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Low Grade Gliomas

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Alberta Health Services
CancerControl Alberta

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Background

Diffusely infiltrating low-grade gliomas (LGGs) are categorized as WHO grade I and II diffuse astrocytic and oligodendroglial tumours. The term diffuse infiltrating means there is no identifiable border between the tumour and the normal brain tissue, even if the borders appear well defined on imaging.

The broad category glioma represents approximately 27% of all primary brain and CNS tumours.[1] The median age at time of diagnosis ranges between 43 and 48, depending on histologic subtype.[2] Using data from the Surveillance, Epidemiology and End Results (SEER) database which is run by the National Cancer Institute (NCI), the largest population-based assessment of overall survival (OS) in patients with LGG found an overall mortality of 51.2% for patients with grade II gliomas.[3] However, the study also demonstrated that the median survival of patients with grade II gliomas increased from 44 months (in 1999) to 57 months (in 2010). The most common presenting symptom in patients with LGG is seizures, which occur in 70-90% of patients.[4] MRI is the imaging modality of choice for diagnosing LGGs. LGGs are isointense to hypointense compared to white matter on T1-weighted images, and show mass-like hyperintense signals on T2-weight (or FLAIR images).

Patients with LGGs may survive for long periods, but the majority will recur, often with their tumours progressing to a higher grade lesions. There is currently no cure for LGGs. The goals of therapy in patients with LGGs are therefore to prolong OS and progression-free survival (PFS) while minimizing morbidity. However, no consensus exists as to the standard of care for patients with LGGs. The challenge for treating clinicians lies between providing too much therapy too early, or too little therapy too late.[4] Surgery, radiation therapy (RT), and chemotherapy all have a role to play in the management of LGGs and molecular biology is increasingly useful is identifying subsets of LGGs with better prognosis and increased change of responding to treatment.

Guideline Questions

1. Which prognostic factors can help discriminate between favourable and unfavourable patients with LGG?
2. Based on molecular characterization of tumours are there subgroups of patients that benefit from more aggressive treatment modalities?
3. Should patients with imaging suggestive of LGG undergo observation or surgery?
4. What is the impact of extent of resection on PFS and OS in patients with LGG?
5. What is the role of RT in the management of patients with LGG?
6. What is the role of chemotherapy in the management of patients with LGG?
7. How should patients with recurrence be managed?

Search Strategy

The current guideline update was largely an adaptation of recommendations from a series of LGG clinical practice guidelines published by the Journal of Neuro-Oncology in 2015. [5-9]

Medical journal articles were searched using the Medline, EMBASE, Cochrane Database of Systematic Reviews, and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Glioma [MeSH heading], Brain Neoplasms [MeSH heading], Astrocytoma [MeSH heading], Oligodendroglioma [MeSH heading], LGG, practice guidelines, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and clinical trials. Articles were excluded from the review if they: had a non-English abstract, were case studies involving less than five patients, involved pediatric patients, or were published prior to the year 2000.

A review of the relevant existing practice guidelines for LGGs, astrocytomas, and oligodendrogliomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency, National Comprehensive Cancer Network, the Australian Cancer Network, Cancer Care Ontario, American Society of Clinical Oncology, European Society of Medical Oncology and the National Institute for Health and Clinical Excellence.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with grade 2 gliomas. Different principles may apply to pediatric patients.

Recommendations

Prognostic and Predictive Factors

1. Several clinical, histologic, and molecular prognostic factors have been identified that are prognostic of worse overall survival (OS) in patients with LGG, including: 40 years of age or older, astrocytoma histology subtype, largest diameter of tumour greater than or equal to 6 cm, tumour crossing the midline, presence of neurologic deficit before surgery, incomplete resection particularly in patients under 40 years of age, isocitrate dehydrogenase (IDH) wild-type, and 1p/19q intact tumours.
2. Testing for IDH gene mutation and 1p/19q chromosomal deletions in all patients is recommended for classification, prognosis and potential treatment planning.

Surgery

3. The role of immediate surgical resection versus delayed resection is controversial and data are limited to observational studies. Unless contraindicated, immediate surgical resection is an option over observation to improve OS.
4. Although no randomized controlled trials (RCTs) have evaluated the extent of surgery on outcomes in LGG, numerous observational studies suggest that greater extent of resection (EOR) improves OS and seizure control. Maximizing tumour resection while keeping the surgically induced deficit at an acceptable level is recommended over simple debulking.
5. Surgery alone is not curative in patients with LGG and additional therapy with RT and/or chemotherapy will likely be required at some point in their disease trajectory.

Radiation Therapy

6. The optimal timing of RT in the management of LGG is controversial. Early postoperative RT alone has been shown in a multicenter RCT to improve PFS and seizure control, but not OS. High-risk LGG patients with 3 or more risk factors, including age >40 years, largest preoperative tumour diameter of more than 6 cm, tumour crossing the corpus callosum, astrocytoma histology, and preoperative neurological function deficits should be considered for immediate postoperative radiation therapy. For low-risk LGG patients, the radiation oncologist, in consultation with the patient, will decide to proceed with, or delay treatment.
7. Several RCTs have demonstrated no significant survival difference between patients receiving low dose or high dose RT. However, patients receiving high dose RT report significantly more side-effects. Although a radiation dose of 54 Gy is recommended, a dose between 45-54 Gy is acceptable at the discretion of the radiation oncologist.
8. Provided no contraindication to chemotherapy and a consideration for patient preference, The Alberta Provincial CNS Tumour Team recommends combining RT and chemotherapy rather than using either modality alone.

Chemotherapy

9. PCV has been shown in randomized trials to improve survival in patients with grade 2 and 3 diffuse glioma, and yet it is associated with significant toxicity; most patients on trial were unable to complete the full six planned PCV cycles. While there are no randomized trials to establish an equal benefit using temozolomide (TMZ), TMZ could be reasonably offered following an open discussion with patients about the treatment's potential risks and benefits.
10. In particular, patients with 1p/19q codeleted tumours may benefit from the addition of PCV to RT, but this is based on RCTs completed in patients with anaplastic oligodendrogliomas. Molecular analysis of patients on RTOG 9802 was unable to confer this benefit in patients with LGG due to the small number of samples and events in each subgroup.
11. The genetic and clinical similarities between LGG with wild-type IDH and primary glioblastoma (GBM) support the inclusion of this type of LGG within the broad spectrum of GBM. There is currently no evidence to support patients with wild-type tumours would benefit from chemoradiation. However, the Stupp Protocol (concurrent radiotherapy and TMZ followed by six cycles of monthly TMZ) could be reasonably offered following an open discussion with patients about the treatment's potential risks and benefits. For patients who show improvement or stability on therapy, additional cycles of TMZ may be considered. The maximum number of cycles being evaluated in current randomized clinical trials is 12.

Recurrence

12. Surgery, RT, and chemotherapy (with either TMZ or PCV) are all options that can be used in the management of patients with recurrent or progressive disease. While no RCT exists to guide the exact choice of treatment, the Alberta Provincial CNS Tumour Team advocates maximal safe

resection if possible. If not possible, radiation therapy and chemotherapy should be considered standard treatment.

Discussion

Glioma Classification

The most recent 2016 WHO Classification of Tumours of the Central Nervous System categorizes tumours based on histologic and molecular criteria, moving away from diagnoses based solely on microscopy and towards a system that incorporates genotyping into the classification and management of brain tumours.[10] One category that has seen major restructuring is the diffuse gliomas. While the 2007 WHO classification of gliomas was based on histological subtype (astrocytic, oligodendrocytic, and oligoastrocytic)[11], the 2016 classification groups together astrocytic and oligodendroglial tumours and further defines specific entities based on IDH mutation and 1p/19q codeletion status.[10]

The previous histopathological classification of LGGs suffered from high intra-observer and inter-observer variability.[12] For example, prior diagnoses of oligoastrocytoma and anaplastic oligoastrocytoma were subject to high interobserver discordance. The introduction of molecular testing has resulted in almost all cases being classified as either astrocytoma or oligodendroglioma. The designation NOS (not otherwise specified) may be used in the absence of diagnostic molecular testing or in the rare instance of dual genotype oligoastrocytoma.[10] It is generally expected that the introduction of genotypic parameters will increase the objectivity of all glioma diagnoses and improve patient management overall.[10]

A seminal study in the introduction of molecular diagnostics to CNS classification was The Cancer Genome Atlas Network's genomic analysis of diffuse LGGs. The authors performed genomewide analyses of 293 adults with previously untreated LGGs (WHO grades II and III), including 100 astrocytomas, 77 oligoastrocytomas, and 116 oligodendrogliomas.[12] Exome sequencing, DNA copy-number profiling, messenger RNA sequencing, microRNA sequencing, DNA methylation profiling, TERT promoter sequencing, and reverse-phase protein lysate array (RPPA) profiling were performed. These data were integrated and tested for correlation with clinical outcomes. Two unsupervised, integrative genomewide analyses independently uncovered three primary LGG disease classes that were best represented by IDH and 1p/19q status: LGG with an IDH mutation had either 1p/19q codeletion or a TP53 mutation in a mutually exclusive fashion and the majority of LGGs with wild-type IDH showed remarkable genomic and clinical similarity to primary (wild-type IDH) glioblastoma (GBM). Figure 1, reprinted from the Cancer Genome Atlas Research Network summarizes the study's major molecular findings.[12]

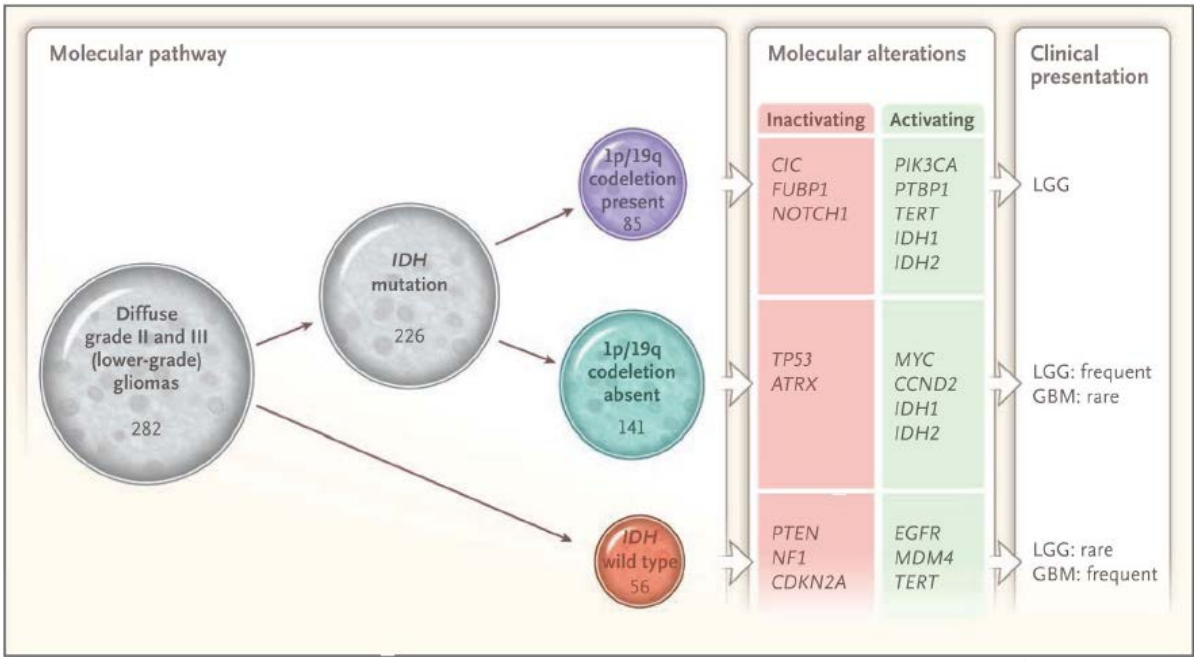

Figure 1. Summary of major findings (TCGA Research Network, 2015).[12]

Prognostic and Predictive Factors

Prognostic Factors

A prognostic factor is a clinical or molecular characteristic that predicts patient outcome irrespective of treatment. The European Organization for Research and Treatment of Cancer (EORTC) conducted two large phase III trials (22844 and 22845) to investigate the role of RT in LGG. In both trials, the same set of baseline variables presumed to be of prognostic influence were recorded.[13,14] Pignatti et al. constructed a prognostic scoring system on one data set (EORTC 22844), and validated its predictability on the other set (EORTC 22845).[15] Multivariate analysis on the construction set showed that 40 years of age or older, astrocytoma histology subtype, largest diameter of tumour ≥6 cm, tumour crossing the midline, and presence of neurologic deficit before surgery were unfavourable prognostic factors for survival. The presence of up to two of these factors identified a low-risk patient, whereas three or more risk factors identified a high-risk patient group. Seeking to independently validate this prognostic index with a separate collected dataset (Intergroup 86-72-51), Daniels et al. found that although the low risk groups by EORTC criteria had a superior PFS and OS to the high risk group, this was primarily due to the influence of histology and tumour size.[16] A pooled analysis of phase III trials conducted by the EORTC (22844 and 22845), the Radiation Therapy Oncology Group (RTOG 98-02), and the North Central Cancer Treatment Group (NCCTG 86-72-51) showed that both PFS and OS were negatively influenced by the presence of baseline neurological deficits, a shorter time since first symptoms (<30 weeks), an astrocytic tumour type, and tumours larger than 5 cm in diameter.[17] Of note, age was not prognostically important. The recent RTOG 9802 trial examined the effects of RT versus RT plus PCV in patients with unfavourable LGG. Unfavourable characteristics in

this study included patients 40 years of age or younger with incomplete resection, as well as patients 40 years of age or older who had undergone biopsy or any extent of LGG resection.[18]

The influence of tumour biology on patient outcome is likely to be of equal or greater importance than the factors listed above. IDH mutations (IDH1 and IDH2) have been identified in approximately 65-90% of LGGs.[19] Sun et al. conducted a meta-analysis of 10 studies (937 patients) that evaluated the correlation between IDH mutation and OS in adult LGGs.[19] Overall, the pooled hazard ratio (HR) for OS was 0.585 (95% CI [confidence interval], 0.376-0.911, p=0.025) for patients with IDH mutations versus patients without mutation suggesting that IDH mutation was associated with better OS of LGGs. In The Cancer Genome Atlas Research Network study, patients who had LGGs with wild-type IDH had substantially shorter OS than did those with LGGs with mutated IDH (age-adjusted HR for death, 7.4; 95% confidence interval [CI], 4.0-13.8).[12] Their prognosis (median survival, 1.7 years) was intermediate between those of persons who had glioblastomas with wild-type IDH (median survival, 1.1 years) and persons who had glioblastomas with mutated IDH (median survival, 2.1 years). In comparison, persons who had lower-grade gliomas with an IDH mutation and 1p/19q codeletion had a median survival of 8.0 years, and those with an IDH mutation and no codeletion had a median survival of 6.3 years. Using prospectively collected patients (n=98) enrolled in two North Central Cancer Treatment Group (NCCTG) LGG trials, Jenkins et al. reported that median survival was prolonged in patients with tumours with 1p/19q codeletion compared with those without the codeletion (11.9 versus 10.3 years).[20] Codeletion of 1p/19q was also reported as a favourable prognostic factor for OS versus one or no deletion (median OS, 12.6 versus 7.2 years, p=0.03) in Daniel et al.'s validation of the EORTC prognostic factors for adults with LGG.[16]

Predictive Factors

Two randomized trials, EORTC 26951 and RTOG 9402 in newly diagnosed anaplastic oligodendroglioma have offered the possibility of a more personalized treatment approach for grade III tumours.[21,22] In both trials molecular features were shown to be a better way to select patients for adjuvant chemotherapy compared with classical histology. While both of these trials showed a benefit to 1p/19q codeleted tumours by the addition of PCV to RT, both also indicated that a larger population than patients with 1p/19q codeleted tumours alone benefited from adjuvant PCV chemotherapy, although the optimal identification of this population was not clearly defined. The currently suggested marker of benefit is either the presence of IDH mutations, tumours positive for cytosine-phosphate-guanine island methylated phenotype (CIMP), or O^6-DNA methylguanine-methyltransferase (MGMT) promoter methylation.[21,23] Despite claims of the predictive value of IDH mutational status for benefit to PCV, statistical tests for interaction remained negative in RTOG 9402.[23] MGMT promoter methylation appeared to be the most predictive factor in the EORTC 26951 trial, but it's possible the trial enrolled a number of patients with GBM.[24] The RTOG 9802 trial found patients with IDH1-R123H mutations are associated with longer PFS and OS, regardless of treatment. Patients with the mutation had a median PFS of 7.6 years (vs 1.5 years no mutation, $p < 0.001$) and an OS of 13.1 years (vs 5.1 years no mutation, $p = 0.002$). Within the IDH1-R123H mutation group, patients who received RT + PCV had longer PFS and OS than patients who received

RT alone. Tissue sufficient for the determination of other genetic alterations was available in only 25% of patients (n = 63), so reliable assessment of OS and PFS as a function of 1p/19q LOH status and other molecular signatures could not be made.[18,25]

Management

Surgery

For patients presenting with large tumours or extensive neurologic symptoms, immediate surgery is considered standard practice to establish diagnosis and debulk the tumour. However, in patients with limited disease and symptoms such an aggressive treatment approach is controversial. While surgical morbidity has the potential to compromise functional status, the risk of deferring surgery includes the future management of a larger tumour as well as the possibility that the tumour may undergo anaplastic transformation.[26] In a comparative population-based study in patients with newly diagnosed LGG (n=153), Jakola et al. reported a survival benefit for patients treated at a hospital advocating early resection compared to a center favouring diagnostic biopsy and subsequent watchful waiting.[27] While not considered Level 1 evidence, this study presents the best available data comparing immediate versus delayed resection in LGG. In this study, median survival was 5.9 years (95%CI, 4.5-7.3) with the approach favouring biopsy only and was not reached with the approach favouring early resection. The estimated 5-year survival was 60% for biopsy and watchful waiting and 74% and early resection. In an adjusted multivariable analysis the relative HR was 1.8 (95% CI, 1.1-2.9, p=0.03) when treated at the center favoring biopsy and watchful waiting.

EOR. While no randomized studies have been published that evaluate the extent of surgery on OS and PFS, findings from numerous retrospective studies suggest that a more extensive resection improves OS. Hardesty and Sanai reviewed every major peer-reviewed clinical publication on the role of EOR in glioma outcome between the years 1990 to 2012.[28] Eleven LGG articles were examined for quality of evidence, expected EOR, and survival benefit. Of these, three studies using volumetric analysis to determine EOR in LGG pts (n=462, range 90-216) demonstrated a benefit to increasing EOR in univariate and/or multivariate analysis. Five-year OS was improved in all studies; median survival and time to disease progression was not always reported. Among the eight non-volumetric studies that examined survival benefit associated with EOR for patients with LGG, seven (n=982, range 82-203) demonstrated a benefit with increasing EOR. Five-year OS was increased in all series from 50–70% in subtotal resections (STR) to 80–95% in GTR. In one of the volumetric studies included in Hardesty and Sanai's review, Smith et al. reported that patients with at least 90% EOR had 5- and 8-year OS rates of 97%, and 91%, respectively, whereas patients with less than 90% EOR had 5- and 8-year OS rates of 76% and 60%, respectively.[29] After adjusting each measure of tumour burden for age, Karnofsky performance score (KPS), tumour location, and tumour subtype, OS was predicted by EOR ($p<0.001$), log preoperative tumour volume ($p=0.004$), and postoperative tumour volume ($p=0.03$). PFS was predicted by log preoperative tumour volume ($p\leq0.001$) and postoperative tumour volume ($p=0.035$), and malignant PFS (defined as the time between initial surgery and demonstration of gadolinium enhancement on follow-up imaging and/or higher-grade

tumour on subsequent biopsy or death) was predicted by EOR (p=0.005) and log preoperative tumour volume (p=0.002). In 1998 the RTOG initiated a phase II trial of observation for adults younger than 40 years of age with cerebral LGG who underwent a neurosurgeon-determined GTR. Patients (n=111) were observed following GTR and underwent MR imaging every 6 months. The OS rates at 2 and 5 years were 99% and 93%, respectively, whereas the PFS rates at 2 and 5 years were 82% and 48%, respectively. These data suggest that young adult patients with LGG who undergo a neurosurgeon-determined GTR have a greater than 50% risk of tumour progression 5-years postoperatively, thus warranting close follow-up and consideration for adjuvant treatment.[30]

Seizure control. Seizures are the most common presenting symptom of LGGs, and because the median duration of survival of patients with LGGs is relatively long, seizures are a significant determinant of a patients' quality of life. Chang et al. performed a retrospective chart review of all cases involving adult patients who underwent initial surgery for LGGs to identify factors that influenced perioperative seizure characteristics and postoperative seizure control.[31] Of the 269 patients with seizures, 49% had multiple recurrent seizures despite treatment with anti-epileptic drugs before surgery. Twelve-months after surgery 67% of patients were seizure free, 17% had rare seizures, 8% had a meaningful improvement, and 9% had no improvement or worse. The factors associated with freedom from seizures were GTR, preoperative seizure history of less than 1 year, and nonsimple partial seizure type

Radiotherapy

Survival. Surgery alone is not curative in patients with LGG and additional therapy with RT and/or chemotherapy is ultimately recommended for all patients. In the EORTC 22845 trial, after surgery, 311 adults with LGG were randomized to either early RT of 54 Gy in fractions of 1.8 Gy within 8 weeks of surgery or deferred RT until the time of progression.[32] Median progression-free survival was 5.3 years in the early RT group and 3.4 years in the deferred RT group (p<0.0001). However, OS was similar between groups: median survival in the RT group was 7.4 years compared with 7.2 years in the deferred RT group (p=0.872). In the deferred RT group, 65% of patients received RT at progression. The authors concluded that early RT after surgery lengthens the period without progression but does not affect OS. However, whether the difference in time to progression was a reflection of time to clinical deterioration was unknown because quality of life was not studied.

Seizure Control. In the EORTC 22845 trial, at 1 year neurological signs and symptoms were analyzed in patients who were still progression-free at 2 years to investigate whether patients free from progression had any neurological signs and symptoms.[32] The use of this subset ensured that the acute effects of treatment had subsided. Post-hoc analysis found no differences between 2 groups for cognitive deficit, focal deficit, performance status, and headache. Although at baseline no differences between 2 groups in seizure control (p=0.8701), at 1 year 25% patients irradiated had seizures vs 41% pts not irradiated (p=0.0329).

Dosing. Several randomized controlled trials have demonstrated no significant survival difference between patients receiving low dose (45 – 50.4 Gy) and high dose (59.4 - 64.8 Gy) RT.[13,33] In the

phase III EORTC 22844 trial adult patients with cerebral LGG (n=379) were randomized to receive postoperative RT with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks.[13] With a median follow-up of 6.2 years, no significant difference in terms of OS (58% for the low-dose group and 59% for the high-dose group) or PFS (47% and 50%) was noted between the two groups. A quality of life (QoL) questionnaire that assessed a range of physical, psychological, social, and symptom domains was included in EORTC 22844 to measure the impact of treatment over time. Patients who received high-dose RT reported lower levels of functioning and more symptom burden following completion of RT. These group differences were statistically significant for fatigue/malaise and insomnia immediately after RT and in leisure time and emotional functioning at 7±15 months after randomization.[34] In another phase III trial by the North Central Cancer Treatment Group/RTOG/Eastern Cooperative Oncology Group, adults with supratentorial LGG (n=203) were randomized to either low-dose RT (50.4 Gy/28 fractions) or high-dose RT (64.8 Gy/36 fractions). Survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64%, respectively, with high-dose RT (p=0.48). The 2-year actuarial incidence of grade 3 to 5 radiation necrosis was 2.5% with low-dose RT and 5% with high-dose RT.[33]

Side Effects. Klein et al. reported on a cross-sectional study that aimed to differentiate between the effects of the tumour (e.g. disease duration, lateralization) and treatment effects (neurosurgery, RT, antiepileptic drugs) on cognitive function and on relative risk of cognitive disability in 195 patients with LGG (104 of whom received RT).[35] With a mean follow-up of 6 years after diagnosis, all patients performed significantly poorer in all cognitive domains than the healthy controls. Although analyses showed that RT alone or in combination with lengthened duration of disease was associated with reduced cognitive function, high total RT doses were not related to increased risk of disability in any cognitive domains. However, high fraction doses were associated with disability in nearly all memory-related outcome measures. Data from post-hoc analyses with correction for differences in age, sex, education, and disease duration showed that cognitive disability was mainly present in patients who received fraction doses exceeding 2 Gy (range 2.1-3.0 Gy). The patients who received high-dose RT (>2 Gy) (n=18) were significantly older than patients who received fraction doses equal to or less than 2 Gy (p=0.028), but did not differ significantly in tumour localization or in disease duration. A total of 65 patients from the Klein study who had stable disease since the first cognitive assessment completed a follow-up assessment. At a mean follow-up of 12 years, the patients who had RT (49%) did worse than those who did not have RT in three of the six measured cognitive domains: executive functioning (p=0.03), information processing speed (p=0.05), and attention (p=0.003). The significant change in attentional performance in the patients who had RT was independent of fraction dose, tumour lateralization, extent of resection, age, and antiepileptic drug use.[36] Based on these study results, the authors concluded that the risk of long-term cognitive and radiological compromise that is associated with RT should be considered in treatment planning.

Chemotherapy

Combined with RT. Only one prospective randomized trial has been published evaluating the role of chemotherapy in newly diagnosed patients with LGG. In 1998, RTOG 9802 was opened for adults

with supratentorial LGGs.[37] Patients were divided into two risk groups: favourable (age 18 to 39 years with surgeon-defined gross total resection of their tumour) and unfavourable (age ≥ 40 years, or with subtotal resection or biopsy, irrespective of age). Patients in the unfavourable risk group (n=251) were randomly assigned to RT alone (54 Gy given in 30 fractions) or RT followed by six cycles of procarbazine, lomustine, and vincristine chemotherapy (PCV). Median OS time and 5-year OS rates for RT alone versus RT plus PCV were 7.5 years versus not reached and 63% versus 72%, respectively (HR; 0.72; 95% CI, 0.47-1.10; p=0.33).

Early reports found RT + PCV treatment in patients with LGG prolonged PFS, but not OS, when compared to RT alone.[37] The final results of RTOG 9802 have since been published: long term follow-up (median 11.9 years) shows patients in the RT + PCV arm had longer median survival time compared to the RT alone arm (13.3 vs. 7.8 years, HR=0.59, p=0.03) as well as longer median PFS (10.4 vs. 4.0 years, HR=0.50, p=0.002).[18,38] The 10-year PFS and OS rates for the RT + PCV arm were 51% (95% CI, 42-59%) and 60% (95% CI, 51-69%), respectively, while the RT arm had corresponding rates of 21% (95% CI, 14-28%) and 40% (95% CI, 31-49%).[18] A chemoradiation benefit was observed with all histological diagnoses (oligodendroglioma, oligoastrocytoma, and astrocytoma), although the difference in overall survival between treatment arms did not reach significance in patients with astrocytoma (HR=0.73, p=0.31). In patients with IDH1-R132H mutations, RT plus PCV was associated with longer PFS and OS compared with RT alone. It could not be determined whether RT plus PCV was beneficial for patients with wild-type tumoural IDH because the number of events among this group was too small.[18,39].

In RTOG 0424, a single-arm phase II study, 129 patients with high-risk LGG were treated with RT (54 Gy in 20 fractions) and concurrent and adjuvant temozolomide (TMZ).[40] High risk LGGs patients were defined as having three or more risk factors for recurrence, including: age ≥40 years, astrocytoma histology, bihemispherical tumour, preoperative tumour diameter ≥ 6 cm, or a preoperative neurological function status of >1. Outcomes were compared to those of historical controls.[15,16] The study was designed to detect a 43% increase in median survival time from 40.5 to 57.9 months and a 20% improvement in 3-year OS rate from 54% to 65% at a 10% significance level (1-sided) and 96% power. While the median survival time was not yet reached at the time of publication, the 3-year OS rate was 73.1% (95% CI, 65.3%–80.8%), which was significantly improved compared to that of pre-specified historical control values (p<0.01). The study authors concluded that this data should be considered as hypothesis generating, lending strong support for further studies of combined chemoradiation in LGGs and for the use of TMZ in combination with RT to treat LGGs.

Molecular markers. As previously mentioned, The Cancer Genome Atlas Research Network classifies LGG into three categories: LGG with an IDH mutation and a 1p/19q codeletion, LGG with an IDH mutation and no 1p/19q codeletion, and LGG with wild-type IDH; the majority of which show a genomic and clinical similarity to primary (wild-type IDH) glioblastoma (GBM).[12] RTOG 9802 was unable to find evidence to support the benefit of RT + PCV in wild-type IDH patients; however, the genetic and clinical similarities between LGG with wild-type IDH and GBM suggest that these patients

may benefit from treatment using the Stupp Protocol (concurrent radiotherapy and TMZ followed by six cycles of adjuvant TMZ).[41]

Deferred RT. Baumert et al. reported findings from the randomized phase III trial EORTC 22033-26033 that compared primary chemotherapy to standard RT.[42] After stratification for 1p-status, 477 patients with LGG who were progressive, symptomatic or high-risk requiring treatment other than surgery were randomized to either conformal RT (50.4 Gy in 28 fractions) or dose-dense TMZ (75 mg/m² daily for 21 days, every 28 days up to a maximum 12 cycles). Analysis was performed after 246 progression events (median follow-up 45.5 months), at which time PFS was not significantly different (p=0.23), and median OS had not been reached. 1p deletion was a positive prognostic factor irrespective of treatment (p-value stratified by treatment (PFS: 0.0003; HR=0.59 95% CI, 0.45-0.78)/ OS: 0.002; HR=0.49 95% CI, 0.32-0.77). A post hoc analysis of molecular markers showed that mutation of the IDH1 or 2 (IDH mutant) regardless of 1p/19q codeletion was also a positive prognostic factor. Exploratory analysis of these patients showed that patients with IDH mutant/non-codeleted tumours had a shorter PFS after treatment with TMZ than after RT (HR 1.86; 95% CI, 1.21-2.87; p=0.0043), while no difference was observed between these treatments for patients with IDH wild-type (unmutated), and IDH mutant/co-deleted tumours. However, the authors noted that maturation of survival data was needed to derive firmer conclusions. An additional analysis of the cohort found no significant difference in health-related quality of life (HRQOL) or global cognitive functioning between the TMZ and the RT groups over 36 months of follow-up.[43]

Toxicity of Preferred Regimens. PCV and TMZ are the most commonly studied chemotherapy regimens in patients with LGG. However, it is unclear which of the two may actually be the optimal regimen for a specific patient. To date no randomized controlled trial has compared PCV to TMZ in patients with LGG. Although RTOG 9802 showed that PCV added to RT leads to a survival benefit, many clinicians prefer TMZ because it is easier to administer and is better tolerated by patients. In RTOG 9802 the incidence of grade 3 and 4 hematological toxicity was 8% and 3% with RT alone compared with 51% and 15% with RT plus PCV ($p<0.01$).[37] There is no trial equivalent to RTOG 9802 evaluating the long-term benefit of TMZ in patients with LGG. However, in RTOG 0424, 43% and 10% of patients experienced grade 3 and grade 4 adverse events, respectively; the majority of which were hematologic.[40] A study of procarbazine and CCNU (PC) versus PCV is warranted in patients with LGG given that vincristine has been argued to add toxicity with little if any clinical benefit since it doesn't cross the blood-brain barrier.[44]

Recurrence

Despite a more favourable prognosis than patients with high-grade gliomas, 50-75% of patients with LGGs eventually die of either tumour progression or degeneration to higher malignant grade.[45] Factors that have been consistently shown to be associated with tumour recurrence or malignant degeneration include preoperative contrast enhancement, tumour size, and STR.[46]

RT. Combs et al. retrospectively evaluated the efficacy of fractionated stereotactic reirradiation in 71 patients with recurrent LGG treated in a single institution.[47] The median time between primary RT and

reirradiation was 48 months. Fractionate stereotactic RT was performed with a median dose of 36 Gy in a median fractionation of 5 x 2 Gy per week. Median OS after primary diagnosis was 111 months, and median survival after reirradiation was 22 months. PFS after fractionated stereotactic RT was 12 months. Only minor temporary side effects were noted, including alopecia, headaches, nausea/vomiting, and skin erythema. The study authors concluded that fractionated stereotactic RT was well tolerated and may be effective in patients with recurrent LGG.

Chemotherapy. Quinn et al. reported on a phase II trial of TMZ in 46 patients with progressive LGG (16 astrocytoma, 20 oligodendroglioma, 5 mixed, and 5 pilocytic astrocytoma).[48] Patients received TMZ orally once a day for 5 consecutive days at a starting dose of 200 mg/m^2/d. Treatment cycles were repeated every 28 days. In the absence of disease progression or unacceptable toxicity, patients continue to receive TMZ for up to a maximum of 12 cycles. The reported objective response rate was 61% (24% complete response and 37% partial response), with an additional 35% of patients having stable disease. Median PFS was 22 months (95% CI, 15-infinity months) with a 6-month PFS of 98% (95% CI, 94%-100%) and a 12-month PFS of 76% (95% CI, 63%-92%). Toxicity was observed in 6 patients. Pace et al. reported on a second phase II trial of TMZ in 43 patients with progressive LGG (29 astrocytoma, 4 oligodendroglioma and 10 mixed) (2003).[49] TMZ was administered orally once a day for 5 consecutive days every 4 weeks, at a starting dose of 200 mg/m^2/day if not pretreated, or 150 mg/m^2/day in PCV pretreated patients, with dose escalation to 200 mg/m^2/day in the absence of toxicity. A complete response was observed in 4 patients, 16 had partial responses, 17 had stable disease (with four minor responses) and 6 had progressive disease. Median duration of response was 10 months (95% CI, 8-12), with a 76% rate of PFS at 6 months, and a 39% rate of PFS at 12 months. A relevant clinical benefit was noted in the 31 patients presenting with uncontrolled epilepsy. Both authors concluded that because of the high response rates, TMZ chemotherapy is a valid treatment options for patients with progressive LGG.

Soffietti et al. reported on a phase II study designed to determine the benefits and toxicity of PCV chemotherapy in patients with recurrent LGG (oligodendrogliomas and oligoastrocytomas) after surgery alone or surgery with RT.[50] Of the 26 patients 62% responded to PCV: 12% experienced complete response, 50% experienced partial response, 31% had stable disease, and 8% had a progressive disease. Both oligodendrogliomas and oligoastrocytomas responded to PCV, with complete responses occurring in association with pure tumours only. The median time to tumour progression of all 26 patients was 24 months and was significantly longer for those with oligodendrogliomas compared with those with oligoastrocytomas (32 versus 12 mo) ($p< 0.001$). Chemotherapy was well tolerated, with mild hematological toxicity and rare skin rashes being the most frequent sequelae.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial CNS Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in August, 2008. This guideline was previously revised in December 2009 and May 2012.

Maintenance

A formal review of the guideline will be conducted in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

CIMP, cytosine-phospate-guanine island methylated phenotype; EOR, extent of resection; EORTC, European Organization for Research and Treatment of Cancer; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma; GTR, gross total resection; Gy, gray; IDH, isocritrate dehydrogenase; KPS, Karnofsky performance score; LGG, low-grade glioma; MGMT, O6-DNA methylguanine-methyltransferase; MRI, magnetic resonance imaging; NCCTG, North Central Cancer Treatment Group; NCI, National Cancer Institute; OS, overall survival; PCV, procarbazine + CCNU + vincristine; PFS, progression-free survival; QoL, quality of life; RCT, randomized control trial; RPPA, reverse-phase protein lysate array; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SEER, Surveillance, Epidemiology, and End Results database; STR, subtotal resection; TERT, telomerase reverse transcriptase; TMZ, temozolomide; WHO, World Health Organization

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest

Participation of members of the Alberta Provincial CNS Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial CNS Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.