT03343197) [40]. A phase III study comparing the efficacy of vorasidenib to placebo (INDIGO trial) is currently ongoing in patients with residual or recurrent grade 2 IDHmt glioma who have undergone surgery only as initial treatment with PFS as the primary endpoint (NCT04164901). Preliminary result of a phase 1 study using another IDH1 inhibitor, DS-1001b showed objective minor response in two and stable disease in seven out of 9 patients with recurrent non-enhancing IDHmt gliomas (NCT03030066) [41]. Phase I assessment of BAY1436032 (NCT02746081), an oral mutant IDH1 inhibitor in patients with IDH1 mutant

solid tumors demonstrated a median maximal reduction of plasma 2-HG of 76% and was well tolerated. The best clinical response was seen in patients with lower grade glioma with an objective response of 11% and stable disease in 43% of patients [42]. The oral agent FT 2102 is currently under investigation in a phase I/II study in patients with advanced solid tumor and glioma with IDH1 mutation (NCT03684811). A phase I/II study of enasidenib (AG-221), an IDH2 inhibitor, in advanced solid tumors including glioma and T cell lymphoma with IDH2 mutation has been performed and completed in 2016 (NCT02273739). However, results of this trial have not yet been reported.

Another approach under study for IDHmt gliomas incorporates poly (ADP-Ribose) polymerase (PARP) inhibitors, agents that target DNA damage repair pathways. 2-HG produced by mutant IDH induces a homologous recombination DNA repair defect through histone methylation, thereby establishing a "BRCAness" phenotype, rendering IDHmt glioma cells sensitive to PARP inhibitors [34, 43, 44]. Preclinical studies seem to indicate increase effectiveness of PARP inhibition when combined with RT or temozolomide [45, 46]. Several ongoing phases I and II studies using PARP inhibitors olaparib alone or in combination with temozolomide or immune check point inhibitors (NCT03561870, NCT03212274, NCT03991832, NCT05188508) and BGB290 with temozolomide (NCT03914742, NCT03749187) are under evaluation for treatment of recurrent IDHmt gliomas. The initial results of the phase II OLAGLI trial (NCT03561870) showed oliparib monotherapy was well tolerated in 35 patients with recurrent IDHmt high-grade gliomas [47]. The median PFS was 2.3 months and OS 15.9 months. Partial response was observed in 2 of 35 patients (5%) and stable disease in 14 (37%). In a phase II basket trial of olaparib and durvalumab (NCT03991832), which included nine patients with recurrent IDHmt glioma (two patients with 1p/1q codeletion; two with grade 2, four with grade 3, and three with grade 4 IDHmt glioma), also demonstrated safety with the combination treatment, but appears to lack adequate antitumor activity [48]. Objective response was observed in only one patient with IDHmt GBM, two had stable disease, while six patients had tumor progression after 2 cycles.

Immunotherapy has also been explored in the treatment of IDHmt gliomas. A recent phase I trial (NOA-16) demonstrated safety and immunogenicity of IDH1 R132H peptide vaccine in 33 patients with newly diagnosed IDHmt grades 3 and 4 astrocytoma (NCT02454634) [49•]. Pseudoprogression occurred in 37.5% of patients, providing radiological evidence of vaccine-induced intratumoral inflammatory response. Additionally, tumor-infiltrating T cell immune responses were identified in 87% (26 of 30) and B cells in 93% (28 of 30) of patients. Vaccine-related adverse events were limited to grade 1, and no regimen-limiting toxicity was observed [49•]. Other IDH1 peptide vaccines are under investigation: PEPIDH1M vaccine with temozolomide in recurrent grade 2 gliomas (RESIST study; NCT02193347), IDH1 R132H peptide vaccine with or without avelumab in progressive diffuse glioma (AMPLIFY-NEOVAC study; NCT03893903), and IDH1 R132H-DC vaccine with RT and chemotherapy in IDHmt glioma (NCT02771301). Immune checkpoint inhibitor that targets programmed death-ligand (PD-L1), avelumab in combination with hypofractionated RT in patients with IDHmt glioma that progressed to grade 4 after chemotherapy (NCT02968940) and nivolumab, an anti-programmed death receptor-1 (PD-1) in recurrent or progressive grades 2, 3,

or 4 IDHmt gliomas with prior treatment with alkylating agents (NCT035573590) are under investigation.

Due to the extent of hypermethylation induced by IDH mutation, DNA methylation inhibitors have also been considered in the treatment of IDHmt gliomas [33, 34]. A phase I study exploring the activity of decitabine, a hypomethylating agent, in combination with cedazuridine, a cytosine deaminase inhibitor that prevents degradation of decitabine in the gastrointestinal tract, is ongoing (NCT03922555).

Assessment of response and imaging surveillance

MRI is the standard diagnostic modality for assessment of disease status and treatment response in glioma, using the Response Assessment in Neuro-Oncology (RANO) criteria [50, 51]. Surveillance imaging based on available data on the time and pattern of relapse as well as based on initial treatments received in patients with IDHmt grade 3 gliomas has been recently proposed [52]. MRI study at least every 6 months until progression for IDHmt grade 3 astrocytoma and every 6–9 months in grade 3 oligodendroglioma treated with both RT and chemotherapy is recommended. In patients with grade 3 oligodendroglioma treated with either RT alone or chemotherapy alone, MRI as frequently as every 3–4 months for the first 5 years after completion of treatment, then as often as every 6 months until tumor progression is recommended, while every 3–4 months until progression is reasonable in patients with grade 3 astrocytoma. After tumor recurrence, MRI every 2–3 months for grade 3 IDHmt astrocytoma and every 3–4 months for grade 3 oligodendroglioma is advisable [52]. In patients with MRI changes raising concern for possible tumor progression, obtaining a short interval MRI of 4-12 weeks is advisable. It is also necessary to determine a reference MRI (nadir scan, post-surgery, or post-treatment) for longitudinal comparison to assess treatment responses in these patients who are usually followed for several years after diagnosis and treatment. Clinical factors such as changes in seizure frequency, new or worsening neurological signs and symptoms, or the need to initiate or increase corticosteroids warrant MR imaging outside the planned surveillance schedule [52].

Summary and recommendations

Molecular subtypes as defined by the updated 2021 WHO classification (Table 2) guide treatment recommendations of grade 3 gliomas. Maximal safe resection is the initial treatment for both grade 3 IDHmt astrocytoma and IDHmt, 1p/19q codeleted oligodendroglioma. In patients with grade 3 IDHmt, codeleted oligodendroglioma, RT and PCV is the standard of treatment, based on RTOG 9402 and EORTC 26951. Temozolomide is often favored due to its toxicity profile, although it remains unclear whether the efficacy of temozolomide is equivalent to PCV. The ongoing phase III CODEL trial addresses this question. Based on the updated results of CATNON trial, RT followed by 12 cycles of temozolomide is the recommended treatment for patients with grade 3 IDHmt astrocytoma. At recurrence, salvage therapies include re-resection, re-irradiation, other alkylating agents, and potential roles of targeted agents and

Table 2. Recommended treatments for newly diagnosed WHO grade 3 gliomas

Tumor type	Recommended initial treatment
Astrocytoma, Grade 3, IDHmt	Maximum safe resection followed by RT (59.4 Gy) and adjuvant temozolomide (150-200 mg/m^2) 4-week cycles for 12 cycles (CATNON)
Oligodendroglioma, Grade 3, IDHmt, 1p/19q codeleted	Maximum safe resection followed by RT 59.4 Gy (1.8 Gy x 33 fractions) and PCV PCV Doses: RTOG 9402: CCNU 130 mg/m^2 po day 1; Procarbazine 75 mg/mg^2 po on days 8-21; Vincristine 1.4 mg/m^2 IV on days 8 and 29; every 6 weeks for 4 cycles EORTC 26951: CCNU 110 mg/m^2 po day 1; Procarbazine 60 mg/m^2 po days 8-21; Vincristine 1.4 mg/m^2 IV days 8 and 29; every 6 weeks for 6 cycles

IDHmt: IDH mutant; RT: Radiation therapy; PCV: Procarbazine, CCNU and vincristine regimen

immunotherapies. Because of the critical role of IDH mutation in early gliomagenesis in these tumors, several novel IDH-directed therapies including IDH inhibitors, PARP inhibitors, and DNA methylations inhibitors are under investigation. Clinical studies using immunotherapies such as IDH1 peptide vaccines and immune checkpoint inhibitors are also underway.

Despite evidence of improved survival with RT and chemotherapy, treatment decisions remain challenging due to the anticipated long-term treatment-related neurotoxicity, particularly in patients with grade 3 IDHmt codeleted oligodendroglioma. Much work remains to find a treatment approach that maximizes survival while preserving quality of life and cognition.

Declarations

Conflict of Interest

Jasmin Jo declares that she has no conflict of interest. David Schiff has served as a co-chair for ECOG-ACRIN Brain Tumor Working Group and an advisory board member for AstraZeneca.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-73.
This paper first described the high frequency of IDH mutation in gliomas.

2. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol. 2008;116(6):597–602.

3. Olar A, Wani KM, Diefes K, Heathcock LE, van Thuijl HF, Gilbert MR, et al. IDH mutation status and role of WHO grade and mitotic index in overall survival in grade II-III diffuse gliomas. Acta Neuropathol. 2015;129(4):585–96.

4.•• Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231-51.

This paper discusses the new classification and grading of CNS tumors based on the molecular phenotypes of the tumors.

5.•• Lassman A, Won M, Cairncross JG, Shaw EG, Ashby L, Souhami L, et al. ACTR-13. Final results with chemoradiotherapy for anaplastic oligodendroglial tumors from NRG oncology/RTOG 9402. Neuro-Oncology. 2019;21(6):vi15.

This is one of the major RCT that demonstrates survival benefit with the addition of PCV to radiation therapy in grade 3 oligodendroglioma.

6.•• van den Bent MJ, Hoang-Xuan K, Brandes A, Kros JM, Kouwenhoven MCM, Taphoorn M, et al. LTBK-12. EORTC 26951, Randomized study of adjuvant PCV after 59.4 Gr radiotherapy: very long term follow-up. Neuro-Oncology. 2019;21(Suppl_6):vi285.

This is one of the major RCT that shows improvement of survival with the addition of PCV to radiation therapy in grade 3 oligodendroglioma.

7.• Schiff D, van den Bent M, Vogelbaum MA, Wick W, Miller CR, Taphoorn M, et al. Recent developments and future directions in adult lower-grade gliomas: Society for Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO) consensus. Neuro Oncol. 2019;21(7):837-53.

This article presents updated treatment recommendations for lower-grade gliomas.

8. Kawaguchi T, Sonoda Y, Shibahara I, Saito R, Kanamori M, Kumabe T, Tominaga T. Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q codeletion. J Neurooncol. 2016;129:505–14.

9. Ding W, Wang Z, Che D, Wang Y, Zhao Z, Sun C, et al. The prognostic value of maximal surgical resection is attenuated in oligodendroglioma subgroup of adult diffuse glioma: a multicener retrospective study. J Neuro-Oncol. 2018;140:591–603.

10. Geurts M, Snijders TJ, van den Bent MJ. Treatment of anaplastic gliomas: evidences and controversies. Curr Opin Oncol. 2021;33(6):621–5.

11. Fujii Y, Muragaki Y, Maruyama T, Nitta M, Saito T, Ikuta S, Iseki H, Hongo K, Kawamata T. Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI. J Neurosurg. 2018;129(1):1–9.

12. Rossi M, Gay L, Ambrogi F, Conti Nibali M, Sciortino T, Puglisi G, Leonetti A, Mocellini C, Caroli M, Cordera S, Simonelli M, Pessina F, Navarria P, Pace A, Soffietti R, Rudà R, Riva M, Bello L. Association of supratotal resection with progression-free survival, malignant transformation, and overall survival in lower-grade gliomas. Neuro Oncol. 2021;23(5):812–26.

13.• Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170-86.

This paper presents updated EANO treatment recommendations of diffuse glioma in adults.

14. Lassman A, Iwamoto FM, Cloughesy T, Aldape K, Rivera AL, Eichler AF, et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. Neuro Oncol. 2011;13(6):646–59.

15. Chang S, Zhang P, Cairncross G, Gilbert M, Bahary JP, Dolinskas CA, et al. Phase III randomized study of radiation and temozolomide versus radiation and nitrosurea therapy for anaplastic astrocytoma: results of NRG Oncology RTOG 9813. Neuro Oncol. 2017;19(2):252–8.

16. Wick W, Roth P, Hartmann C, Hau P, Nakamura M, Stockhammer F, Sabel MC, Wick A, Koeppen S, Ketter R, Vajkoczy P, Eyupoglu I, Kalff R, Pietsch T, Happold C, Galldiks N, Schmidt-Graf F, Bamberg M, Reifenberger G, et al. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. Neuro Oncol. 2016;18(11):1529–37.

17. Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM, Berger MS. Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg. 2006;105:34–40.

18. Beiko J, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, Shonka N, Gilbert MR, Sawaya R, Prabhu SS, Weinberg J, Lang FF, Aldape KD, Sulman EP, Rao G, McCutcheon I, Cahill DP. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro-Oncology. 2013;16(1):81–91.

19.•• van den Bent MJ, Tesileanu CMS, Wick W, Sanson M, Brandes AA, Clement PM, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(6):813-23.

This trial demonstrates improved outcome with adjuvant temozolomide in IDH mutant grade 3 gliomas and the lack of benefit of the addition of temozolomide to radiotherapy in IDH wild type gliomas.

20. Darlix A, Rigau V, Fraisse J, Goze C, Fabbro M, Duffau H. Postoperative follow-up for selected diffuse low-grade gliomas with WHO grade III/IV foci. Neurology. 2020;94(8):e830–e41.

21. Salvati M, Pesce A, Palmieri M, Floriana Brunetto GM, Santoro A, Frati A. The role and real effect of an iterative surgical approach for the management of recurrent high-grade glioma: an observational analytic cohort study. World Neurosurg. 2019;124:e480–e8.

22. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. Neurosurgery. 2014;75(5):491–9 discussion 8-9.
23. Kanamori M, Kumabe T, Shibahara I, Saito R, Yamashita Y, Sonoda Y, Suzuki H, Watanabe M, Tominaga T. Clinical and histological characteristics of recurrent oligodendroglial tumors: comparison between primary and recurrent tumors in 18 cases. Brain Tumor Pathol. 2013;30:151–9.
24. Fallon KB, Palmer CA, Roth KA, Nabors LB, Wang W, Carpenter M, Banerjee R, Forsyth P, Rich K, Perry A. Prognostic value of 1p, 19q, 9p, 10q, and EGFR-RISH analyses in recurrent oligodendrogliomas. J Neuropath Exp Neurol. 2004;63(4):314–22.
25. Navarria P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, Galaverni M, Amelio D, Scartoni D, Scoccianti S, Krengli M, Masini L, Draghini L, Maranzano E, Borzillo V, Muto P, Ferrarese F, Fariselli L, Livi L, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). J Neurooncol. 2019;142(1):59–67.
26. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. J Clin Oncol. 2005;23(34):8863–9.
27. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. J Clin Oncol. 1999;17(9):2762–71.
28. Brada M, Stenning S, Gabe R, Thompson LC, Levy D, Rampling R, Erridge S, Saran F, Gattamaneni R, Hopkins K, Beall S, Collins VP, Lee SM. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. J Clin Oncol. 2010;28(30):4601–8.
29. Chamberlain MC. Salvage therapy with lomustine for temozolomide refractory recurrent anaplastic astrocytoma: a retrospective study. J Neurooncol. 2015;122(2):329–38.
30. Balana C, Alonso M, Hernandez A, Perez-Segura P, Pineda E, Ramos A, et al. SEOM clinical guidelines for anaplastic gliomas (2017). Clin Transl Oncol. 2018;20:16–21.
31.• van den Bent M, Klein M, Smits M, Reijneveld JC, French PJ, Clement PM, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol. 2018;19:1170-79.
This study demonstrates no benefit in OS, PFS or cognitive function with the addition of bevacizumab in patients with first contrast-enhancing recurrent non-codeleted lower grade glioma.
32. Han CH, Batchelor T. Isocitrate dehydrogenase mutation as a therapeutic target in gliomas. Chin Clin Oncol. 2017;6(3).
33. Youssef G, Miller JJ. Lower Grade Gliomas. Curr Neurol Neurosci Rep. 2020;20(7):21.
34. Gatto L, Franceschi E, Tosoni A, Di Nunno V, Maggio I, Lodi R, et al. IDH inhibitors and beyond: the cornerstone of targeted glioma treatment. Mol Diagn Ther. 2021;25(4):457–73.
35. Huang J, Yu J, Tu L, Huang N, Li H, Luo Y. Isocitrate dehydrogenase mutations in glioma: from basic discovery to therapeutics development. Front Oncol. 2019;9(506):506.
36. Fan B, Mellinghoff IK, Wen PY, Lowery MA, Goyal L, Tap WD, Pandya SS, Manyak E, Jiang L, Liu G, Nimkar T, Gliser C, Prahl Judge M, Agresta S, Yang H, Dai D. Clinical pharmacokinetics and pharmacodynamics of ivosidenib, an oral, targeted inhibitor of mutant IDH1, in patients with advanced solid tumors. Investig New Drugs. 2020;38:433–44.
37. Mellinghoff IK, Ellingson BM, Touat M, Maher E, De La Fuente MI, Holdhoff M, et al. Ivosidenib in isocitrate dehydrogenase 1-mutated advance glioma. J Clin Oncol. 2020;38:3398–406.
38. Mellinghoff IK, Penas-Prado M, Peters KB, Cloughesy TF, Burris H, Maher E, et al. ACTR-31. Phase 1 study of AG-881, an inhibitor of mutant IDH1 and IDH2: Results from the recurrent/progressive glioma population. Neuro Oncol. 2018;20(Suppl. 6):18.
39. Mellinghoff IK, Peters KB, Cloughesy TF, Burris H, Maher E, Janku F, et al. Vorasidenib (VOR; AG-881), an inhibitor of mutant IDH1 and IDH2, in patients (pts) with recurrent/progressive glioma: updated results from the phase I non-enhancing glioma population. JCO. 2020;38(15_suppl.2504):2504-.
40. Mellinghoff IK, Cloughesy TF, Wen PY, Taylor J, Maher E, Arrillaga-Romany I, et al. ACTR-66 A phase 1, open-label, periopereative study of ivosidenib (AG-120) and vorasidenib (AG-881) in recurrent IDH1 mutant, low-grade glioma: updated results. Neuro Oncol. 2019;21(Suppl_6):vi28-vi9.
41. Natsume A, Wakabayashi T, Miyakita Y, Narita Y, Mineharu Y, Arakawa Y, et al. Phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001b in patients with recurrent or progressive IDH1 mutant gliomas. J Clin Oncol. 2019;37(15_suppl):2004-.
42. Wick A, Bahr O, Schuler M, Rohrberg K, Chawla SP, Janku F, et al. Phase I assessment of safety and therapeutic activity of BAY1436032 in patients with IDH1-mutant solid tumors. Clin Cancer Res. 2021;27(10):2723–33.
43. Sulkowski PL, Corso CD, Robinson ND, Scanlon SE, Purshouse KR, Bai H, Liu Y, Sundaram RK, Hegan DC, Fons NR, Breuer GA, Song Y, Mishra-Gorur K, de Feyter HM, de Graaf RA, Surovtseva YV, Kachman M, Halene S, Günel M, et al. 2-Hydroxyglutarate produced by neomorphic IDH mutations suppress homologous recombination and induces PARP inhibitor sensitivity. Sci Transl Med. 2017;9(375):2463.

44. Sim HW, Galanis E, Khasraw M. PARP inhibitors in glioma: a review of therapeutic opportunities. Cancers (Basel). 2022;14(4):1003.
45. Higuchi F, Nagashima H, Ning J, Koerner MVA, Wakimoto H, Cahill DP. Restoration of temozolomide sensitivity by PARP inhibitors in mismatch repair deficient glioblastoma is independent of base excision repair. Clin Cancer Res. 2020;26:1690–9.
46. Wang Y, Wild AT, Turcan S, Wu WH, Sigel C, Klimstra DS, et al. Targeting therapeutic vulnerabilities with PARP inhibition and radiation in IDH-mutant gliomas and cholangiocarcinomas. Sci Adv. 2020;6(17):eaaz3221.
47. Ducray F, Sanson M, Chinot OL, Fontanilles M, Rivoirard R, Thomas-Maisonneuve L, et al. Olaparib in recurrent IDH-mutant high-grade glioma (OLAGLI). J Clin Oncol. 2021;39(15_suppl.2007):2007-.
48. Ramos R, Climans SA, Adile A, Ghiassi P, Baker S, Phillips MJ, et al. Combination olaparib and durvalumab for patients with recurrent IDH-mutated gliomas. J Clin Oncol. 2021;39(15_suppl).
49.• Platten M, Bunse L, Wick A, Bunse T, Le Cornet L, Harting I, et al. A vaccine strategy targeting mutant IDH1 in newly diagnosed glioma. Nature 2021;592(7854):463-8.
This is the first-in-human study demonstrating the safety and immunogenecity of IDH1 peptide vaccine in newly diagnosed grade 3 and 4 IDH mutant astocytoma.
50. Chukwueke UN, Wen PY. Use of the response assessment in neuro-oncology (RANO) criteria in clinical trials and clinical practice. CNS Oncol. 2019;8(1):CNS28.
51. Ellingson BM, Bendszus M, Boxerman J, Barboriak D, Erickson BJ, Smits M, Nelson SJ, Gerstner E, Alexander B, Goldmacher G, Wick W, Vogelbaum M, Weller M, Galanis E, Kalpathy-Cramer J, Shankar L, Jacobs P, Pope WB, Yang D, et al. Consensus recommendations for a standardized brain tumor imaging protocol in clinical trials. Neuro Oncol. 2015;17(9):1188–98.
52. Jo J, van den Bent MJ, Nabors B, Wen PY, Schiff D. Surveillance imaging frequency in adult patients with lower-grade (WHO grade 2 and 3) gliomas. Neuro Oncol. 2022;24:1035–47.

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