Published in final edited form as:

Semin Radiat Oncol. 2015 July ; 25(3): 203–209. doi:10.1016/j.semradonc.2015.02.008.

Indications for Treatment: Is Observation or Chemotherapy Alone a Reasonable Approach in the Management of Low Grade Gliomas?

Lauren R. Schaff, MD and Andrew B. Lassman, MD

Department of Neurology (LRS, ABL) & Herbert Irving Comprehensive Cancer Center (ABL),
Columbia University Medical Center

Abstract

The treatment of newly diagnosed low grade gliomas (LGG) remains controversial. Recently published results from the long-term follow up of Radiation Therapy Oncology Group (RTOG) trial 9802 demonstrated medically meaningful and statistically significant survival prolongation by adding chemotherapy with procarbazine, lomustine, and vincristine (PCV) after radiotherapy vs. radiotherapy alone for “high” risk patients (median 13.3 vs. 7.8 years, HR 0.59, $p=0.03$). However, in the 17 years since that trial was launched there have been advances in the understanding of LGG biology and patient heterogeneity, an increased recognition of late neuro-cognitive injury from early radiotherapy and the emergence of temozolomide as an alternative chemotherapy to PCV. These and other changes in the treatment landscape make the applicability of results from RTOG 9802 to all patients less clear. Moreover, in some patients, especially those at the lowest risk for early disease progression, deferred radiotherapy in favor of active surveillance or chemotherapy alone may remain reasonable treatment approaches.

INTRODUCTION

Currently, there is no consensus on the treatment of World Health Organization (WHO) grade II oligodendrogliomas, astrocytomas, and mixed oligo-astrocytomas (low grade gliomas, LGGs).¹ On the one hand, post-resection chemo-radiotherapy is thought a reasonable approach,² similar to the typical treatment of newly diagnosed glioblastoma, a WHO grade IV glioma.³ On the other, observation or chemotherapy alone, in some cases, are also deemed reasonable treatment options. Finally, among chemotherapy options, recently presented results² demonstrated the efficacy of procarbazine, lomustine (CCNU),

Correspondence: Andrew B. Lassman, MD; 710 West 168th Street; New York, NY, USA; Tel 212-342-0571; Fax 212-342-1246; ABL7@cumc.columbia.edu.

Disclosures:

ABL (last 12 months): Consultant or Advisory board membership: Celgene, Midatech, Genentech, Foundation Medicine, Novartis, Heron; Research Support: Aeterna Zentaris, Pfizer, Amgen, Genentech, Merck, Novartis, Bayer, AbbVie, Karyopharm, Agenus, GSK, Stemline, Northwest Biotherapeutics, Plexxicon, Millenium, Novocure, Celldex. LRS: None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and vincristine (PCV),⁴ and it is unclear whether other chemotherapy agents such as temozolomide, which is a simpler and less toxic therapy, would yield similar benefit.

The lack of consensus results in part from a paucity of phase III prospective trials that randomized patients to either observation or radiotherapy sparing approaches such as chemotherapy alone. However, the lack of phase III trials is not entirely surprising. Trials for LGGs are difficult to conduct because the tumors are rare. There is no diagnostic biomarker that completely distinguishes them from other histologies such as anaplastic (WHO grade III) tumors, leading to discrepancies in pathologic diagnoses. In addition, when conducted, trials for LGGs are difficult to complete (>10 years) because they are relatively indolent requiring lengthy follow-up when overall survival is a trial endpoint. Simultaneously, we are still expanding our understanding of both tumor and patient factors. It has becoming increasingly evident that LGGs are heterogeneous tumors. By extension, not all patients with LGGs should necessarily be treated identically.

Prognostic Factors in LGG

Clinical Prognostic Factors—There are clinical, histologic, and molecular features that prevent a uniform approach to all patients with LGG. Rather, patients are stratified into different “risk” groups. For example, Pignatti et al conducted a multivariate analysis on the data from European Organization for Research and Treatment of Cancer (EORTC) trials 22844⁵ and 22845⁶ (which studied the dose and timing of radiotherapy in LGGs).⁷ These results suggested that patient prognostic factors such as age > 40 years, pre-operative tumor diameter > 6 cm or crossing the midline, and the presence of neurologic deficits (other than seizures) prior to surgery were all considered unfavorable.⁷ In addition, a finding of astrocytic dominant histology was a tumor factor that correlated with shortened overall survival.⁷ Patients with ≥ 2 of these negative prognostic factors were considered to have “low-risk” disease, and median overall survival was doubled to approximately 7 years. By contrast, patients with ≥ 3 prognostic factors were at “high-risk” and median overall survival was approximately 3.5 years.⁷ Although the extent of resection was not prognostic in this analysis, the resectability of a tumor is clearly linked with both initial tumor size and the extent of the tumor involving both cerebral hemispheres are both independently significant prognostic factors. Further investigation with independent data sets confirmed the EORTC risk groups (10.8 years vs. 3.9 years, $p < 0.0001$),⁸ suggesting that initial tumor size and histologic subtype were the main drivers of this “risk” classification scheme,⁸ and showed that other clinical factors (e.g., mini-mental status score, extent of resection) were independently prognostic.^{8–10}

However, the definition of “risk” remains subject to debate. For example, Radiation Therapy Oncology Group (RTOG) trial 9802 defined “favorable” LGGs as those occurring in adults <40 years old without residual post-operative disease (neurosurgeon defined); they were observed without radiotherapy or chemotherapy after diagnosis, with 2 and 5-year survival rates of 99% and 93%, respectively.⁹ However, more than half (52%) of patients suffered progression within 5 years, which was alarming and faster than anticipated.⁹ Accordingly, even among “favorable” cases, there is substantial heterogeneity. For example, post-hoc analysis demonstrated patients with small (< 4 cm pre-operatively) completely resected (<1

cm residual confirmed by MRI) oligodendrogliomas had 2 and 5-year progression-free survival (PFS) rates of 100% and 70%, respectively, whereas patients with none of these factors fared far worse: 60% and 13%, respectively.⁹

Also enrolled to RTOG 9802 were adults with “unfavorable” LGGs who were either ≥ 40 years old, or had residual disease post-operatively (also neurosurgeon defined). Such patients were randomized to radiotherapy with or without PCV chemotherapy. Recently presented long-term follow-up results demonstrated a statistically significant (HR 0.59, $p=0.03$) improvement in survival that was also medically meaningful from the addition of PCV (median 13.3 vs. 7.8 years).² However, further analysis also demonstrated substantial heterogeneity within the unfavorable group. For example, median survival was 13.3 years among patients with oligodendrogliomas treated with chemoradiotherapy, but only 7.7 years for those with astrocytomas treated the same way.²

Other trials have used still different definitions of “risk,” further clouding a homogenous approach to treatment. For example, ECOG/NCCTG trial E3F05 defined “high” risk simply as age ≥ 40 with clinically or radiographic evidence of progressive disease.¹¹ Patients were to be randomized to radiotherapy with or without temozolomide. (However, the trial accrual has recently been halted when overall survival after radiotherapy alone was found inferior to chemoradiotherapy with PCV in RTOG 9802. The study was halted on the assumption that results with radiotherapy alone would be inferior to radiotherapy and temozolomide)

Finally, EORTC 22033/26033, NCIC CE5, accrued patients with LGGs who “required treatment” defined as several unfavorable factors such as age ≥ 40, but additional prognostic factors that were not solely identified by the Pignatti analysis.⁷ Patients were randomized to either radiotherapy or temozolomide alone, but were stratified by loss of chromosome 1p in tumor DNA which is a favorable molecular factor (results discussed below).¹²

Molecular Prognostic Factors—Recent advances identified several molecular features as prognostic. Loss of chromosomes 1p and 19q, O6-Methylguanine-DNA-methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase (IDH) mutations are among the best-understood biomarkers, although several others are emerging.

1p19q co-deletion is clearly prognostic in both anaplastic oligodendroglial tumors^{13–17} and LGGs, although it is less well studied in the latter.^{18–21} In anaplastic tumors, it is also now recognized as predictive of benefit from PCV^{16,17} and likely from temozolomide as well.^{15,22} MGMT promoter methylation has been observed in many cancers, including up to 93% of LGGs²³ and 45% of glioblastomas.²⁴ Debate surrounds whether MGMT promoter methylation is a prognostic favorable factor regardless of therapy,²⁵ or is specifically a predictive factor of increased sensitivity to alkylator therapy in glioblastoma²⁴ and LGGs.²³ MGMT promoter methylation may also be reflective of a broader methylated milieu called the “glioma CpG island methylator phenotype” (G-CIMP).^{26,27} IDH 1 and 2 mutations are also prognostic favorable factors that occur with high frequency in LGGs,^{28,29} and also predict response of LGGs to alkylating chemotherapy agents.³⁰ In addition, IDH mutation induces methylation of many genes (G-CIMP), which may partially explain the effect of MGMT methylation at specific sites in the promoter.^{27,31} Tumors with 1p19q co-deletion

appear to represent a subset of those with *IDH* mutation.^{29,32,33} Surprisingly, one study suggested that in the natural history of a low grade astrocytoma, untreated patients with tumors harboring methylated *MGMT* promoters had a shorter PFS than untreated patients without *MGMT* methylated tumors.³⁴

Nearly all phase III trials, and most phase II trials for LGG were designed before the prognostic and predictive importance of these molecular biomarkers were recognized. For example, biomarker analyses have not yet been conducted on tissue from RTOG 9802 at this time, although the molecular findings will undoubtedly further refine the risk groups and inform interpretation.

TREATMENT APPROACHES FOR LGG TUMORS

How do these clinical and molecular factors inform treatment? Part of the answer depends on an assessment of neuro-cognitive impairment and its impact on quality of life.³⁵ Over 30 years ago, it was recognized that long-term survivors of low grade glioma can suffer from deleterious effects on neuro-cognitive function from early radiotherapy.³⁶ Therefore, as some patients with LGGs survive decades, late toxicities and their impact on quality of life are real concerns. Arriving at a useful assessment of late neuro-cognitive impairment is complicated by the continued adoption of evolving treatment modalities and a trend towards individualizing therapies. Modern, highly conformal radiotherapy techniques, advanced imaging, surgical advancements, and new chemotherapy agents continue to alter the treatment options available.

Long-term neuro-cognitive outcomes have not yet been reported from RTOG 9802. 5-year follow-up data suggests that the addition of PCV chemotherapy to radiotherapy did not cause neuro-cognitive impairment.³⁷ In fact, both patients treated with radiotherapy and PCV and those treated with radiotherapy alone experienced improved cognition (as measured by mini mental status examination) over time, suggesting improved tumor control results in improved symptoms.³⁷ This finding was underscored by a study of patients with brain metastases treated with whole brain radiotherapy in which tumor burden correlated with neuro-cognitive function, suggesting that, by corollary, increased tumor burden has a greater impact on neuro-cognition than treatment related effects from radiotherapy.³⁸

However, these studies evaluated neurocognitive function months to a few years following radiotherapy -- too early for definitive assessments on the late toxicity of radiotherapy. For example, longer follow-up (mean of 12 years) among patients with LGGs treated with early radiotherapy demonstrated late neuro-cognitive deficits including (*e.g.*, impaired attention, executive function, and information processing speed) than among patients who deferred radiotherapy.³⁹ Importantly, these detrimental effects were not apparent after 5–6 years of follow-up. In the same⁴⁰ or similar⁴¹ populations, it was concluded that only large (2 Gy) radiotherapy fractions or the use of anticonvulsants were predictive of late neuro-cognitive deficits.⁴⁰ Larger fraction sizes may indeed lead to dementia after briefer interval follow-up.⁴² However, patients treated with early radiotherapy for LGGs do not appear to escape late brain injury, regardless of the RT fraction size. Overall, patients in RTOG 9802 survived a median of 13.3 years following combined radiotherapy and PCV chemotherapy.

Accordingly, at least 50% of patients treated in this manner may be at risk for late neuro-cognitive injury and would only be detectable after approximately 10 years.³⁹

Personalized Treatment Approach to LGG

High Risk Disease—Among patients with the highest risk disease, where survival is unlikely to reach 12 years, late neurocognitive effects from early radiotherapy is less of a concern and more aggressive treatment appears warranted. For example, astrocytic dominant histology is a clear negative prognostic factor.^{7,8} A post-hoc subset analysis of RTOG 9802 demonstrated that median survival among patients with low-grade astrocytomas was 4.4 years after radiotherapy alone and 7.7 years with the addition of PCV.² Therefore, patients with astrocytoma histology generally do not survive long enough to experience any late neurocognitive effects of early radiotherapy, and early radiotherapy is sensible in most patients. Moreover, in the randomized trial EORTC 22845 of observation vs. radiotherapy, there was no difference in survival (median 7.4 vs. 7.2 years, HR 0.97, $p=0.872$), but early radiotherapy did improve disease control (median PFS 5.3 vs. 2.4 years, HR 0.59, $p<0.0001$).⁶ Furthermore, the improved disease control from early radiotherapy correlates with improved neuro-cognitive function in the short-term,⁴⁰ and also led to improved seizure control.⁶

The updated results from RTOG 9802 demonstrated improved PFS in the subset of patients with low grade astrocytomas (median 3.7 years vs. 1.7 years, HR = 0.58) by adding PCV to radiotherapy vs. radiotherapy alone).² A lack of formal statistical significance ($p=0.06$ by log-rank) should not be interpreted as lack of a difference, as it almost certainly resulted from under-powering of this subset² and the need to continue to allow the data to mature.⁴³ Therefore, when radiotherapy is administered, combined treatment with chemotherapy enhances tumor control, likely prolongs survival, and by extension, may improve neuro-cognitive function. However, no improvement was noted when an inadequate metric such as mini-mental status examination was used,³⁷ and the acute toxicity of PCV can also be profound. It remains to be seen whether a subset with a particular molecular marker drives the survival benefit associated with the addition of PCV chemotherapy.

On first glance, it appears mysterious why patients with low grade astrocytomas benefited from adding PCV to radiotherapy in RTOG 9802, as astrocytomas are considered less chemo-sensitive than oligodendrogliomas, and they rarely harbor 1p19q co-deletion which is typically linked with response to chemotherapy. There are at least two potential explanations. First, the improvement among astrocytomas in PFS (HR 0.58) was not as profound and did not quite reach statistical significance ($p=0.06$ by log-rank), whereas the benefit in oligodendrogliomas was far greater (HR 0.36) and clear ($p<0.001$ by log-rank).² Therefore, some astrocytomas may be chemosensitive, but oligodendrogliomas are more so. Second, the benefit in astrocytomas may be limited to a specific subset of patients. Looking at the data from trials of anaplastic oligodendroglial tumors,^{16,17} it appears that *IDH* mutant³³ or *MGMT* methylated³¹ tumors benefit from PCV when added to radiotherapy, even in the absence of 1p19q co-deletion. *IDH* mutation is far more common in LGGs than anaplastic tumors,²⁹ and *MGMT* methylation is linked with and possibly dependent on *IDH* mutation,^{44,45} regardless of histologic subtype. Therefore, it is not entirely surprising that a

subset of low grade astrocytomas may benefit from the addition of chemotherapy, as most LGGs, including astrocytomas, are *IDH* mutant. In summary, similar to patients with anaplastic oligodendroglial tumors,³³ those with LGGs harboring both 1p19q co-deletion and *IDH* mutation may benefit most from PCV, explaining the clear improvement in oligodendrogliomas which are typically 1p19q co-deleted. However, those with *IDH* mutation and no 1p19q co-deletion may still derive benefit, just less so.³³ Pending molecular analyses will confirm or refute this hypothesis.

Finally, it should be noted that 43% of patients with low grade astrocytomas who were considered to have unfavorable LGGs on clinical grounds (regardless of histology, age 40 years old or less than gross-total resection as assessed by the neurosurgeon) were alive 10 years after radiotherapy and PCV in RTOG 9802.² Therefore, although the median did not reach 10 years, a non-inconsequential subset of patients with low-grade astrocytoma may be at risk of developing late neurocognitive deficits following early radiotherapy. Moreover, some studies demonstrate late neuro-cognitive injury may occur approximately 7 years after early radiotherapy. This timeframe is less than the median survival of 7.7 years in RTOG 9802.⁴⁶ Therefore, all of these risk and benefits must be weighed when deciding a management strategy.

Low Risk Disease—Patients with lower risk disease, such as those with oligodendrogliomas, are another matter. In RTOG 9802, they lived 13.3 years (median not reached) following radiotherapy and PCV, a statistically significant improvement over 10.8 years with radiotherapy alone (HR 0.43, $p=0.008$ by log-rank).² As neuro-cognitive injury from radiotherapy may manifest during this time frame, the risk must be considered carefully when deciding to initiate treatment. Active surveillance (depending on tumor size and location) or chemotherapy alone in lieu of early radiotherapy may be reasonable options. Notably, the current practice guidelines for brain tumors from the National Comprehensive Cancer Network support these approaches,⁴⁷ although revision has not occurred since presentation of mature RTOG 9802 results.² Neuro-cognitive outcomes among “favorable” adults accrued to the observation arm of RTOG 9802 (age <40 with gross-total resection)⁹ have not been reported yet.

A North Central Cancer Treatment Group (NCCTG)/Mayo Clinic trial treated 28 patients with low grade oligodendroglial tumors who had residual disease post-operatively with an intensified⁴⁸ regimen of PCV, deferring radiotherapy until progression.⁴⁹ Blinded neuroradiology review demonstrated imaging improvement in 52% of 25 evaluable cases.⁴⁹ Retrospective studies and several prospective trials also demonstrate responses to chemotherapy with temozolomide in 20–81% of newly diagnosed or recurrent low grade and anaplastic gliomas, with the wide range resulting from differences in study methodology and population evaluated.^{23,48,50–66} Neo-adjuvant chemotherapy, deferring radiotherapy until progression, also improves symptoms such as seizure control.⁶⁵ Therefore, one option for patients with favorable clinical and molecular factors is to start with chemotherapy, and reserve a decision about radiotherapy until response is determined. This approach is supported by the lack of difference in the results from RTOG trial 9402¹⁶ and EORTC trial 26951.¹⁷ Both trials treated patients with anaplastic oligodendroglial tumors using radiotherapy +/- PCV, both showed PCV improved survival (in 1p19q co-deleted cases),

and it did not appear to matter whether PCV was administered before¹⁶ or after radiotherapy.¹⁷ By extrapolation, it appears reasonable to give chemotherapy first without detriment. Chemotherapy alone (generally temozolomide) with deferred radiotherapy is the treatment recommended most frequently among neuro-oncologists for patients with 1p19q co-deleted anaplastic oligodendroglial tumors which are even more aggressive than lower grade tumors.^{67,68} Accordingly, deferred radiotherapy appears to represent a reasonable strategy in some LGGs. Regardless of recommended therapy, many patients with LGGs refuse radiotherapy outright.

Temozolomide or PCV

Whether temozolomide should replace PCV is not clear. Among patients with anaplastic tumors, it has already done so⁶⁸ as it is undoubtedly less toxic and easier both to prescribe and receive.⁶⁹ For example, RTOG 0424 was a single arm study that treated patients with high risk LGGs⁷ using radiotherapy and temozolomide.⁷⁰ The frequency of grade 3 treated related toxicities was lower in RTOG 0424 than among patients treated with radiotherapy and PCV in RTOG 9802.² However, temozolomide may not be as efficacious as PCV, as reviewed elsewhere.⁶⁹ For example, median survival in RTOG 0424 has not been reached, but early results demonstrated median PFS of 4.5 years and a 3 year-PFS rate of 59%.⁷⁰ These results with temozolomide appear inferior to those with PCV from RTOG 9802 in which median PFS was 10.4 years and the 3-year PFS rate was 75%–80% (estimated from Kaplan-Meier curve),² although cross-trial comparisons are fraught with difficulty because of differences in entry criteria and study populations.

Narrowing the analysis to patients treated with chemotherapy alone, the EORTC and the National Cancer Institute of Canada (NCIC) trial EORTC 22033-26033, NCIC CE5 randomized 477 patients with LGGs “requiring treatment” (clinical or radiographic worsening, intractable seizures, and/or age 40) to neoadjuvant intensified temozolomide alone (75mg/m² days 1–21/28) or radiotherapy alone (50.4 Gy).¹² Median PFS was 3.3 years after temozolomide and 4.6 years when restricted to cases with 1p deletion.¹² Similarly, a trial of protracted temozolomide (75mg/m² days 1–49 of 77) enrolled 44 chemotherapy naïve patients with high risk (defined as those with elevated proliferative index on histology or progressive tumor after observation or radiotherapy) LGGs; median PFS was 3.2 years, and 3.75 years among those with 1p or 19q deletion.⁶⁶ Finally, a United Kingdom trial of temozolomide alone for 30 patients with LGGs showed a 3-year PFS rate of 66% among all patients (not exclusively oligodendrogliomas or those with 1p deletion) and median PFS was not reached after median follow-up of 3 years.⁶⁵ It is unclear how these results with temozolomide compare against PCV. In the NCCTG/Mayo trial of neoadjuvant PCV in low grade oligodendroglial tumors,⁴⁹ survival results were immature and some biomarker analyses were incomplete at publication in all of these trials. Comparing response rates to temozolomide or PCV alone among these trials is impossible because of differences in the patient populations and response criteria. However, PFS associated with temozolomide (3.75- 4.6 years) was dramatically inferior to the median of 10.1 years among patients with 1p deleted oligodendrogliomas (all of which also harbored 19q deletion on further analysis) treated with a PCV like regimen (substituting nimustine, ACNU, for lomustine, CCNU) in one Japanese retrospective series.⁷¹ Again, differences in study design

and patient population confound interpretation; nonetheless, the shorter PFS reported with temozolomide is concerning.

A prospective randomized study is required to compare temozolomide against PCV alone, but will never occur. The “CODEL” trial, for patients with newly diagnosed anaplastic oligodendroglial tumors harboring 1p19q codeletion, will compare radiotherapy with either PCV or temozolomide. It will also accrue a small cohort of patients to a non-comparative arm treated with temozolomide alone. Therefore, this trial will compare the chemotherapy regimens, but only in conjunction with radiotherapy. Recent redesign will allow accrual of patients with LGGs, but results are years if not decades away.

CONCLUSIONS

All patients with LGG are not the same, and the treatment must be individualized based on two sets of risks: risk for rapid progression and risk of treatment induced toxicity. Patients with the highest risk tumors, such as those over 40 with un-resectable, symptomatic, large astrocytomas that cross the mid-line, should be treated with radiotherapy. RTOG 9802 suggests chemotherapy should be added as well, and pending molecular analyses may identify the subset most likely to benefit from PCV. Those with the lowest risk disease, such as young adults with small, resected, asymptomatic, unilateral oligodendrogliomas, will have to deal with the late consequences of aggressive therapy delivered at diagnosis (*e.g.*, potential neuro-cognitive injury from radiotherapy and the potential for myelodysplasia, pulmonary fibrosis, and neuropathy from PCV chemotherapy). If radiotherapy is delivered, chemotherapy should also be given. Based on analysis from RTOG 9802, the survival benefit for oligodendrogliomas was both medically meaningful and statistically significant. However, depending on the circumstances, both active surveillance and chemotherapy alone (with radiotherapy deferred until progression) may also be reasonable options.

Notably, in this paradigm, patients with the most treatment responsive disease (oligodendrogliomas with favorable molecular markers) may, thus, receive the least amount of treatment because of the potential toxicity of both radiotherapy and chemotherapy. The antiquated and blunt nature of available approaches underlie the apparent inconsistency. Brain radiotherapy techniques have substantially improved, but late neurocognitive deficits may still emerge. The PCV regimen that is resurging now was first published 35 years ago.⁴ Better treatments are needed. Unfortunately, while the pace of molecular discovery is exploding, therapeutic applications have lagged behind. For example, the potential importance of 1p19q co-deletion as a predictor of benefit from chemotherapy was reported 17 years ago,¹³ yet it remains “a marker not a mechanism” (J.G. Cairncross, personal communication). More promising may be IDH inhibitors now in clinical trials, only 7 years after description of *IDH* mutation as a potential target for treatment of gliomas.⁷² Hopefully the coming decade will lead to more effective therapies with less toxicity than those available now, allowing patients to live with LGGs as a chronic but manageable (if incurable) condition, without requiring them to choose between uncontrolled tumor and intolerable toxicities.

Acknowledgments

ABL was supported in part by Cancer Center Support Grant P30 CA013696-40 and NCI Community Oncology Research Program (NCORP) Project 1UG1CA189960-01.

CITATIONS

1. Louis, DN.; Ohgaki, H.; Wiestler, OD., et al. WHO Classification of Tumours of the Central Nervous System. 4. Lyon: International Agency for Research on Cancer; 2007.
2. Buckner JC, Shaw EG, Pugh SL, et al. R9802: Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: results by histologic subtype. *Neuro Oncol.* 2014; 16:v11, Abstract AT-3. oral presentation update.
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England journal of medicine.* 2005; 352:987–96. [PubMed: 15758009]
4. Levin VA, Edwards MS, Wright DC, et al. Modified procarbazine, CCNU, and vincristine (PCV 3) combination chemotherapy in the treatment of malignant brain tumors. *Cancer treatment reports.* 1980; 64:237–44. [PubMed: 7407756]
5. Karim AB, Afra D, Cornu P, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. *International journal of radiation oncology, biology, physics.* 2002; 52:316–24.
6. 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; 366:985–90. [PubMed: 16168780]
7. Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol.* 2002; 20:2076–84. [PubMed: 11956268]
8. 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. *International journal of radiation oncology, biology, physics.* 2011; 81:218–24.
9. Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. *Journal of neurosurgery.* 2008; 109:835–41. [PubMed: 18976072]
10. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol.* 2008; 26:1338–45. [PubMed: 18323558]
11. Schiff D, Brown PD, Giannini C. Outcome in adult low-grade glioma: the impact of prognostic factors and treatment. *Neurology.* 2007; 69:1366–73. [PubMed: 17893297]
12. Baumert B, Mason W, Ryan G, et al. Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade glioma: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033–26033). *J Clin Oncol.* 2013; 31:Abstract 2007.
13. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst.* 1998; 90:1473–9. [PubMed: 9776413]
14. Ino Y, Betensky RA, Zlatescu MC, et al. Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. *Clin Cancer Res.* 2001; 7:839–45. [PubMed: 11309331]
15. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol.* 2009; 27:5874–80. [PubMed: 19901110]
16. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol.* 2013; 31:337–43. [PubMed: 23071247]

17. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013; 31:344–50. [PubMed: 23071237]
18. Iwamoto FM, Nicolardi L, Demopoulos A, et al. Clinical relevance of 1p and 19q deletion for patients with WHO grade 2 and 3 gliomas. *J Neurooncol.* 2008; 88:293–8. [PubMed: 18345516]
19. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. *Cancer Res.* 2006; 66:9852–61. [PubMed: 17047046]
20. Mariani L, Deiana G, Vassella E, et al. Loss of heterozygosity 1p36 and 19q13 is a prognostic factor for overall survival in patients with diffuse WHO grade 2 gliomas treated without chemotherapy. *J Clin Oncol.* 2006; 24:4758–63. [PubMed: 16966689]
21. Kujas M, Lejeune J, Benouaich-Amiel A, et al. Chromosome 1p loss: a favorable prognostic factor in low-grade gliomas. *Annals of neurology.* 2005; 58:322–6. [PubMed: 16049942]
22. Vogelbaum MA, Wang M, Peereboom DM, et al. RTOG 0131: Phase II trial of pre-irradiation and concurrent temozolomide in patients with newly diagnosed anaplastic oligodendrogliomas and mixed anaplastic oligoastrocytomas – updated survival and progression free survival analysis [Abstract NO-56]. *Neuro-Oncol.* 2012; 14:vi75–vi6.
23. Everhard S, Kaloshi G, Criniere E, et al. MGMT methylation: a marker of response to temozolomide in low-grade gliomas. *Annals of neurology.* 2006; 60:740–3. [PubMed: 17192931]
24. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *The New England journal of medicine.* 2005; 352:997–1003. [PubMed: 15758010]
25. Rivera AL, Pelloski CE, Gilbert MR, et al. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol.* 2010; 12:116–21. [PubMed: 20150378]
26. Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer cell.* 2010; 17:510–22. [PubMed: 20399149]
27. van den Bent MJ, Gravendeel LA, Gorlia T, et al. A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. *Clin Cancer Res.* 2011; 17:7148–55. [PubMed: 21914791]
28. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J Clin Oncol.* 2009; 27:4150–4. [PubMed: 19636000]
29. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *The New England journal of medicine.* 2009; 360:765–73. [PubMed: 19228619]
30. Houillier C, Wang X, Kaloshi G, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. *Neurology.* 2010; 75:1560–6. [PubMed: 20975057]
31. van den Bent MJ, Erdem-Eraslan L, Idbaih A, et al. MGMT-STP27 methylation status as predictive marker for response to PCV in anaplastic Oligodendrogliomas and Oligoastrocytomas. A report from EORTC study 26951. *Clin Cancer Res.* 2013; 19:5513–22. [PubMed: 23948976]
32. Labussiere M, Idbaih A, Wang XW, et al. All the 1p19q codeleted gliomas are mutated on IDH1 or IDH2. *Neurology.* 2010; 74:1886–90. [PubMed: 20427748]
33. Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. *J Clin Oncol.* 2014; 32:783–90. [PubMed: 24516018]
34. Komine C, Watanabe T, Katayama Y, et al. Promoter hypermethylation of the DNA repair gene O6-methylguanine-DNA methyltransferase is an independent predictor of shortened progression free survival in patients with low-grade diffuse astrocytomas. *Brain Pathol.* 2003; 13:176–84. [PubMed: 12744471]
35. Li J, Bentzen SM, Li J, et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *International journal of radiation oncology, biology, physics.* 2008; 71:64–70.
36. Lieberman AN, Foo SH, Ransohoff J, et al. Long term survival among patients with malignant brain tumors. *Neurosurgery.* 1982; 10:450–3. [PubMed: 6285218]

37. 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; 32:535–41. [PubMed: 24419119]
38. Li J, Bentzen SM, Renschler M, et al. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol*. 2007; 25:1260–6. [PubMed: 17401015]
39. 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; 8:810–8. [PubMed: 19665931]
40. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet*. 2002; 360:1361–8. [PubMed: 12423981]
41. Laack NN, Brown PD, Ivnik RJ, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. *International journal of radiation oncology, biology, physics*. 2005; 63:1175–83.
42. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology*. 1989; 39:789–96. [PubMed: 2725874]
43. van den Bent MJ, Jaeckle K, Baumert B, et al. RTOG 9802: good wines need aging. *J Clin Oncol*. 2013; 31:653–4. [PubMed: 23295798]
44. Mulholland S, Pearson DM, Hamoudi RA, et al. MGMT CpG island is invariably methylated in adult astrocytic and oligodendroglial tumors with IDH1 or IDH2 mutations. *International journal of cancer Journal international du cancer*. 2012; 131:1104–13. [PubMed: 22020830]
45. Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature*. 2012; 483:479–83. [PubMed: 22343889]
46. Surma-aho O, Niemela M, Vilkkii J, et al. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. *Neurology*. 2001; 56:1285–90. [PubMed: 11376174]
47. National Comprehensive Cancer Network (NCCN). [Accessed January 13, 2015] Clinical Practice Guidelines in Oncology: central nervous system cancers (Version 2.2014). 2014. at <http://www.nccn.org>
48. Cairncross G, Macdonald D, Ludwin S, et al. Chemotherapy for anaplastic oligodendroglioma. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1994; 12:2013–21. [PubMed: 7931469]
49. Buckner JC, Gesme D Jr, O'Fallon JR, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. *J Clin Oncol*. 2003; 21:251–5. [PubMed: 12525516]
50. Mason WP, Krol GS, DeAngelis LM. Low-grade oligodendroglioma responds to chemotherapy. *Neurology*. 1996; 46:203–7. [PubMed: 8559376]
51. Paleologos NA, Vick NA, Kachoris JP. Chemotherapy for low-grade oligodendrogliomas? *Annals of neurology*. 1994; 36:294–5.
52. Stege EM, Kros JM, de Bruin HG, et al. Successful treatment of low-grade oligodendroglial tumors with a chemotherapy regimen of procarbazine, lomustine, and vincristine. *Cancer*. 2005; 103:802–9. [PubMed: 15637687]
53. Lebrun C, Fontaine D, Bourg V, et al. Treatment of newly diagnosed symptomatic pure low-grade oligodendrogliomas with PCV chemotherapy. *Eur J Neurol*. 2007; 14:391–8. [PubMed: 17388986]
54. Soffietti R, Ruda R, Bradac GB, et al. PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. *Neurosurgery*. 1998; 43:1066–73. [PubMed: 9802850]
55. Frenay MP, Fontaine D, Vandenbos F, et al. First-line nitrosourea-based chemotherapy in symptomatic non-resectable supratentorial pure low-grade astrocytomas. *Eur J Neurol*. 2005; 12:685–90. [PubMed: 16128869]
56. Higuchi Y, Iwadate Y, Yamaura A. Treatment of low-grade oligodendroglial tumors without radiotherapy. *Neurology*. 2004; 63:2384–6. [PubMed: 15623706]
57. van den Bent MJ, Chinot O, Boogerd W, et al. Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy:

- EORTC Brain Tumor Group phase II study 26972. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2003; 14:599–602. [PubMed: 12649108]
58. Pace A, Vidiri A, Galie E, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2003; 14:1722–6. [PubMed: 14630675]
59. Quinn JA, Reardon DA, Friedman AH, et al. Phase II trial of temozolomide in patients with progressive low-grade glioma. *J Clin Oncol*. 2003; 21:646–51. [PubMed: 12586801]
60. 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; 68:1831–6. [PubMed: 17515545]
61. Pouratian N, Gasco J, Sherman JH, et al. Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas. *J Neurooncol*. 2007; 82:281–8. [PubMed: 17082887]
62. Tosoni A, Franceschi E, Ermani M, et al. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. *J Neurooncol*. 2008; 89:179–85. [PubMed: 18431544]
63. Sanson M, Cartalat-Carel S, Taillibert S, et al. Initial chemotherapy in gliomatosis cerebri. *Neurology*. 2004; 63:270–5. [PubMed: 15277619]
64. Levin N, Gomori JM, Siegal T. Chemotherapy as initial treatment in gliomatosis cerebri: results with temozolomide. *Neurology*. 2004; 63:354–6. [PubMed: 15277636]
65. Brada M, Viviers L, Abson C, et al. Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2003; 14:1715–21. [PubMed: 14630674]
66. Kesari S, Schiff D, Drappatz J, et al. Phase II study of protracted daily temozolomide for low-grade gliomas in adults. *Clin Cancer Res*. 2009; 15:330–7. [PubMed: 19118062]
67. Abrey LE, Louis DN, Paleologos N, et al. Survey of treatment recommendations for anaplastic oligodendroglioma. *Neuro Oncol*. 2007; 9:314–8. [PubMed: 17435180]
68. Panageas KS, Iwamoto FM, Cloughesy TF, et al. Initial treatment patterns over time for anaplastic oligodendroglial tumors. *Neuro Oncol*. 2012; 14:761–7. [PubMed: 22661585]
69. Lassman AB. Success at last: a molecular factor that informs treatment. *Current oncology reports*. 2013; 15:47–55. [PubMed: 23247800]
70. Fisher BJ, Lui J, Macdonald DR, et al. A phase II study of a temozolomide-based chemoradiotherapy regimen for high-risk low-grade gliomas: Preliminary results of RTOG 0424. *J Clin Oncol*. 2013; 31:Abstract 2008.
71. Iwade Y, Matsutani T, Hasegawa Y, et al. Favorable long-term outcome of low-grade oligodendrogliomas irrespective of 1p/19q status when treated without radiotherapy. *J Neurooncol*. 2011; 102:443–9. [PubMed: 20721680]
72. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008; 321:1807–12. [PubMed: 18772396]