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Chemotherapy and diffuse low-grade gliomas: a survey within the European Low-Grade Glioma Network

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Abstract

Background. Diffuse low-grade gliomas (DLGGs) are rare and incurable tumors. Whereas maximal safe, functional-based surgical resection is the first-line treatment, the timing and choice of further treatments (chemotherapy, radiation therapy, or combined treatments) remain controversial.

Methods. An online survey on the management of DLGG patients was sent to 28 expert centers from the European Low-Grade Glioma Network (ELGGN) in May 2015. It contained 40 specific questions addressing the modalities of use of chemotherapy in these patients.

Results. The survey demonstrated a significant heterogeneity in practice regarding the initial management of DLGG patients and the use of chemotherapy. Interestingly, radiation therapy combined with the procarbazine, CCNU (lomustine), and vincristine regimen has not imposed itself as the gold-standard treatment after surgery, despite the results of the Radiation Therapy Oncology Group 9802 study. Temozolomide is largely used as first-line treatment after surgical resection for high-risk DLGG patients, or at progression.

Conclusions. The heterogeneity in the management of patients with DLGG demonstrates that many questions regarding the postoperative strategy and the use of chemotherapy remain unanswered. Our survey reveals a high recruitment potential within the ELGGN for retrospective or prospective studies to generate new data regarding these issues.

Key words

diffuse low-grade glioma, clinical practice, chemotherapy, PCV, temozolomide.

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Diffuse low-grade gliomas (DLGGs) (WHO grade II gliomas[1]) are rare tumors typically affecting young patients.[2] They are characterized by a continuous growth and an almost unavoidable anaplastic transformation.[3] Median overall survival (OS) ranges from 5 to more than 15 years[2,4,5] depending on tumor phenotype, isocitrate dehydrogenase (IDH) mutation and 1p19q codeletion, tumor size, and spontaneous imaging growth rate.[2,6] The positive prognostic impact of the extent of resection has been demonstrated.[5,7] Surgery is considered as the first-line treatment.[8] However, the timing and choice of further treatments (chemotherapy, radiation therapy [RT], or combined treatments) remain controversial.[9–16] To reach a treatment decision, several parameters are classically taken into account on a case-by-case basis: the presence of a residual fluid-attenuated inversion recovery (FLAIR)/T2 disease,[9] known prognostic factors such as older age, neurological deficit(s), astrocytic origin, IDH/1p19q status, and tumor crossing the midline,[17,18] but also rapid imaging growth rate[2] (increase of the mean tumor diameter [MTD] ≥8 mm per year before or following surgery[6]), and pathological neurocognitive status.[18]

Temozolomide (TMZ),[19–22] an oral chemotherapy drug, and a multidrug regimen consisting of procarbazine, CCNU (lomustine), and vincristine (PCV),[4,23,24] have a demonstrated efficacy in DLGGs. To date, no trial has compared PCV to TMZ as an adjuvant treatment after surgery or at progression in DLGG. The Radiation Therapy Oncology Group (RTOG) 9802 trial demonstrated a clear survival benefit of PCV following RT in patients with "high-risk" DLGG.[4] However, this result did not necessarily influence practice[10,11,16,25] as clinicians still largely propose TMZ to patients, in the absence of studies comparing both regimens and considering the ease of administration of TMZ and the toxicity of PCV.

To date, there are unresolved questions with regards to the management of DLGG patients, in particular regarding the timing of the introduction of a medical treatment after surgery, the position, type, and duration of chemotherapy, and whether it should be administered alone or combined with RT.

The European Low-Grade Glioma Network (ELGGN) was initiated in 2006 and gathers surgical and neuro-oncological centers with dedicated teams in charge of DLGG patients. An online survey evaluating the current practices in the management of DLGG patients was sent to participating ELGGN centers in 2015, after the presentation of the results of the RTOG 9802 trial at the 2014 American Society of Clinical Oncology (ASCO) meeting. The general results of this survey have been previously published[26] along with detailed results regarding its cognitive,[27] surgical,[28] and imaging[29] aspects. In this article, we describe the results of the survey pertaining to the use of chemotherapy in DLGG.

Material and Methods

The methodology of the survey has been previously described.[26] In brief, an online survey investigating the management of DLGG patients (that is, patients with diffuse grade II glioma according to the WHO 2007 classification[1]) was designed by a panel of experts from the ELGGN using Google forms and sent to all participating centers (n = 28) in May 2015. It was specified that only one form had to be completed for each center and recommended that it should be filled out by all physicians involved during a multidisciplinary meeting. The survey contained 69 multiple- and single-choice questions divided into 10 sections based on the chronological order of events in the management of DLGG.

Here we focus on 40 questions specifically addressing the use of chemotherapy in DLGG (Table 1). They address major issues in the medical management of DLGG patients, including 1) the timing of the introduction of chemotherapy in patients with resectable or unresectable tumors; 2) the choice of the chemotherapy regimen; 3) the value of chemotherapy alone compared to RT or combined treatments; and 4) the follow-up on and following chemotherapy. Of note, tumors were considered as resectable if a residual tumor volume of less than 10 cm^3 to 15 cm^3 was anticipated.

Results

Answers to the survey were obtained from 21/28 centers (response rate 75%) distributed across 11 European countries.[26] In these centers, the median number of DLGG patients treated with chemotherapy in the "low-grade" period (before the anaplastic transformation) is 6 patients per year per center (range, 0-75) (15 respondents). A small proportion of these patients are included in clinical trials evaluating chemotherapy: 0 in 14/21 centers (66.7%), 1-5 in 4/21 centers (19%), 6-10 in 2/21 (9.5%), and >10 patients in 1/21 (4.8%) in 2014. Interestingly, 10/21 centers (47.6%) have a computerized structured database for DLGG patients (updated in 5 centers).

In the following sections, the most relevant results are reported. Detailed responses to all questions are provided in the Supplementary materials.

Timing and Position of Chemotherapy in the Management of DLGG Patients

Initial "wait-and-watch" strategy

In unresectable tumors, an initial "wait-and-watch" strategy is recommended depending on risk factors in most centers (14/21, 66.7%). Criteria to discontinue this strategy vary by centers: until demonstration of morphologic MRI growth in 8/15 (53.3%), detection of contrast enhancement in 6/15 (40.0%), significant spectroscopic changes in 3/15 (20.0%), and/or significant perfusion changes in 2/15 (13.3%). Chemotherapy (TMZ or PCV) is started (after obtaining a histopathological diagnosis by biopsy) based on the following criteria in unresectable tumors: clinical parameters in 16/20 centers (80.0%), tumor volume in 10/20 (50.0%), growth kinetics in 12/20 (60.0%), contrast enhancement in 12/20 (60.0%), MRI multimodality parameters in 8/20 (40.0%), nuclear imaging parameters in 1/20 (5.0%), and 1p19q status in 5/20 (25.0%). Of note, the duration of the "wait-and-watch" period is ≤6 months in 13/16 centers (81.2%).

Table 1 Questions on Chemotherapy in the ELGGN Survey

General questions	
Q1	In your center, how many patients with a DLGG receive chemotherapy each year (in the low-grade period)?
Q2	In your center, how many patients with a DLGG have been entered into a therapeutic trial (chemotherapy) in 2014?
Resectable gliomas initial strategy	
Q3	Do you recommend an initial "watch and wait" period in resectable DLGG?
Q3bis	If yes, how long?
Q3ter	On average, this "watch-and-wait" period is about?
Q4	Do you recommend an initial "watch and wait" period in unresectable DLGG?
Q4bis	If yes, how long?
Q4ter	On average, this "watch and wait" period is about?
Q5	For unresectable DLGG, on which criteria do you start chemotherapy (PCV or TMZ)?
Q6	What do you most commonly recommend as a first line of treatment in unresectable DLGG?
Q7	In some cases, do you prescribe chemotherapy at first line with the objective of optimizing surgical removal ("neoadjuvant chemotherapy")?
Q8	If our group (European DLGG network) proposes a study on "neoadjuvant chemotherapy," would you participate?
Postoperative strategy	
Q9	In case of complete resection of FLAIR, what's your recommendation?
Q10	In case of subtotal resection of FLAIR (residue less than 10 cc), what's your recommendation?
Q11	In case of wait and watch, do you evaluate quantitatively the growth rate of the residue?
Q12	Would you say that the selection of adjuvant treatment (either wait and watch, TMZ, PCV, RT alone, concomitant TMZ and RT, or RT plus PCV) is influenced by one of the following proposals?
Choice of chemotherapy (unresectable and resectable DLGGs)	
Q13	For DLGG, which chemotherapy do you usually propose as first line?
Q14	Have the results of the Radiation Therapy Oncology Group 9802 study (54 Gy of RT vs the same RT followed by adjuvant PCV chemotherapy in high-risk DLGG – median overall survival 7.8 years (RT) to 13.3 years (RT + PCV) – hazard ratio of death of 0.59/log rank: $P = .002$) changed your management of DLGG?
Q15	If yes, have you changed your practice?
Q16	Despite significant toxicity (hematological, general, and long-term toxicities), would you agree to prescribe PCV (in place of TMZ) as first-line treatment if its prolonged response (after the end of treatment) is confirmed ("median duration of 3.4 years after PCV onset and 2.7 years after the end of PCV" as described by Peyre et al,[24] Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherapy in low-grade gliomas, *Neuro Oncol.* 2010;12(10):1078–1082)?
Q17	In which cases do you preferentially use PCV?
Follow-up on chemotherapy	
Q18	Which maximal number of successive TMZ cycles do you usually prescribe?
Q19	Do you think it is necessary to systematically evaluate cognition before (during) and after chemotherapy?
Q20	Do you think it is necessary to systematically evaluate quality of life before (during) and after chemotherapy?
Q21	Except clinical trials, do you systematically evaluate patients on quality of life before (during) and after chemotherapy?
Q22	Except clinical trials, do you systematically evaluate patients from a cognitive point of view before (during) and after chemotherapy?
Q23	If our group (European DLGG network) reaches an agreement on a minimal standardized cognitive assessment, would you agree to follow the recommendations before (during) and at the end of chemotherapy?
Q24	If our group (European DLGG network) reaches an agreement on a minimal quality-of-life assessment, would you agree to follow the recommendations before (during) and at the end of chemotherapy?
Q25	If our group (European DLGG network) reaches an agreement on a minimal standardized cognitive assessment, would you have the humans resources (neuropsychologists and speech therapists) to systematically evaluate patients before (during) and at the end of chemotherapy?
Q26	If our group (European DLGG network) reaches an agreement on a minimal quality-of-life assessment, would you have the human resources to systematically evaluate patients before (during) and at the end of chemotherapy?
Q27	How often do you perform MRI evaluation in a patient undergoing chemotherapy (TMZ or PCV)?
Q28	For a given patient on chemotherapy, do you always perform MRI on the same machine?
Q29	For a given patient on chemotherapy, do you always perform a systematic volumetric assessment?
Q30	If yes, which technique do you use?
Q31	If yes, who performs the tumor volume assessment?

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Table 1 Continued

Q32	It is always the same person who performs the tumor volume assessment?
Q33	For stopping chemotherapy because of a progression without anaplastic transformation, which radiological criteria do you consider relevant?
Q34	For response assessment, do you use RANO criteria?
Q35	In your opinion, is the volumetric assessment through the 3 diameters method reproducible?
Q36	In your opinion, is the volumetric assessment through segmentation reproducible?
Q37	In your opinion, is the volumetric assessment essential for the monitoring of an DLGG patient on chemotherapy?
Q38	In your opinion, is the rCBV essential for the monitoring of an DLGG patient on chemotherapy?
Q39	In your opinion, is the spectroscopy essential for the monitoring of an DLGG patient on chemotherapy?
Q40	For multitreated and reshaped lesions, with difficulties of volumetric quantification, which parameter(s) among the following may modify your strategy?

Abbreviations: DLGG, diffuse low-grade glioma; ELGGN, European Low-Grade Glioma Network; FLAIR, fluid-attenuated inversion recovery; PCV, procarbazine, CCNU (lomustine) and vincristine; RANO, Response Assessment in Neuro-Oncology; rCBV, relative cerebral blood volume; RT, radiotherapy; TMZ, temozolomide.

In resectable tumors, an initial "wait-and-watch" strategy is always recommended in 3/19 centers (15.8%), never recommended in 10/19 (52.6%), and recommended depending on risk factors in 6/19 (31.6%). When decided, the average duration of the "wait-and-watch" period is short (≤6 months) in all responding centers. It is maintained for about 3 months in 8/11 centers (72.7%), until morphologic MRI growth in 3/11 (27.3%), detection of contrast enhancement in 4/11 (36.4%), significant spectroscopic changes in 1/11 (9.1%), and/or significant perfusion changes in 2/11 (18.2%).

Initial treatment in unresectable tumors

TMZ is commonly proposed as first-line treatment in 15/21 centers (71.4%), followed by RT in 5/21 (23.8%), RT+PCV in 2/21 (9.5%), PCV in 1/21 (4.8%), and Stupp regimen in 1/21 (4.8%). Fourteen of 20 centers (70.0%) sometimes recommend first-line chemotherapy (in a "neoadjuvant" setting) to possibly optimize the extent of resection. Eighteen of 21 (85.7%) would be interested in participating in a clinical trial evaluating this strategy.

Postoperative strategy (resectable tumors)

In case of a total resection of the FLAIR tumor volume, most centers (16/20, 80.0%) recommend a "wait-and-watch" strategy. A systematic and immediate adjuvant treatment is never recommended. Molecular tumor markers influence the choice of starting an adjuvant treatment in a minority of centers, especially the IDH mutation in 2/20 (10.0%), the 1p19q codeletion in 2/20 (10.0%), and/or the MGMT promoter methylation in 2/20 (10.0%). In case of a subtotal resection of the tumor (residual FLAIR volume ≤10 cm^3), 11/19 centers (57.9%) recommend a "wait-and-watch" strategy and 2/19 (10.5%) an immediate treatment. In that case, the decision is influenced by the IDH mutation in 4/19 centers (21.1%), the 1p19q codeletion in 4/19 (21.1%), and/or the MGMT promoter methylation in 2/19 (10.5%).

Position of chemotherapy vs RT and combined treatments

The choice of the type of adjuvant treatment is influenced by the IDH mutation in 8/20 centers (40.0%), the 1p19q codeletion in 10/20 (50.0%), the MGMT promoter methylation in 3/20 (15.0%), and by none of these parameters in 8/20 centers (40.0%).

The results of the RTOG 9802 clinical trial (median OS 13.3 years in patients treated with RT-PCV vs 7.8 years in patients treated with RT)[4] modified the management of DLGG patients in 7/20 centers (35.0%). This resulted in a change of practices in high-risk patients in only 8/8 centers.

Choice of chemotherapy regimen

TMZ is preferred over PCV as first-line chemotherapy in 16/21 centers (76.2%). Ten of 20 centers (50.0%) would agree to prescribe first-line PCV if the prolonged responses after the end of PCV initially reported by Peyre et al are confirmed.[24] PCV is preferentially used in case of 1p19q codeletion in 8/21 centers (38.1%), clinical progression (headache, neurological deficit, intractable epilepsy) in 5 (23.8%), contrast enhancement in 4 (19.0%), large tumor volume in 3 (14.3%), growth kinetics >6 mm per year in 3 (14.3%), young patients in 2 (9.5%), and/or based on nuclear imaging in 1 (4.8%). PCV is never used as first-line treatment in 6 centers (28.6%).

Follow-up and response assessment of chemotherapy

The maximal number of successive TMZ cycles prescribed is 12 in 9/21 centers (42.9%), 18 in 3/21 (14.3%), 24 in 4/21 (19.0%), and unlimited in 5/21 (23.8%). Next to new contrast enhancement, which defines transformation to a higher grade, the following criteria are used to decide the discontinuation of TMZ because of progression: FLAIR volume increase >25% compared to baseline imaging in 15/21 centers (71.4%), FLAIR volume increase >25% between 2 successive

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MRIs in 8/21 (38.1%), perfusion imaging (relative cerebral blood volume [rCBV] increase) in 3/21 (14.3%), and/or significant spectroscopy changes in 5/21 (23.8%).

A systematic evaluation of the neurocognitive function is considered necessary to evaluate DLGG patients during and after chemotherapy in 15/21 centers (75.0%). In daily practice (clinical trials excluded), only 3/21 centers (14.3%) systematically perform such evaluation. Most centers (15/18) would agree to follow ELGGN recommendations if an agreement on a minimal standardized cognitive assessment was reached. Many of them (13/21) would have the human resources available to do so.

In 19/21 centers (90.5%), a systematic evaluation of quality of life (QOL) is considered necessary during and after chemotherapy, but is performed systematically in only 8/21 centers (38.1%) in daily practice. Most centers (20/21) would agree to follow ELGGN recommendations if an agreement on a minimal QOL assessment was reached and would have the resources to do so (17/21).

Regarding imaging evaluation of DLGG patients receiving chemotherapy, 95.3% of centers perform an MRI every 2 or 3 cycles (20/21 centers). Volumetric assessment of the FLAIR tumor volume is considered as essential in 16/19 centers (80.0%). It is systematically performed in 10/21 centers (47.6%), based on a segmentation technique in most cases (12/14), and always by the same person in 13/16 centers (81.3%). Volumetric assessment through segmentation is considered reproducible in 15/20 centers (75.0%) while it is considered reproducible in only 4/20 centers (20.0%) when performed using the 3 diameters method.

Twelve of 21 centers (57.1%) use the Response Assessment in Neuro-Oncology (RANO) criteria for response assessment in DLGG patients. rCBV and spectroscopic parameters (choline/*N*-acetyl-aspartate index) are considered essential in the monitoring of DLGG patients receiving chemotherapy in 19% (4/21) and 25% (5/20) of centers, respectively. For multitreated and reshaped tumors, with difficulties for the volumetric measurements, the treatment strategy is modified by contrast enhancement in 19/21 centers (90.5%), rCBV in 15/21 (71.4%), and spectroscopic changes in 6/21 (28.6%).

Discussion

This study describes the daily clinical practices regarding the use of chemotherapy in DLGG patients among specialized European centers. The high participation rate (75%) shows that the ELGGN centers are highly involved in the management of these patients and in the network. For comparison, a response rate of only 30.2% was achieved in a survey sent to neurosurgeons, neuro-oncologists, and radiation therapists from Australia and New Zealand.[11] One limitation, however, is that despite our recommendations, we cannot be certain that a multidisciplinary consensus was reached for the responses.

Despite the low incidence of DLGG, the recruitment of patients receiving chemotherapy at the low-grade stage of the disease is significant among participating centers (about 200 patients per year total). This recruitment would allow for large retrospective or prospective studies within the ELGGN. To date, despite the specialization of the ELGGN teams in the management of DLGG, only a few patients are included in clinical trials evaluating chemotherapy, probably because of the paucity of trials and because early RT is often used as a comparative arm or in association with chemotherapy in these trials.

Timing and Position of Chemotherapy in the Management of DLGG Patients

Initial strategy

Overall, we found that, whatever the tumor resectability, treatment is usually started shortly after the tumor diagnosis. Indeed, it is our opinion that patients should receive treatment(s) as soon as a volumetric tumor growth has been demonstrated, to reduce the tumor volume and the risk of anaplastic transformation.[5] Treatment is started earlier in resectable compared with unresectable tumors: no "wait-and-watch" period in 52.6% for resectable tumors, compared with 19.0% for unresectable tumors. When decided, the "wait-and-watch" period is also shorter for resectable tumors (always ≤6 months vs 6-12 months in 18.8% of centers for unresectable tumors). Surprisingly, the treatment is started only when contrast enhancement appears in a significant proportion of centers, whatever the resectability of the tumor (36% and 40% of centers for resectable and unresectable tumors, respectively). However, this result could be due to a misinterpretation of the question (when contrast enhancement appears there is an undisputable indication for treatment). In unresectable tumors, the decision to start a "medical" treatment is based on various factors including clinical, imaging (tumor volume, growth rate, contrast enhancement, MRI multimodality parameters, nuclear imaging), and biological parameters (1p19q codeletion). In 60% of centers, this decision is based on the detection of contrast enhancement.This could mean that in a proportion of centers, the anaplastic transformation of the disease (as reflected by the occurrence of contrast enhancement) is a strong signal of the necessity for a treatment. Again, this result could also be due to a misinterpretation of the question.

Interestingly, a large proportion of centers do not propose a "wait-and-watch" period, whatever the tumor resectability, despite the demonstrated prognostic value of the spontaneous growth rate.[6] This might be partly because a number of centers do not have a reliable method for accurately calculating the spontaneous growth rate.

In patients with an unresectable DLGG, first-line chemotherapy to optimize the extent of resection can be proposed by 70% of the centers, many of which would be interested in participating in a retrospective or prospective study. This strategy has been investigated in several single-center studies[30–32] and seems to constitute a promising option. It needs to be further evaluated in larger studies and validated in prospective trials, possibly within the ELGGN.

Postoperative strategy

A postoperative "wait-and-watch" period is largely preferred by the responding centers following a total (80%

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of centers) or subtotal resection (57.9% of centers) of the FLAIR volume, despite the recent results of the RTOG 9802 study that promote postoperative RT and chemotherapy in high-risk DLGG patients (of note, the questionnaires were sent after the presentation of the results at the 2014 ASCO meeting but before the 2016 publication of Buckner et al[4]; it remains unknown whether the full publication might have changed the responses). After subtotal resection, the decision of adjuvant treatment is influenced by molecular data in a minority of centers. Indeed, the use of molecular parameters alone to predict outcome and determine treatment strategies is questionable. As an example, IDH wild-type DLGG, classically associated with a poor prognosis, can have prolonged survival after surgery.[33] Therefore, we believe that IDH status should not be considered alone to make treatment decisions (including adjuvant treatment after surgery), but in association with other parameters including not only tumor biology (including but not limited to molecular features) but also clinical (age, neurological, and neurocognitive status), imaging parameters (spontaneous growth rate, volume of the FLAIR residue,[9] perfusion, spectroscopy, and nuclear imaging parameters), and extent of resection (MRI-quantified total resection and supratotal resection). This raises the question of the definition of "high-risk" patients who should receive immediate adjuvant treatment after surgery. In the past, several prognostic scores have been designed[17,18]; however, none of them has included the spontaneous growth rate,[6] tumor molecular biology, treatment modalities (including the extent of resection), or functional parameters. The planned European Organization for Research and Treatment of Cancer (EORTC) I-WOT study comparing immediate adjuvant treatment ("treat") to follow-up ("wait") following resection in IDH-mutant, 1p19q-intact lower-grade glioma patients will provide new data regarding this question.

Place of Chemotherapy vs RT and Combined Treatments

RT is an effective treatment and was long considered as the standard treatment following surgery in DLGG.[34] However, the EORTC 22845 phase III trial found that early RT had no impact on OS compared to late RT, despite an increased progression-free survival (PFS).[35] Moreover, it is associated with early and late cognitive toxicity.[36,37]

Efficacy of chemotherapy alone (TMZ or PCV) in DLGG patients has been reported in several studies.[19–24] It was recently confirmed by 2 large prospective studies,[4,38] including the long-term results of the RTOG 9802 phase III trial comparing RT alone to RT-PCV in high-risk DLGG patients.[4] The EORTC 22033 trial showed no significant difference in PFS in patients receiving dose-dense TMZ or RT as initial adjuvant treatment.[38] Of note, high-risk IDH-mutant non-codeleted DLGG individuals had a shorter PFS in the TMZ arm compared with the RT-alone arm in this study; however, the groups are small and data on OS are not yet available, precluding any definitive conclusion.

Owing to the demonstrated efficacy of chemotherapy in DLGG, the absence of benefit on OS of early (vs late) RT, and the evidence of decreased neurocognitive functioning following RT, many physicians choose to delay RT until a later stage of the disease and to prefer chemotherapy alone as initial treatment. In our survey, we found that chemotherapy alone is still chosen by a number of centers either right after surgery in an "adjuvant" setting or later at progression.

This strategy is being currently challenged by the recent results of the RTOG 9802 trial, which evaluated multimodal treatment combining RT and chemotherapy.[4] This study demonstrated a clear survival benefit of adding chemotherapy to RT in "high-risk" patients (median OS 13.3 vs 7.8 years in patients treated with RT alone, hazard ratio [HR] of death 0.59). However, several concerns have been highlighted, precluding any generalization of this strategy and explaining why the management of patients remains heterogeneous from center to center.[11] First, the population of patients included in this trial might not be a good representation of a "true" DLGG population. Indeed, 38% of patients presented with contrast enhancement on imaging (vs 15% to 20% in previous studies on DLGG[2]). Moreover, only a moderate proportion of patients (61% to 64%) had an IDH-mutant tumor, a quite surprising fact for a DLGG series. Second, the survival analyses did not take into account the extent of resection, which has been shown to be a positive prognostic factor.[5,7] Importantly, only a few patients underwent gross total resection (9% in the RT arm and 11% in the combined treatment arm). Third, it would have been interesting to compare the results of RT and combined RT-PCV arms to that of PCV alone. Finally, the lack of comparative QOL data is a main issue, as well as the insufficiency of the neurocognitive assessment, which included only a MMSE with no prolonged follow-up.[36] Of note, the interim results from the CATNON trial (EORTC 26053-22054) of RT with concurrent and adjuvant TMZ for 1p19q-intact anaplastic gliomas suggest an increased survival for patients receiving adjuvant TMZ.[39] However, extrapolating this result to low-grade astrocytomas is delicate.

A recent population-based study from the retrospective United States (US) National Cancer Database has provided interesting data regarding the use of the association of RT and chemotherapy.[40] It included 1054 patients with "high-risk" DLGG (as defined by the RTOG 9802 trial) receiving medical treatment within the first 6 months after diagnosis. A total of 496 patients (47.1%) received chemotherapy alone (one drug in 89.3% of cases, most likely TMZ) and 558 (52.9%) underwent radiochemotherapy (with one drug in 92.5% of cases, most likely TMZ). The group of combined treatment was not associated with improved OS ($P = .125$). However, this study has some limitations. First, the duration of the follow-up is short (median 4.6 years) while the RTOG 9802 study (median follow-up 11.9 years) demonstrated a separation of the OS curves (RT alone vs RT-PCV) after 4 years.[4] Secondly, the chemotherapy group is favored with 22.8% of patients having a 1p19q-codeleted tumor compared with 7.5% in the radiochemotherapy group ($P < .001$). Finally, the analysis suffers from missing data regarding the IDH mutation (missing in all cases), the 1p19q-codeletion status (missing in 78% of cases), the extent of resection (missing in 53% of cases), or the tumor volume (missing in 37% of cases).

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In another study from the US National Cancer Database, 1466 DLGG patients treated with RT alone were compared with 787 patients treated with chemotherapy alone as first-line treatment after surgery.[41] In the multivariate analysis (including patient's age and extent of resection), chemotherapy was the only factor associated with improved survival (HR: 0.405, $P < .001$). Again, this study suffers from limitations, in particular the fact that molecular biology parameters could not be considered in the multivariate analysis because of missing data (1p19q status unknown in 83% of cases). This limitation is all the more important given that, among patients with a known 1p19q status, 66.8% in the chemotherapy group had a codeleted tumor compared with 33.82% in the RT group.

In our survey, the choice of the adjuvant treatment (chemotherapy vs RT vs combined treatment) is influenced by the IDH status in 40.0% of centers, the 1p19q status in 50.0%, and none of these parameters in 40%. Indeed, a positive effect of chemotherapy has been shown whatever the molecular status, including in DLGG patients with unfavorable molecular features.[22,31,32] In the study by Ricard et al, 50% of 38 patients with a 1p19q–non-codeleted DLGG had a minor or partial response under TMZ, and 39.5% showed a stable disease.[22] In another study of patients treated with TMZ in a "neoadjuvant" setting, the IDH and 1p19q status had no significant impact on the velocity of the MTD decrease.[31]

In summary, the decision regarding oncological treatments all along the DLGG evolution should rely, on a case-by-case basis, on the integration of many factors including age, cognitive and epileptic status, tumor growth kinetics, extent of resection, molecular markers, and comparison between survival and expected toxicity.[13] In this context, well-conducted, prospective population-based studies at the international level are of the upmost importance to better evaluate treatment strategies according to these multiple factors.

Choice of Chemotherapy Regimen

Several chemotherapy regimens have shown efficacy in DLGG. An efficacy of TMZ in newly diagnosed or recurrent DLGGs has been demonstrated in multiple phase II studies,[19–21,42] including studies with volumetric assessment of the MTD.[22,31] In a series of 39 DLGG patients receiving TMZ, 92% experienced an initial decrease of the MTD,[22] with a longer duration of response for patients with a 1p19q-codeleted tumor, confirming previous data.[21] Of note, in a recent study of 120 IDH-mutant DLGGs included in the EORTC 22033 trial, a high MGMT methylation score was predictive of a benefit from TMZ treatment, regardless of 1p19q status.[43]

Objective responses rates have been shown with PCV in multiple single-arm studies in DLGG,[23,24] including studies with volumetric assessment.[24,44] The impact of PCV on survival has been recently confirmed by the RTOG 9802 trial.[4]

Although they have not been compared prospectively in DLGG, TMZ and PCV appear to be associated with different patterns of response. The time to maximum tumor volume reduction is shorter with TMZ: median time to maximum response 12 months (range, 3-30 months) with TMZ,[21] median time to maximal MTD decrease 40.8 months with PCV.[24] The duration of response is longer with PCV: median duration of MTD decrease 40.8 months with PCV,[24] median PFS 28 months with TMZ.[21] Data regarding this question of TMZ vs PCV come from studies in anaplastic gliomas. In the German Neuro-Oncology Working Group (NOA)-04 trial, patients enrolled in the chemotherapy arm were randomized to receive either TMZ or PCV. No difference in outcome has been demonstrated so far.[45] In a randomized, clinical trial comparing PCV vs 2 different schedules of TMZ in high-grade glioma patients at first recurrence, there was no survival benefit of PCV.[46] Of note, the ongoing CODEL trial (NCT00887146) evaluating RT with TMZ or PCV includes patients with anaplastic glioma and patients with "high-risk" DLGG, and will provide further data.

Our survey shows that for most centers within the ELGGN, TMZ remains the reference treatment in DLGG, as there are currently not enough data supporting the use of PCV over TMZ, and considering the ease of administration of TMZ and the feared toxicity of PCV. PCV is used as the first-line treatment in a wide range of situations. The disparity of responses shows that there is no consensus.

Follow-up and Response Assessment of Chemotherapy

Evaluation of the imaging response

Imaging monitoring seems fairly codified in DLGG patients treated with chemotherapy (MRI every 2 or 3 cycles). The RANO group recently proposed new criteria to define tumor response in DLGG.[47] These criteria are not systematically used within the responding ELGGN centers (57% of centers). Indeed, while the effort to standardize tumor response and to incorporate FLAIR signal changes and clinical status (including steroids use) to the response criteria must be emphasized, the lack of 3-dimensional volumetric assessment of FLAIR signal changes is a major limitation, in particular for the evaluation of residual reshaped tumors after surgery.[48–50] Our survey shows that the volumetric assessment of FLAIR volume is considered essential in most ELGGN centers (80%). Indeed, the value of 3-dimensional volumetric assessment of FLAIR signal changes has been well described.[22,24,49–51] When segmentation is used, it is considered reproducible in most centers. It is indeed reproducible and independent of the physician, the medical specialty, or years of experience.[52] Moreover, autopsy studies have demonstrated a good correlation between the measured volume using segmentation and the real volume.[53] Despite these considerations, a volumetric assessment of the FLAIR volume in DLGG patients receiving chemotherapy is systematically performed in only half of the responding centers, probably linked to the lack of available and appropriate software and to the fact that the manual segmentation technique is time consuming. Semi-automated segmentation techniques are being developed and will be of great assistance. In our opinion, modified RANO criteria including a volumetric assessment of the FLAIR volume should be evaluated further.

Evaluation of QOL and neurocognitive functioning on chemotherapy

Data regarding the impact of chemotherapy on QOL and neurocognitive functioning in DLGG are scarce. A few studies seem to indicate no alteration of QOL in DLGG

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patients receiving TMZ[19,30,54–56] and a reversible alteration of QOL during the PCV regimen and shortly after PCV. Only a few studies have performed an extensive and longitudinal assessment of cognitive function on chemotherapy.[30] Yet, it has been established that neurocognitive deficits lead to lower QOL in DLGG patients.[57] The neurocognitive assessment was limited to the restrictive MMSE evaluation in several recent clinical trials.[55,58] Moreover, the follow-up period is often short.[30,55] A baseline evaluation is not always included, altering the interpretation of the results as several variables affect neurocognitive functioning: the tumor itself, epilepsy and antiepileptic drugs, surgery, the premorbid level of cognition, and psychopathological affects.[34,59]

The impact of TMZ followed by surgery on cognition and QOL was evaluated in 10 patients with an unresectable DLGG, in a neoadjuvant setting or at recurrence after partial surgery.[30] After completing the whole protocol (TMZ and surgery), 3 patients had no cognitive deficit while 7 patients had only a slight deficit (verbal episodic memory and executive function mostly). QOL was preserved. In the EORTC 22033-26033 phase III trial (first-line TMZ vs RT in high-risk DLGG patients), no difference in MMSE score was found, but the follow-up was short (36 months).[55] In the RTOG 9802 trial, the adjunction of PCV to RT did not affect the proportion of patients with an MMSE score decline (maximum follow-up 5 years).[4] Other data regarding the cognitive impact of chemotherapy are available from studies in anaplastic gliomas, but the extrapolation of results to DLGG patients seems problematic because anaplastic gliomas are more aggressive tumors frequently associated with more severe deficits, and patients are often treated with RT along with chemotherapy and less frequently with TMZ.[60]

In our survey, most centers consider the evaluation of QOL and neurocognitive functioning in patients receiving chemotherapy necessary and would agree to follow ELGGN recommendations if an agreement on a minimal standardized assessment (ie, as proposed by Klein[59]) was reached. Resources seem to be more or less sufficient in participating centers; however, it might not be the case in all neuro-oncological centers.

In summary, data regarding the impact of TMZ on QOL and neurocognitive functioning in DLGG patients are scarce. It is important, however, to accurately evaluate these aspects in consideration of young age, generally preserved QOL at diagnosis, possible implications of the disease on the professional (DLGG patients are often still active), social, and familial domains, and relatively long survival of these patients. In the absence of a curative treatment for DLGG, preserving patients' QOL is indeed a major goal.

Summary

At the individual level, several criteria must be considered when evaluating DLGG patients treated with chemotherapy to determine the best individualized strategy. These criteria must also be taken into account in clinical trials. In patients treated with chemotherapy (in particular with TMZ), they must be considered altogether when deciding the duration of treatment. Indeed, while the PCV regimen is usually administered for 4 to 6 cycles, the question of the duration of treatment needs to be clarified in DLGG patients treated with TMZ. It is not clear yet if, like PCV, TMZ should be discontinued after a predetermined number of cycles or if it should be continued as long as the tumor volume decreases, considering that the treatment can be continued if tolerance is good (including regarding QOL and neurocognitive functioning) and the volumetric response clearly documented.

Conclusion

The survey demonstrated a significant heterogeneity in practices among expert centers within the ELGGN regarding the initial management of DLGG patients and the use of chemotherapy. Combined RT and chemotherapy has not imposed itself as the gold-standard treatment after surgery, despite the recent results of the RTOG 9802 study.[4] This is certainly linked in part to the fact that patients included in this trial were highly selected and represent only a subpopulation of DLGG. TMZ is largely used as first-line treatment after surgical resection for "high-risk" DLGG patients, or at progression. Many questions regarding the postsurgical management of DLGG patients and the use of chemotherapy remain unanswered. Our survey reveals a high recruitment potential within the ELGGN for retrospective or prospective studies to generate some new data regarding these issues. For example, the ELGGN will aim in the near future at assessing the survival and functional benefit of first-line PCV vs TMZ, as well as of upfront RT-PCV compared with a more "sequential" strategy delaying RT and PCV.

Supplementary Material

Supplementary data are available at *Neuro-Oncology Practice* online.

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References

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131(6):803–820.
2. Capelle L, Fontaine D, Mandonnet E, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. *J Neurosurg.* 2013;118(6):1157–1168.

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3. Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol.* 2003;53(4):524–528.
4. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med.* 2016;374(14):1344–1355.
5. Jakola AS, Skjulsvik AJ, Myrmel KS, et al. Surgical resection versus watchful waiting in low-grade gliomas. *Ann Oncol.* 2017;28(8):1942–1948.
6. Pallud J, Blonski M, Mandonnet E, et al. Velocity of tumor spontaneous expansion predicts long-term outcomes for diffuse low-grade gliomas. *Neuro Oncol.* 2013;15(5):595–606.
7. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. *Acta Neurochir (Wien).* 2016;158(1):51–58.
8. Soffietti R, Baumert BG, Bello L, et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. *Eur J Neurol.* 2010;17(9):1124–1133.
9. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: proposal of a multistage and individualized therapeutic approach. *Neuro Oncol.* 2015;17(3):332–342.
10. Laack NN, Sarkaria JN, Buckner JC. Radiation Therapy Oncology Group 9802: controversy or consensus in the treatment of newly diagnosed low-grade glioma? *Semin Radiat Oncol.* 2015;25(3):197–202.
11. Field KM, Rosenthal MA, Khasraw M, Sawkins K, Nowak AK. Evolving management of low grade glioma: No consensus amongst treating clinicians. *J Clin Neurosci.* 2016;23:81–87.
12. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol.* 2017;18(6):e315–e329.
13. The European Low-Grade Glioma Network. Evidence-based management of adult patients with diffuse glioma. *Lancet Oncol* 2017;18(8):e429.
14. Rudà R, Soffietti R. Controversies in management of low-grade gliomas in light of new data from clinical trials. *Neuro Oncol.* 2017;19(2):143–144.
15. Mandonnet E, Duffau H. An attempt to conceptualize the individual onco-functional balance: why a standardized treatment is an illusion for diffuse low-grade glioma patients. *Crit Rev Oncol Hematol.* 2018;122:83–91.
16. Chamberlain MC. Does RTOG 9802 change practice with respect to newly diagnosed low-grade glioma? *J Clin Oncol.* 2013;31(5):652–653.
17. Chang EF, Clark A, Jensen RL, et al. Multiinstitutional validation of the University of California at San Francisco Low-Grade Glioma Prognostic Scoring System. Clinical article. *J Neurosurg.* 2009;111(2):203–210.
18. Daniels TB, Brown PD, Felten SJ, et al. Validation of EORTC prognostic factors for adults with low-grade glioma: a report using intergroup 86-72-51. *Int J Radiat Oncol Biol Phys.* 2011;81(1):218–224.
19. Brada M, Viviers L, Abson C, et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. *Ann Oncol.* 2003;14(12):1715–1721.
20. Hoang-Xuan K, Capelle L, Kujas M, et al. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. *J Clin Oncol.* 2004;22(15):3133–3138.
21. Kaloshi G, Benouaich-Amiel A, Diakite F, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. *Neurology.* 2007;68(21):1831–1836.
22. Ricard D, Kaloshi G, Amiel-Benouaich A, et al. Dynamic history of low-grade gliomas before and after temozolomide treatment. *Ann Neurol.* 2007;61(5):484–490.
23. Soffietti R, Rudà R, Bradac GB, Schiffer D. PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. *Neurosurgery.* 1998;43(5):1066–1073.
24. Peyre M, Cartalat-Carel S, Meyronet D, et al. Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherapy in low-grade gliomas. *Neuro Oncol.* 2010;12(10):1078–1082.
25. Schaff LR, Lassman AB. Indications for treatment: is observation or chemotherapy alone a reasonable approach in the management of low-grade gliomas? *Semin Radiat Oncol.* 2015;25(3):203–209.
26. Mandonnet E, Wager M, Almairac F, et al. Survey on current practice within the European Low-Grade Glioma Network: where do we stand and what is the next step? *Neurooncol Pract.* 2017;4(4):241–247.
27. Rofes A, Mandonnet E, Godden J, et al. Survey on current cognitive practices within the European Low-Grade Glioma Network: towards a European assessment protocol. *Acta Neurochir (Wien).* 2017;159(7):1167–1178.
28. Spena G, Schucht P, Seidel K, et al. Brain tumors in eloquent areas: a European multicenter survey of intraoperative mapping techniques, intraoperative seizures occurrence, and antiepileptic drug prophylaxis. *Neurosurg Rev.* 2017;40(2):287–298.
29. Freyschlag CF, Krieg SM, Kerschbaumer J, et al. Imaging practice in low-grade gliomas among European specialized centers and proposal for a minimum core of imaging [published online ahead of print July 10, 2018]. *J Neurooncol.* doi:10.1007/s11060-018-2916-3.
30. Blonski M, Taillandier L, Herbet G, et al. Combination of neoadjuvant chemotherapy followed by surgical resection as a new strategy for WHO grade II gliomas: a study of cognitive status and quality of life. *J Neurooncol.* 2012;106(2):353–366.
31. Blonski M, Pallud J, Gozé C, et al. Neoadjuvant chemotherapy may optimize the extent of resection of World Health Organization grade II gliomas: a case series of 17 patients. *J Neurooncol.* 2013;113(2):267–275.
32. Jo J, Williams B, Smolkin M, et al. Effect of neoadjuvant temozolomide upon volume reduction and resection of diffuse low-grade glioma. *J Neurooncol.* 2014;120(1):155–161.
33. Di Carlo DT, Duffau H, Cagnazzo F, Benedetto N, Morganti R, Perrini P. IDH wild-type WHO grade II diffuse low-grade gliomas. A heterogeneous family with different outcomes. Systematic review and meta-analysis [published online ahead of print June 26, 2018]. *Neurosurg Rev.* doi:10.1007/s10143-018-0996-3.
34. Karim AB, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys.* 1996;36(3):549–556.
35. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet.* 2005;366(9490):985–990.
36. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810–818.
37. Jaeckle K, Vogelbaum M, Ballman K, et al. CODEL (ALLIANCE-N0577; EORTC-26081/2208; NRG-1071; NCIC-CEC-2): phase III randomized study of RT vs. RT + TMZ vs. TMZ for newly diagnosed 1p/19q-codeleted anaplastic glioma. Analysis of patients treated on the original protocol design. Abstract ATCT-16, Society for Neurooncology (SNO) meeting, San Antonio, TX, USA, November 2015. 2015;17(Suppl 5):v1–v9.
38. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1521–1532.
39. van den Bent MJ, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent

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and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. *Lancet.* 2017;390(10103):1645–1653.

40. Jhaveri J, Liu Y, Chowdhary M, et al. Is less more? Comparing chemotherapy alone with chemotherapy and radiation for high-risk grade 2 glioma: an analysis of the National Cancer Data Base. *Cancer.* 2018;124(6):1169–1178.
41. Wu J, Neale N, Huang Y, et al. Comparison of adjuvant radiation therapy alone and chemotherapy alone in surgically resected low-grade gliomas: survival analyses of 2253 cases from the National Cancer Data Base. *World Neurosurg.* 2018;112:e812–e822.
42. Wahl M, Phillips JJ, Molinaro AM, et al. Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. *Neuro Oncol.* 2017;19(2):242–251.
43. Bady P, Kurscheid S, Delorenzi M, et al. The DNA methylome of DDR genes and benefit from RT or TMZ in IDH mutant low-grade glioma treated in EORTC 22033. *Acta Neuropathol.* 2018;135(4):601–615.
44. Taal W, van der Rijt CC, Dinjens WN, et al. Treatment of large low-grade oligodendroglial tumors with upfront procarbazine, lomustine, and vincristine chemotherapy with long follow-up: a retrospective cohort study with growth kinetics. *J Neurooncol.* 2015;121(2):365–372.
45. Wick W, Roth P, Hartmann C, 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):1529–1537.
46. Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol.* 2010;28(30):4601–4608.
47. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* 2011;12(6):583–593.
48. Schmitt P, Mandonnet E, Perdreau A, Angelini ED. Effects of slice thickness and head rotation when measuring glioma sizes on MRI: in support of volume segmentation versus two largest diameters methods. *J Neurooncol.* 2013;112(2):165–172.
49. Mandonnet E, Pallud J, Clatz O, et al. Computational modeling of the WHO grade II glioma dynamics: principles and applications to management paradigm. *Neurosurg Rev.* 2008;31(3):263–269.
50. Jakola AS, Moen KG, Solheim O, Kvistad KA. "No growth" on serial MRI scans of a low grade glioma? *Acta Neurochir (Wien).* 2013;155(12):2243–2244.
51. Pallud J, Llitjos JF, Dhermain F, et al. Dynamic imaging response following radiation therapy predicts long-term outcomes for diffuse low-grade gliomas. *Neuro Oncol.* 2012;14(4):496–505.
52. Ben Abdallah M, Blonski M, Wantz-Mezieres S, Gaudeau Y,Taillandier L, Moureaux JM. Statistical evaluation of manual segmentation of a diffuse low-grade glioma MRI dataset. *Conf Proc IEEE Eng Med Biol Soc.* 2016;2016:4403–4406.
53. Prodhomme O, Seguret F, Martrille L, et al. Organ volume measurements: comparison between MRI and autopsy findings in infants following sudden unexpected death. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(6):F434–F438.
54. Liu R, Solheim K, Polley MY, et al. Quality of life in low-grade glioma patients receiving temozolomide. *Neuro Oncol.* 2009;11(1):59–68.
55. Reijneveld JC, Taphoorn MJ, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1533–1542.
56. Fountain DM, Allen D, Joannides AJ, Nandi D, Santarius T, Chari A. Reporting of patient-reported health-related quality of life in adults with diffuse low-grade glioma: a systematic review. *Neuro Oncol.* 2016;18(11):1475–1486.
57. Boele FW, Zant M, Heine EC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neurooncol Pract.* 2014;1(2):40–46.
58. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol.* 2014;32(6):535–541.
59. Klein M. Treatment options and neurocognitive outcome in patients with diffuse low-grade glioma. *J Neurosurg Sci.* 2015;59(4):383–392.
60. Habets EJ, Taphoorn MJ, Nederend S, et al. Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. *J Neurooncol.* 2014;116(1):161–168.

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