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Surveillance imaging frequency in adult patients with lower-grade (WHO Grade 2 and 3) gliomas

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Abstract

With improved outcome following aggressive treatment in patients with grade 2 and 3 IDH-mutant (IDHmt), 1p/19q codeleted oligodendroglioma and IDHmt, non-codeleted astrocytoma, prolonged surveillance is desirable for early detection of tumor growth and malignant transformation. Current National Comprehensive Cancer Network (NCCN) guidelines provide imaging follow-up recommendations based on molecular classification of lower-grade gliomas, although individualized imaging guidelines based on treatments received and after tumor recurrence are not clearly specified. Other available guidelines have yet to incorporate the molecular biomarkers that inform the WHO classification of gliomas, and in some cases do not adequately consider current knowledge on IDHmt glioma growth rate and recurrence patterns. Moreover, these guidelines also do not provide specific recommendations for concerning clinical symptoms or radiographic findings warranting imaging studies out of prespecified intervals. Focusing on molecularly defined grade 2 and 3 IDHmt astrocytomas and oligodendrogliomas, we review current knowledge of tumor growth rates and time to tumor progression for each tumor type and propose a range of recommended MRI surveillance intervals for both the newly diagnosed and recurrent tumor setting. Additionally, we summarize situations in which imaging is advisable outside of these intervals.

Keywords

astrocytoma | imaging | IDH mutated glioma | lower-grade glioma | oligodendroglioma

Background and Importance

Recent changes in glioma classification and data on the growth and recurrence rate of gliomas warrant a reassessment of commonly utilized guidelines addressing frequency of MRI surveillance of these tumors during and following treatment. Herein we will address "lower-grade gliomas" (LrGG), a term that came into widespread use several years ago, based upon the recognition that most nonglioblastoma diffuse gliomas harbor mutations of the isocitrate dehydrogenase (*IDH*) gene and share a much more favorable prognosis than glioblastoma. Prior to the release of the 2021 WHO classification, LrGG referred to grades II and III astrocytomas and oligodendrogliomas.[1,2] The 2021 WHO classification includes three fundamental types of diffuse gliomas: IDH-mutant (IDHmt) astrocytoma, IDHmt, and 1p/19q codeleted oligodendroglioma, and IDH-wild type (IDHwt) glioblastoma.[3] All IDHmt astrocytomas are considered a single type and are graded as WHO grade 2, 3, or 4. In comparison, the 2016 WHO classification assigned different grading to each glioma

types: IDH mutation and 1p/19q codeletion oligodendroglioma (IDHmt/codeleted WHO, grades II and III), diffuse astrocytoma with IDH mutation without 1p/19q codeletion (IDHmt/non-codeleted grades II-IV), and those lacking IDH mutation (IDH wild type, grade II-IV).[1,2,4] The presence of *CDKN2A/B* homozygous deletion has been associated with shorter survival in patients with IDHmt astrocytoma, having clinical behavior similar to WHO grade 4.[5–7] In the 2021 WHO classification, the presence of *CDKN2A/B* homozygous deletion in IDHmt astrocytoma is currently recognized as "Astrocytoma, IDH-mutant, grade 4", even in the absence of microvascular proliferation or necrosis.[3,5,6] Due to the significant difference in the outcome of IDHmt versus IDHwt LrGG and IDHmt grade 4 astrocytoma, our discussion will be focused on IDHmt LrGG. In this review, we will refer to LrGG as grade 2 and 3 (as opposed to grade II and III) in accordance with the 2021 WHO classification.

Significant therapeutic advances have been made in the management and outcome of patients with LrGG. Despite a lack of randomized controlled trials (RCT), several retrospective studies demonstrated improvement of survival and reduced risk of early malignant transformation with early complete surgical resection.[8–11] Most recently, several RCTs have demonstrated improvement of progression-free survival (PFS) and overall survival (OS) in newly diagnosed LrGG with adjuvant radiation therapy (RT) and chemotherapy.[1,12]

With improved survival following aggressive treatment, patients with LrGG can anticipate prolonged follow-up. The aim of surveillance after initial diagnosis and treatment, as well as after treatment for recurrent or progressive tumor, is to detect tumor growth or malignant transformation before symptoms develop and neurological function is irreparably compromised. In general, earlier growth detection and recognition of smaller tumor volume are desirable in permitting smaller radiation fields, safer surgical resection, less neurological morbidity, and presumably improved survival.[1,12,13]

Several retrospective studies have examined the value of surveillance imaging in pediatric CNS tumors and suggest greater benefit in low-grade than in high-grade tumors.[14–18] A small retrospective, single-institution study of adults with glioblastoma and anaplastic glioma failed to identify improved outcomes in patients with recurrence detected on routine surveillance imaging compared to detection at symptomatic recurrence.[19] This finding, if confirmed, could be due to the limited life-extending treatment options at recurrence in patients with glioblastoma and IDHwt anaplastic glioma.

To date, the optimal frequency and serial imaging follow-up studies for LrGG are not well-defined.[20] National Comprehensive Cancer Network (NCCN) guidelines advocate follow-up MRI every 3–6 months for 5 years then at least every 6–12 months or as clinically indicated thereafter for grade 2 glioma. For grade 3 glioma, MRI every 2–4 months for 3 years then every 3–6 months indefinitely is the recommendation.[21] Another imaging guideline utilized by many American health insurers is the Evicore Healthcare imaging policy. Evicore recommends surveillance MRI every 3 months for 2 years, every 6 months for 3 years, then annually for patients with grade 2 glioma; while those with grade 3 glioma should have MRI every 3 months for 3 years and every 6 months thereafter.[22] There are no clear recommendations on imaging follow-up after recurrence of LrGG in the Evicore policy.[22] NCCN recommends MRI every 2–3 months while on treatment for recurrent grade 2 glioma, then every 6 months indefinitely; no guideline for recurrent grade 3 gliomas was specified.[21] Consequently, the clinician's ability to order MRIs believed clinically indicated is sometimes administratively constrained. The Evicore guideline does not clearly specify individualized recommendations for follow-up studies based on molecular classification, notwithstanding the lower rate of relapse following treatment in patients with 1p/19q codeleted LrGG compared to those with 1p/19q intact tumors, arguably impacting subsequent radiographic surveillance.[1] Additionally, these guidelines do not provide evidence supporting their suggested decreased frequency of imaging surveillance the further from initial glioma diagnosis. Thus, these widely employed guidelines warrant revisiting.

The determination of the optimal timing of surveillance to maximize detection while minimizing unnecessary, uninformative imaging studies requires analysis of available data on the time and pattern of relapse as well as the risk factors associated with early recurrence. The primary purpose of this manuscript is to review the current data and propose recommendations regarding the optimal frequency for a longitudinal imaging study of IDHmt grade 2 and 3 gliomas, acknowledging that the absence of prospective studies and limitations of existing data limit the level of evidence to expert opinion.

Synthesis of Evidence and Recommendations on Imaging Surveillance

Astrocytoma and Oligodendroglioma WHO Grade 2

Despite the typically relatively indolent behavior of IDHmt grade 2 glioma, progression is unpredictable and varies considerably with median PFS ranging from 3 to 10 years after initial diagnosis and treatment with RT and/or chemotherapy.[23–26] Three stages of clinical and radiographic evolution of diffuse grade 2 gliomas have been proposed: (1) Pre-symptomatic stage: unknown duration of disease, where the tumor is discovered incidentally; (2) Symptomatic stage: about 4–10 years after initial diagnosis or presentation and treatment[23]; and (3) Transformational stage: about 2–3 years of a more rapid tumor progression into higher-grade gliomas.[27,28]

Serial imaging studies.—All available quantitative studies of radiological growth of grade 2 glioma report a spontaneous and continuous growth pattern (Table 1). Analysis of mean tumor diameters (MTD) of patients with untreated grade 2 glioma demonstrated constant tumor growth at a rate of 4.1 mm/year during their premalignant phase.[29] The same authors subsequently demonstrated an inverse correlation between growth rates and survival, with a median survival of 5.16 years in patients with a growth rate of >8 mm/year, and more than 15 years for those with a

Table 1 Serial Imaging Studies on Diffuse Glioma WHO Grade 2

Authors/Year	Patient population	Molecular studies	Description of the study	Outcome/Conclusion
Mandonnet et al. 2003[29]	27 untreated grade 2 O, A, and OA	Not performed	- Retrospective review of tumor growth kinetic before anaplastic malformation. - Median duration of radiological follow-up was 4.75 years.	- Continuous relatively constant growth rate during pre-malignant phase - Mean MTD: 4.1 mm/year (95% CI: 3.8–4.4 mm/yr) - Interpretation is limited due to lack of molecular data
Pallud et al. 2006[30]	143 untreated grade 2 O, A, and OA	Not performed	- Retrospective review to assess the prognostic value of MTD growth rates on successive MRI. - Median duration of repeated tumor measurement was 21.7 months. - Median duration of clinical follow-up was 6.5 years.	- Inverse correlation between growth rates and survival - Median survival: 5.16 years for growth rate of >8 mm/year >15 years for growth rate of <8 mm/year ($P < .001$) - Interpretation is limited due to lack of molecular data
Pallud et al. 2013[31]	407 newly diagnosed grade 2 O, A and OA	IDH mutated in 25/32 patients 1p/19q codeleted in 67/205 patients	- Retrospective study to assess whether spontaneous VDE can predict long-term outcomes - Mean follow-up was 86.5 months	- Mean spontaneous VDE before first-line treatment:5.8+ 6.3 mm/yr. - VDE as a categorical variable (<4, >4 and <8, >8 and <12, >12 mm/yr) was an independent prognostic factor for malignant-free survival and OS; also an independent prognostic factor for OS as a continuous predictor - Spontaneous VDE was slower in codeleted tumors and complete 1p deletion; significantly faster in tumors with p53 overexpression
Hlaihel et al. 2010[32]	22 grade 2 gliomas	Not performed	- Longitudinal study to determine the role of conventional, perfusion and MRS in early detection of malignant transformation	- Mean annual growth rate: 3.65 mm/yr - Growth rate of >3 mm/yr correlated with greater risk of anaplastic transformation: VDE 7.87 mm/year in transformer versus 2.14 mm/year in nontransformer groups - Interpretation is limited due to lack of molecular data
Peyre, et al. 2010[33]	21 grade 2 gliomas treated with PCV	1p/19q codeleted in 4 out of 6 patients	- Retrospective study to evaluate the tumor kinetic growth with first line PCV	- Median MTD during PCV was –10.2 mm/year (-1 to –23 mm/yr); After PCV discontinuation, –4 mm/yr (–1.2 to –15.4 mm/yr) - Mean duration of MTD after PCV onset was 3.4 yrs (0.8–7.7 yrs); 2.7 yrs (0–7 yrs) after discontinuation - 3 of 4 codeleted patients treated showed decreasing MTD at 3.8, 4.8 and 7.5 yrs after PCV onset; 1 patient progressed after completion of PCV -2 non-codeleted patients showed decreased MTD for 2 and 3 years
Mazzocco, et al. 2015[34]	77 grade 2 gliomas treated with TMZ	IDH mutated in 35/54 patients 1p/19q codeleted in 23/70 patients P53 overexpression in 24/59 patients	- Retrospective study to assess whether combining longitudinal tumor size quantitative modeling with a tumor's genetic characterization is an effective means of predicting response to TMZ	- After TMZ onset, MTD decreased by 75% followed by a MTD re-increase. - Median time-to-tumor progression:14.5 months. - P53 and 1p/19q status and tumor observations obtained during first 3 months after TMZ onset correctly predicted tumor response for 2 years, but not beyond 2 years. - IDH mutation status alone did not provide useful information on tumor size dynamics
Pallud et al. 2012[35]	33 supratentorial grade 2 gliomas	IDH mutated in 23/27 patients P53 overexpression in 16/27 patients	- Retrospective study to assess the VDE changes following RT	- Before RT: tumor volume increased in all patients (positive VDE, mean 5.9 mm/yr). - After RT: tumor volume decrease was observed (negative VDE, mean –16.7 mm/yr) during a mean 49-month duration - Lack of IDH mutation, p53 overexpression, large initial tumor volume, and post-RT VDE fast responder were independent prognostic factor of shorter OS
Taal et al. 2015[36]	32 grade 2 O, OA and large and/or multilobe tumors	1p/19q codeleted in 18/32 patients	- Retrospective review to assess whether first-line PCV improves outcome to delay RT	- Median OS: 10 years - Median PFS: 3.8 years - ORR: 72% - 1p/19q codeleted patients: median PFS 5.6 years; median OS: NR after median follow-up of 8.9 years; ORR 78%

Table 1 Continued

Authors/Year	Patient population	Molecular studies	Description of the study	Outcome/Conclusion
Mandonnet et al. 2010[37]	54 grade 2 O, A, and OA, who underwent partial resection	Not performed	- Retrospective review to assess the radiological postoperative kinetics after surgical resection - Median postoperative follow-up was 1.6 years	- Mean growth after partial resection: 4.2 mm/year - Growth rates were grossly unchanged for 80% of cases before and after surgery. - Interpretation is limited due to lack of molecular data
Rees et al. 2009[38]	27 untreated grade 2 O, A, and OA	Not performed	- Prospective study to establish whether measurement of tumor volume and growth can help identify those at high risk of clinical or radiological transformation - Median duration of follow-up from transformation was 23 months	- Average risk of transformation to higher grade was 26% (95% CI 20–31%) per annum in up to 6 months prior to transformation; risk increased to 56% per annum in the final 6 months prior to transformation. - Increased probability of transformation with increasing time from presentation by 9.4% per year (95% CI 2–18%) - Interpretation is limited due to lack of molecular data
Brasil Caseiras, et al. 2009[39]	34 untreated grade 2 O, A, and OA	Not performed	- Prospective study comparing tumor volume, rCBV, and ADC and short-term changes of these parameters as predictors of time to malignant transformation and time to death - Median follow-up was 2.6 years	- 6-month tumor growth helps predict outcome better than rCBV, ADC, age, sex, and histologic findings. - Threshold tumor growth volume of 6.21 mL of growth with mean time of progression of 3.91 years versus 1.82 years - Interpretation is limited due to lack of molecular data
Hathout et al 2015[40]	30 contrast-enhancing grade 2 astrocytomas that underwent tumor progression	Not performed	- Retrospective review to test whether tumor growth kinetics could identify tumors that undergo malignant transformation to higher grades	- Radial expansion rates for both contrast-enhancing ($P = .0040$) andT2 hyperintense regions ($P = .0016$) were significantly higher in those that transformed to GBM than nontransformers - Interpretation is limited due to lack of molecular data
Huang et al. 2020[41]	230 IDHmt, Grade 2 & 3 treated with surgery, RT and chemotherapy	1p/19q codeleted in 118/186 patients	- Retrospective study investigating the volumetric growth pre- and post-treatment to determine whether a significant change in growth rate can serve as imaging endpoint to indicate treatment effect	- Pre-treatment volumetric growth rate: 27.37% per 6 months (95% CI: 23.36–31.51%) - Mean growth rate from the first 2 pretreatment time points: 22.98% per 6-month (95% CI: 18.07–28.10%) versus later 2 time points 33.73% per 6-month (95% CI: 27.83–39.90%; $P = .004$) - Among 95 patients with pre- and post-treatment MRI, volumetric growth rates before treatment 26.63% (95% CI 19.31, 34.40%) and after treatment –15.24% (95% CI: –21.37%, –8.62%; $P < .0001$). - Percentage change in pre- and post-treatment growth rate were not significantly associated with OS (HR = 1.004 for each percent increase, $P = .2093$) or PFS (HR = 1.001, $P = .5611$) - Patients with non-codeletion had a faster mean growth rate versus codeleted group.
Ricard et al 2007[42]	107 grade 2 glioma	1p/19q codeleted in 32/68 patients P53 overexpression in 19/49 patients	- Retrospective study to compare the kinetics of tumor growth before and afterTMZ and to correlate with molecular profile	- BeforeTMZ, mean MTD is slower in 1p/19q codeleted tumors (3.4 vs 5.9 mm/yr; $P = .0016$) and in tumors that did not overexpress p53 (4.2 vs 6.3 mm/yr; $P = .05$) - DuringTMZ, 92% of all patients experience decreased MTD - Lower rate of relapse in 1p/19q codeleted tumors (16.6 vs 58%; $P = .0004$) and in tumors that did not overexpress p53 (26 vs 68%; $P = .003$)

O, Oligodendroglioma; A, Astrocytoma; OA, Oligoastrocytoma; CI, Confidence interval; LGG, Low-grade glioma; IDHmt, IDH mutant; rCBV, relative cerebral blood volume; ADC, Apparent diffusion coefficient; GTR, Gross total resection; PFS, Progression free survival; OS, Overall survival; RT, radiation therapy; TMZ, temozolomide; PCV, procarbazine, CCNU, and vincristine; MTD, mean tumor diameter; VDE, velocity of diametric expansion; ORR, Objective response rate

growth rate of <8 mm/year.[30] Spontaneous velocity of diametric expansion (VDE) also predicted long-term outcomes. The malignant PFS (MPFS) and OS were significantly longer in patients with slow versus those with fast VDE[31,32]; VDE of >3 mm/year was associated with a greater risk of malignant transformation.[32] Untreated IDHmt grade 2 gliomas with 1p/19q codeletion grow significantly slower than those without codeletion (MTD growth 3.4 versus 5.9 mm/year; $P = .0016$).[42] Treatment of diffuse glioma impacts tumor growth kinetics, with a decrease in MTD in patients treated with either procarbazine, CCNU, vincristine (PCV) regimen, temozolomide, or RT.[33–36,42,43] In contrast, the growth rate of residual tumor following partial resection was not statistically different from the pre-operative growth rates.[37] For a subset of patients with a delay between their first MRI and surgery, the intra-patient comparison of pre-operative and postoperative growth rates prior to other therapies were grossly unchanged in 80% of cases, suggesting surgery does not influence the residual tumor kinetics.[37] Furthermore, the PFS, OS, and MPFS were not significantly different when subtotal surgery was performed before or after symptom occurence.[44]

Evidence supports a nonlinear growth rate pattern of grade 2 gliomas, with a significant increase in tumor growth in the final 6 months before malignant transformation.[13,38] Tumors in patients with early malignant transformation had an average annual tumor volume growth rate of 26% prior to the 6 months prior to transformation, increasing to 56% per annum in the final 6 months prior to transformation.[38] The probability of early transformation increases with increasing tumor volume; for every 10% increase in volume, the risk of transformation increased by 29%.[38] Another study determined a tumor volume growth threshold of 6.21 ml within 6 months as a predictor of time to malignant transformation.[39] Further supporting this evidence, patients whose tumors transformed to grade 4 showed a very rapid, dramatic changes in both contrast-enhancing and T2 hyperintense regions when MRIs were evaluated at the time leading up to recurrence, compared to those progressing to grade 3 astrocytoma or to nontransforming at recurrence.[40] Moreover, a continuous growth pattern with accelerating, positive mean growth rates were observed prior to treatment of patients with IDHmt LrGG (22.98% per 6-month between the first two time points; 33.73% per 6-month from the later time points).[41]

Therapeutic studies.—Patients with low-risk grade 2 glioma (adults <40 years old who underwent gross total resection), showed PFS at 2 and 5 years of 82% and 48%, respectively and a median PFS of 4.9 years without adjuvant treatment.[45] For patients with high-risk grade 2 glioma (defined in RTOG 9802 as patients age <40 with less than complete resection or patients >40 years of age; EORTC 22033 as those with age >40 years, progressive disease, tumors >5 cm or crossing the midline, neurological symptoms), phase III trials demonstrated a significant prolongation of both PFS and OS with the combination of radiation and chemotherapy (Table 2).[23,24]

In RTOG 9802, patients receiving RT followed by PCV had a PFS of 10.4 years compared to 4 years in those receiving RT alone.[23,25] Forty-two percent (106/251) of patients were profiled for WHO-defined molecular groups.[26] Treatment with postradiation chemotherapy was associated with longer PFS in the IDHmt/codeleted (not reached versus 5.8 years) and IDHmt/non-codeleted group (10.4 years versus 3.3 years). The 2-year and 5-year PFS in patients with IDHmt/codeletion who received RT/PCV were approximately 95% and 90%, respectively; the PFS plateaus at 80% after 6 years of treatment. Those who received RT alone demonstrated similar 2-year PFS, but a lower PFS of 60% at 5 years, with a decreasing pattern beyond 6 years.[26] In patients with IDHmt/non-codeletion, the PFS at 2 years was similar (approximately 75%). However, the 5-year PFS was significantly higher in RT/PCV group compared to the RT group (approximately 60% versus 20%).[26] The PFS remains at approximately 50% beyond 6 years after treatment with RT/PCV.[26]

In the EORTC 22033-26033 study, the median PFS was not statistically different between patients who received RT alone versus temozolomide alone (3.8 years in RT arm versus 3.25 years in temozolomide arm), after a median follow-up of 4 years.[24] An improved outcome (median PFS: 5.2 years) in patients with IDHmt/codeletion, independent of treatment, compared to patients with non-codeleted IDHmt glioma (median PFS: 4 years) was observed.[24] The 2-year PFS was approximately 73% and 80% in patients with IDHmt/non-codeletion and with codeletion, respectively. Within 5 years, almost 70% of patients with IDHmt/non-codeletion and 50% of those with codeletion have progressed.[24]

RTOG 0424 compared the 3-year OS of patients who received RT with temozolomide to patients who received RT alone from historical controls.[46] With a median follow-up of 9 years, the median PFS of patients who received RT and temozolomide was 4.5 years, while the 3- and 5-year PFS was 59.2% and 46.8%, respectively.[46] No IDH analysis has been reported in this study.

Recommendations for imaging monitoring.—In the aforementioned studies, the median time to tumor progression was greater than 2 years after treatment initiation either with RT alone (PFS of 4 years in RTOG 9802 and 3.8 years in EORTC 22033), RT with chemotherapy (10.4 years in RTOG 9802), and chemotherapy alone (3.25 years in EORTC 22033). Therefore, these data do not support existing guideline recommendations to reduce frequency of monitoring after 2 years in patients who did not receive both RT and chemotherapy. For example, in RTOG 9802, 39% of patients treated with RT and PCV and 56% who received RT alone experienced tumor progression within 5 years, with one-quarter of patients in each arm developing tumor progression within 2 years.[23,25] Among patients with low-risk grade 2 glioma as defined in RTOG 9802, more than 50% developed tumor progression within 5 years postsurgery, emphasizing the desirability of close follow-up beyond the first two years postsurgery if no further postsurgical treatment is given.[45] Nevertheless, among patients with IDH mutation who received both RT and PCV, available data based upon small patient numbers demonstrate improved PFS above 50% 10 years after treatment initiation,[26] suggesting less intensive initial monitoring is reasonable.

Taken together, in patients with IDHmt grade 2 glioma who received both upfront RT and PCV, MRI monitoring

Table 2. Therapeutic Studies on Diffuse Glioma WHO Grade 2

Study	Study type	Patients, Treatments and Median follow-up	Frequency of surveillance imaging	Outcome/Conclusion
RTOG 9802[23,25,26]	Phase III RCT	N=251 High-risk grade II astrocytoma, oligodendroglioma & oligoastrocytoma Treatments: RT vs RT + PCV x 6 cycles Median follow-up: 11.9 yrs	MRI with and without contrast before cycle 3 and cycle 5 of PCV, then every 4 months for 1 year, every 6 months for 2 years, every year thereafter until tumor progression	- Median OS: RT+PCV 13.3 yrs vs RT 7.8 yrs (HR 0.59; $P = .003$) - Median PFS: RT+PCV 10.4 yrs vs RT 4 yrs (HR 0.50; $P =< .001$) - 5-yr PFS: RT+PCV 61% vs RT 44% - 5-yr OS: RT+PCV 72% vs RT 63% - Median OS: 13.1 yrs in IDHmt vs 5.1 yrs in IDHwt ($P = .02$) - Median PFS: 7.6 yrs in IDHmt vs 1.4 yrs in IDHwt ($P = .003$) **IDHmt, 1p/19q codeleted patients** ($n = 37$): RT+PCV vs RT - PFS: NR vs 5.8 years (HR, 0.13; 95% CI, 0.04–0.44, $P < .001$) - OS: NR vs 13.9 years (HR, 0.21; 95% CI, 0.05–0.98, $P = .03$) **IDHmt, 1p/19q non-codeleted** ($n = 43$): RT+PCV vs RT - PFS: 10.4 vs 3.3 yrs. (HR, 0.32; 95% CI 0.15–0.69, $P = .003$) - OS: 11.4 vs 4.3 yrs (HR, 0.38; 95% 0.18–0.84, $P = .01$)
EORTC 22033[24]	Phase III RCT	N=477 High-risk grade II astrocytoma, oligodendroglioma & oligoastrocytoma Treatments: RT vs dose dense temozolomide (75 mg/m2 x 21 days every 28 days) Median follow-up: 4 years	MRI with and without contrast every 6 months after treatment initiation until progression	- Median PFS: RT 46 mos. (3.8 yrs) vs TMZ 39 mos. (3.25 yrs) (HR 1.16; $P = .22$) - Median OS: still immature **Median PFS of molecular subtypes and treatments received:** - IDHmt/codeleted ($n = 104$): 55 mos (4.5 yrs) TMZ vs 61.63 mos (5.1 yrs) RT ($P = .91$) - IDHmt/non-codeleted ($n = 165$): 36 mos (3 yrs) TMZ vs 55.36 mos. (4.6 yrs) RT ($P = .0043$)
RTOG 0424[46]	Phase II	N= 129 High-risk grade II astrocytoma, oligodendroglioma & oligoastrocytoma Treatments: RT (54 Gy in 30 fractions) and concurrent and adjuvant temozolomide Median follow-up: 6.8 years for all patients, 9 years for living patients	MRI with and without contrast 4 weeks post-RT, every 3 months during chemotherapy, every 6 months for 2 years, annually thereafter	- 3-yr OS: 73.5% (95% CI: 65.8–81.1%) versus prespecified historical control values of 54% ($P < .001$) - 3-yr PFS: 59.2% - Median PFS: 4.5 years - Median OS: 8.2 years (95% CI, 5.6–9.1)
RTOG 9802[45]	Phase II observation study	$N = 111$ grade II O, A, and OA, who underwent GTR Median follow-up duration was 4.4 years	MRI every 6 months	- 2-yr OS rate was 99% and 5-year OS rate was 93% - 2-yr PFS rates was 82% and 5-yr PFS was 48% - Young adults who undergo GTR have a >50% risk of tumor progression 5-years postoperatively, warranting close follow-up and consideration for adjuvant therapy

O, Oligodendroglioma; A, Astrocytoma; OA, Oligoastrocytoma; RCT, Randomized controlled trial; OS, Overall survival; PFS, Progression free survival; PCV, procarbazine, CCNU, and vincristine regimen; TMZ, temozolomide; RT, Radiation therapy; NR, not reached; GTR, Gross total resection

at least every 6 months for patients with non-codeletion and every 6–9 months for those with codeletion until first tumor progression is a rational approach. In those who received RT alone or chemotherapy alone, the data support MRI monitoring as often as every 3–4 months in the first 5 years, then as frequently as every 3–4 months but not longer than every 6 months after 5 years from completion of treatment until tumor progression. For those treated with RT and temozolomide, we recommend following guidelines for grade 3 IDHmt astrocytomas (vide infra). Evidence suggests that without postoperative antineoplastic therapy, growth kinetics of the residual tumor are unchanged.[37,44] Consequently, MR surveillance imaging as often as every 3–4 months until tumor progression is recommended in patients treated with surgery only. In patients with completely resected IDHmt/codeleted grade 2 oligodendroglioma, decreasing MRI monitoring to every 6–9 months 5 years postsurgery is also an appropriate approach (Table 4).

Astrocytoma and Oligodendroglioma WHO Grade 3

Oligodendroglioma, IDHmt/codeleted, grade 3.—Two large phase III studies have proven that the addition of PCV to radiation prolongs PFS and OS in patients with grade 3 oligodendroglioma (Table 3).[47–50,54,55] In RTOG 9402, long-term analyses demonstrated that PCV/RT significantly prolonged PFS compared to RT alone in IDHmt/codeleted (9.8 vs 2.9 years). The 5- and 10-year PFS rate of patients with IDHmt/codeletion who received PCV was 62% and 50%, respectively.[48] Similarly, EORTC 26951 reported a significant improvement in both PFS and OS with the addition of adjuvant PCV to RT.[49,50] Among patients with IDHmt/codeletion, the 20-year PFS and median PFS were significantly improved at 31.3% and 13.1 years, respectively in the RT/PCV group compared to 10.8% and 4.2 years, respectively in RT alone group.[49,50] In a large retrospective study, patients with 1p/19q codeletion had prolonged time-to-tumor progression (TTP) of 7.2 years after receiving RT and chemotherapy (either PCV or temozolomide) compared to 3.9 years with chemotherapy alone and 2.5 years with RT alone.[51] The NOA-04 study compared the efficacy and safety of initial RT followed by chemotherapy at progression (Arm A) versus chemotherapy followed by RT at recurrence (Arm B).[52] Among patients with IDHmt/codeletion, the PFS was 8.7 years with RT, 9.4 years with PCV, and 4.5 years with temozolomide.

Astrocytoma, IDHmt, grade 3.—Patients with IDHmt grade 3 astrocytoma have a worse outcome compared to patients with grade 3 oligodendroglioma. In the NOA-04 study, time-to-treatment-failure (TTF) was 4.5 years in patients with IDHmt/non-codeletion versus 9.8 years in those with codeletion. Approximately 45% and 75% of patients with IDHmt/non-codeletion progressed after 2 and 5 years, respectively from treatment initiation, as compared to approximately 25% and 40%, respectively in those with codeletion.[52] After treatment with both RT and PCV, the median PFS in patients with IDHmt/non-codeleted grade 3 astrocytoma was 2.8 years, compared to 1.9 years after RT alone in the RTOG 9402 study.[48] The phase III CATNON trial randomized patients with non-codeleted grade 3 glioma to receive RT, RT with concurrent temozolomide, RT followed by adjuvant temozolomide for 12 cycles, or RT with concurrent and adjuvant temozolomide. In the 67% of patients with IDH mutation, the median PFS of patients receiving any temozolomide was significantly prolonged to 6.4 years, compared to 2.85 years in those treated with RT only. Approximately 23% and 45% of patients with IDH mutation who received temozolomide, and 43% and 70% of those treated with RT alone experienced progression in 2 and 5 years, respectively.[53]

A recent study utilized parametric modeling and recursive partitioning analysis to propose MRI schedules for grade 3 astrocytoma and glioblastoma, stratified by the presence of measurable residual tumor, MGMT methylation, and IDH mutational status.[56] A piecewise exponential distribution, with a criterion of 10% progression rate among the remaining patients at each observation, was used to model the standardized PFS curves to determine the optimal intervals for MRI assessments. Two-thirds of the 99 patients harbored IDHmt grade 3 astrocytoma. Following completion of RT with or without chemotherapy for the entire IDHmt group, the algorithm proposed MRIs at 9.5-month intervals for a 4.6-year surveillance period. A shorter interval of 6.7 months for those with residual tumors and a considerably extended interval of 1.7 years for patients without residual disease were recommended. This small retrospective study requires validation and may be best suited for grade 3 astrocytoma patients predicted to have a favorable outcome.[56,57]

Recommendations for imaging monitoring.—Available data from RCTs demonstrate significant improvement of outcome with upfront RT and chemotherapy, which has become the standard of care in patients with newly diagnosed IDHmt grade 3 gliomas. Patients with grade 3 oligodendroglioma treated with both RT and PCV have a prolonged median survival up to 13-14 years and PFS of 10–13 years.[48,50] In comparison, the median survival is 4–9 years and PFS of 2–6 years in patients with IDHmt grade 3 astrocytoma.[48,53]

Data support MRI monitoring at least every 6–9 months until tumor progression in patients with grade 3 oligodendroglioma and every 6 months in patients with grade 3 astrocytoma who received combined upfront RT and chemotherapy. In those treated with either RT alone or chemotherapy alone, more frequent monitoring every 3–4 months for the first 5 years after completion of treatment, then as often as every 3–4 months, but generally not longer than every 6 months until tumor progression is advisable. In patients with IDHmt grade 3 astrocytoma treated with either RT or chemotherapy alone, MRI monitoring as often as every 3–4 months until tumor progression is reasonable due to earlier tumor progression (Table 4).

Recurrent IDH-Mutant Lower Grade Gliomas

Despite the prolonged median survival with combined chemoradiation in IDHmt LrGG, emerging evidence indicates that IDHmt gliomas are capable of progressing from an indolent course to an accelerated malignant course. A retrospective study of 275 patients with IDHmt LrGG

Table 3 Therapeutic Studies of WHO Grade 3 Glioma

Study	Study type	Patients, Treatments and Median follow-up	Frequency of surveillance imaging	Outcome/Conclusion
RTOG 9402[47,48]	Phase III RCT	*N* = 289 AO and AOA Treatments: PCV q6 weeks x 4 cycles followed by RT versus RT alone Median follow-up: 16.4 yrs (Abstract SNO 2019); 11.3 yrs (2013 report)	MRI or CT scans before each cycle and 4–6 weeks after RT; thereafter, scans were done at increasing intervals, and after 5 years, annually, or as needed	- Initial report (2013): mOS: PCV+RT 4.6 vs RT 4.7 yrs (HR = 0.79; 95%CI,0.60–1.04, *P* = .1) **IDHmt, 1p/19q codeleted:** PCV+RT vs RT(2019 report) - PFS: 9.8 yrs vs 2.9 yrs (HR 0.46, 95% CI 0.3–0.7, *P* < .001) - OS:13.2 vs 7.3 yrs (HR 0.61, 95% CI 0.40–0.94; *P* = .02) **IDHmt, 1p/19q non-codeleted:** PCV+RT vs RT(2019 report) - PFS:2.8 vs. 1.9 yrs (HR 0.58, 95% CI 0.34–0.99, *P* = .046) - OS: 5.5 vs. 3.3 yrs (HR 0.6, 95% CI 0.34–1.03, *P* = .06)
EORTC 26951[49,50]	Phase III RCT	*N* = 368 AO and AOA Treatments: RT followed by PCV q6 weeks x 6 cycles (59.4 Gy) versus RT alone Median follow-up: 18.4 yrs (Abstract SNO 2019); 11.6 years (2013 report)	MRI at baseline and at q3 months until progression	- 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* = .06) - 20-yr survival: 16.8% versus 10% (HR 0.78, 95% CI 0.63–0.98; adjusted *P* = .06) (2019 report) **IDHmt, 1p/19q codeleted** (*n* = 80): PCV+RT vs RT (2019 report) - 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* = .007)
Lassman, et al. (2011)[51]	Retrospective study	*N* = 1013 AO and AOA PCV alone vs TMZ alone; RT/PCV vs RT/TMZ Median follow-up: 5.2 years for median OS; 4 years for median TTP	Not mentioned	- 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* = .003) vs 2.5 yrs (*P* < .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* = .019) **1p/19q non-codeleted:** CT+RT vs CT vs RT - TTP: 3.1 yrs vs 0.9 yrs (*P* = .0124) vs 1.1 yrs (*P* < .0001) - OS: 5 yrs vs 2.2 yrs (*P* = .02) vs 1.9 yrs (*P* < .0001)
NOA-04[52]	Phase III RCT	*N* = 318 Anaplastic glioma Treatment: RT with chemotherapy (PCV or TMZ) deferred until progression versus Chemotherapy (PCV or TMZ) with RT deferred until progression Arm A=RT→chemotherapy Arm B1=PCV→ RT Arm B2=TMZ→ RT Median follow-up: 9.5 years	MRI 4 weeks after completing radiotherapy and every 3-4 months thereafter.	- 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 3 Continued

Study	Study type	Patients, Treatments and Median follow-up	Frequency of surveillance imaging	Outcome/Conclusion
CATNON[53]	Phase III RCT	N=751 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 Median follow-up: 55.7 months (4.67 years)	MRI 4 weeks after the end of RT and every 3 months thereafter until progression	**RT alone versus RT with adjTMZ** - 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; $P < .0001$) - PFS: 19.1 mos or 1.6 yrs vs 42.8 mos or 3.6 yrs ($P < .0001$) **RT with versus without concTMZ** - 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; $P = 0.464$) - PFS: 33 mos 2.75 yrs vs 20.9 mos or 1.74 yrs ($P = .045$) **IDH mutant** (444/660 patients; 67%) - RT with adjTMZ vs RT with concurrent/adjuvant TMZ: 5-yr OS 80.5% vs 82.8% (HR 0.82; 95% CI 0.49–1.36; $P = .44$) - RT with concTMZ vs RT with concurrent/adjuvant TMZ: 5-yr OS 64.8% vs 82.8% (HR 0.49; 95% CI 0.30–0.81; $P = .0050$) - 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; $P < .0001$) PFS: 77 mos or 6.4 yrs vs 34.2 mos or 2.85 yrs (HR 0.48; 95% CI 0.37–0.63; $P < .0001$)

AO, Anaplastic oligodendroglioma grade 3; AOA, Anaplastic oligoastrocytoma grade 3; RCT, Randomized controlled trial; OS, Overall survival; PFS, Progression free survival; TTP, time-to-tumor progression; TTF, time-to-treatment-failure; IDHmt, isocitrate dehydrogenase mutated; TMZ, temozolomide; concTMZ, concurrent temozolomide; adjTMZ, adjuvant temozolomide; PCV, procarbazine, CCNU, and vincristine regimen; RT, Radiation therapy; AE, adverse events; NU, nitrosurea

Table 4. Imaging Surveillance Recommendations for IDH Mutant Lower Grade Glioma

Glioma type	MRI monitoring after diagnosis and initial treatment
Oligodendroglioma, IDH mutated, 1p/19q codeleted, grade 2	After RT and chemotherapy: At least every 6–9 months until progression* After RT or chemotherapy: As often as every 3–4 months in the first 5 years, thereafter as frequently as every 3–4 months, but not longer than 6 months until progression* After surgery only: As frequently as every 3–4 months until tumor progression. For patients who underwent gross total resection, MRI every 6–9 months 5 years postsurgery until tumor progression*.
Astrocytoma, IDH mutated, grade 2	After RT and chemotherapy: At least every 6 months until progression* After RT or chemotherapy: As often as every 3–4 months in the first 5 years, thereafter as frequently as every 3–4 months, but not longer than 6 months until progression* After surgery only: As frequently as every 3–4 months until tumor progression*
Oligodendroglioma, IDH mutated, 1p/19q codeleted grade 3	After RT and chemotherapy: At least every 6–9 months until progression* After RT or chemotherapy: As often as every 3–4 months in the first 5 years, thereafter as frequently as every 3–4 months, but not longer than 6 months until progression*
Astrocytoma, IDH mutated, grade 3	After RT and chemotherapy: At least every 6 months until progression* After RT or chemotherapy: As often as every 3–4 months until progression*
Recurrent oligodendroglioma, IDH mutated, 1p/19q codeleted, grade 2 and grade 3	As often as every 3–4 months*
Recurrent astrocytoma, IDH mutated, grade 2 and grade 3	As often as every 2–3 months*

RT, Radiation therapy; IDH, isocitrate dehydrogenase
*Patients who experience change in seizures, new or worsening neurologic signs and symptoms, and/or new or higher dose steroid requirements suspicious for tumor progression should have MRI study as early as possible.

showed a shorter interval time between first and second tumor recurrence (PFS2) than from the initial diagnosis to first recurrence (3 years versus 5.7 years).[58] Approximately 20% of patients exhibited second progression within 1 year of their first tumor progression. PFS2 duration was also significantly associated with the histologic grading (Grade 2: 4.2 years versus Grade 3: 1.7 years) and molecular diagnosis (oligodendroglioma: 4.2 years versus astrocytoma: 2.6 years). In addition, the median survival after first progression is also significantly shorter compared to the median survival from initial diagnosis (8.3 years versus 18.7 years).[59] Given the small number of patients in each molecular subgroup, there was no significant difference in the PFS1 between each molecular subgroups and treatments received (RT, chemotherapy, or observation only).[59] Other data suggest a more ominous prognosis following first recurrence. In 156 patients with IDHmt grade 3 glioma treated with intensity-modulated radiation therapy, the 6-year relapse-free survival was 75% in patients with grade 3 oligodendroglioma and 48.8% in those with grade 3 astrocytoma.[60] After radiological evidence of progression, the median survival was only 1 year (95% CI: 0.8–1.2 year). In the TAVAREC study, the median survival was 15.2 months (95% CI: 12.9–18.5 months) with either temozolomide alone or combination of bevacizumab and temozolomide after first contrast-enhancing recurrence of IDHmt LrGG.[61]

These data demonstrate that PFS shortens over time in IDHmt gliomas following first recurrence warranting even closer radiographic monitoring after first tumor progression than following initial diagnosis. After first radiological evidence of tumor progression, MRI monitoring as frequently as every 2-3 months in patients with IDHmt grade 2 and 3 astrocytoma and every 3-4 months in patients with grade 2 and 3 oligodendroglioma is reasonable.

Determination of Longitudinal Imaging Comparison

Visual comparison of longitudinal studies is the current clinical practice for surveillance of LrGG. Because LrGG are followed for several years, careful consideration of not only the most recent scans but also the disease trajectory is mandatory.[11,13] Therefore, determination of a reference MRI for comparison is important for tumor growth assessment. The use of the baseline MRI or at least one with more than a year interval as the reference for treatment response assessment, and the scan showing the smallest lesion (nadir scan) as the reference for the diagnosis of tumor progression are recommended.[62] The MRI following the most recent antineoplastic intervention is typically the most relevant reference scan for comparison to the newest scan in the assessment of tumor progression.

Consideration of Treatment Effects

One of the challenges in the follow-up of LrGG is the accurate assessment of therapy response. The phenomenon of pseudoprogression is well recognized following chemoradiation for glioblastoma, in particular, those with MGMT methylated tumors. Pseudoprogression also occurs in approximately 20% of patients with low-grade glioma following RT.[58] Whereas pseudoprogression most commonly occurs within 3 months after completion of RT in patients with high-grade glioma, the time frame for patients with low-grade glioma is quite different, with a median of 12 months.[58] The Response Assessment in Neuro-Oncology (RANO) criteria suggest that an increase

in the enhancement within the first 3 months after completion of chemoradiation should not be considered as tumor progression. Exceptions include new areas of enhancement outside the radiation field or unequivocal evidence of viable tumor on histopathological sampling. RANO criteria recommend short-interval MRI in 4 weeks to assess for a sustained increase of the T2/FLAIR signal for low-grade glioma or contrast enhancement for high-grade glioma to determine progressive disease versus pseudoprogression.[62–65] For this reason, obtaining post-treatment MRI at 4 months is also acceptable.[62] In the event of equivocal findings on surveillance MRI studies, a short-interval MRI (4-8 weeks) is advisable[11]; for patients with IDH mutation, repeat MRI in 12-16 weeks is also reasonable as longer intervals may be required to understand the nature of changes.

Consideration of Clinical Factors

Clinical factors also play important roles in the decision and timing of MRI studies.[62] Seizures are frequent presenting symptoms in patients with diffuse glioma ranging from 70-90%, and seizure frequency may herald tumor growth.[66–70] Thus, seizure assessments have been proposed as a surrogate marker of tumor response in both clinical trial and clinical setting.[71] Otherwise, unexplained clinical deterioration is also a marker of tumor progression.[62,64]The need to initiate corticosteroids to control new or worsening neurologic signs and symptoms should be regarded as suspicious for tumor progression.[62]The presence of these clinical factors raises concern for tumor progression, warranting MR imaging outside the planned surveillance schedule.

Summary and Recommendations

Even in well-defined molecular subgroups with favorable prognosis, a meaningful fraction of patients will experience early tumor progression following first-line therapy. Guidelines that mandate decreased frequency of imaging several years following initial diagnosis are inconsistent with the known PFS data in LrGG. In accordance with available LrGG clinical studies, the recommended imaging surveillance should logically be based on the WHO grade, histopathological and molecular characteristics of the tumor as well as the initial antineoplastic therapies (Table 4). Moreover, guidelines must incorporate flexibility to consider imaging ambiguities and new or worsening symptoms and signs.

We propose that in patients with grade 2 IDHmt astrocytoma and oligodendroglioma who received RT alone or chemotherapy alone, the recommended MRI monitoring after initial treatment is as frequent as every 3–4 months in the first 5 years, then as often as every 3–4 months but typically not longer than every 6 months thereafter until tumor. A longer interval at least every 6 months for patients with IDHmt/non-codeletion and every 6–9 months for patients with IDHmt/codeletion treated with combination of RT and chemotherapy is also appropriate. Following surgical resection without adjuvant treatment, the recommended MRI interval is as often as every 3–4 months until tumor progression. In patients with IDHmt/codeletion who underwent gross total resection, MRI every 6–9 months 5 years postsurgery is also reasonable. In patients incidentally found to have a presumed grade 2 glioma, MRI studies initially as often as every 2-3 months and generally not longer than every 6 months are recommended until a pattern of stability is demonstrated.

Patients with IDHmt grade 3 astrocytoma have a shorter PFS than those with grade 3 oligodendroglioma. We suggest obtaining an 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. Patients with grade 3 oligodendroglioma treated with either RT alone or chemotherapy alone should have MRI as frequently as every 3–4 months for the first 5 years after completion of treatment, then as often as every 3–4 months but typically not longer than every 6 months until tumor progression; while every 3–4 months until tumor progression is reasonable in patients with grade 3 astrocytoma treated with RT or chemotherapy alone.

After first radiological progression or recurrence, MRI monitoring performed as frequently as every 2–3 months in grade 2 and 3 IDHmt astrocytoma and every 3–4 months for oligodendroglioma is advisable. Identification of a reference MR study (nadir scan, postsurgery or post-treatment) should be used for comparison of follow-up scans. In patients with equivocal or suspicious MRI findings, a short-interval follow-up MRI is an appropriate approach, with an interval of one to three months depending upon circumstances. Patients who experience changes in seizures, new or worsening neurological signs and symptoms, or the need for initiation or higher dose of corticosteroids warrant a repeat MRI outside of these recommended MRI monitoring time points to assess for tumor progression.

These suggested MRI surveillance schedules are based on current data concerning the patterns of recurrence of each LrGG molecular subgroup. However, individualized MRI schedules with more or less frequent monitoring are also acceptable when clinically appropriate. Due to the lack of standardized MRI surveillance schedule, additional studies on the optimal timing and intervals of follow-up imaging studies for early detection of malignant transformation and tumor progression in patients with IDHmt LrGG are needed.

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