EDITORIAL

The management of low-grade glioma in adults

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GROSS-TOTAL resection (GTR) of intrinsic low-grade gliomas (LGG) in the brain is often difficult given their infiltrative nature and the risk of neurological morbidity.^{1,12,14} Current data on the value of surgical treatment is mostly based on observational studies.¹² Consequently, the goal of maximum resection in patients with minimal symptoms remains controversial, despite the fact that those studies show improved overall survival (OS) after GTR.^{1,15} Recently, a population-based parallel cohort study conducted in Norway provided very good evidence of improved survival for patients with LGG treated using early surgery as opposed to watchful waiting, the best evidence so far arguing for the former approach.³ Nevertheless, it has been argued that any incremental survival advantage in patients treated with GTR is simply a self-fulfilling prophecy of selection bias.¹² Recent advances in our histopathological, molecular, and genetic understanding of LGG, however, have prompted more nuanced management strategies. Several significant demographic, clinical, and pathological prognostic factors that can aid the treatment team regarding the use of postoperative adjuvant therapy have been reported.² Advanced age, larger tumor volume, subtotal resection, and diffuse astrocytoma subtype have been found to be associated with unfavorable outcomes, and additional therapy has had a beneficial effect in patients with these features.^{9,10} Recent advances in the molecular and genetic profiling of LGG have resulted in more accurate survival predictions, which has necessitated a thorough examination of the utility of adjuvant therapy after subtotal resection (STR).⁶

Adjuvant Chemotherapy

In this issue of *Neurosurgical Focus*, Nitta et al. provide a treatment strategy for LGG based on extent of resection with an emphasis on two WHO Grade II subtypes: diffuse astrocytoma and oligodendroglial tumors. Utilizing results from their retrospective cohort study, these au-

thors highlight the predictors of OS and progression-free survival (PFS).⁹ In both LGG subsets, radiotherapy (RT) did not clearly correlate with an OS or PFS advantage. Alternatively, adjuvant chemotherapy with nimustine hydrochloride (ACNU) and vincristine after STR was strongly associated with increased PFS in the oligodendroglial subtype, but did not confer either an OS or a PFS advantage in patients with a diffuse astrocytoma subtype. These findings suggest that the adjuvant treatment of choice in patients with low-grade oligodendroglioma is chemotherapy and possibly repeat surgery in those with low-grade diffuse astrocytoma. However, chemotherapy resulted in a poorer prognosis in oligodendroglioma patients with wild-type *IDH1* and prolonged PFS in patients with *IDH1* mutation and/or 1p/19q codeletion. Overall survival, but not PFS, was found to be significantly associated with *IDH1* status, and repeat surgery was suggested for patients with wild-type *IDH1* regardless of the histopathological diagnosis.

Adjuvant RT

The role of surgery, extent of resection, and RT in the long-term outcome for patients with LGGs remains unresolved given the paucity of Level 1 data that addresses quality of life and/or OS in both symptomatic and incidental LGGs.^{4,14} The European Organisation for Research and Treatment of Cancer (EORTC) 22845 trial, which looked at the long-term efficacy of early versus delayed RT in adults with LGG, was an attempt to determine the role of adjuvant RT. Trial researchers found statistically significant improvement in PFS in the early-irradiated group. Salvage chemotherapy was also administered to 37% of the irradiated patients who had demonstrated clinical or radiographic recurrence.¹⁵ In the Radiation Therapy Oncology Group (RTOG) 98-02 trial, Shaw et al. demonstrated significantly higher PFS in patients treated with early RT+chemotherapy (procarbazine, lomustine,

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vincristine) as compared with RT alone.^{8,13} Prabhu et al. reported no significant neurocognitive difference between the two RTOG 98-02 treatment arms, decreasing concern over the deleterious effects of chemotherapy in this patient population.¹¹

The Impact of Molecular Profiling

Efforts to molecularly classify LGG have suggested that tumor markers, such as *IDH1* status, TP53 mutations, and 1p/19q loss of heterozygosity (LOH), are stronger predictors of long-term OS than patient demographics, preoperative neurological status, or even the histopathology of the tumor, and these reports have revolutionized contemporary treatment protocols.⁵ Leu et al. demonstrated higher OS in patients with LGG harboring *IDH1* mutations, and this survival advantage was amplified in patients with both an *IDH1* mutation and 1p/19q allelic loss.^{6,7} Mariani et al. emphasized the positive prognostic impact of LOH on chromosomal arms 1p and 19q in the OS of patients with LGG even without chemotherapy, and thus emphasizing the prognostic importance of molecular status.⁷

Conclusions

The treatment of patients with LGG is constantly evolving. New information regarding the molecular profile of LGG is reshaping our understanding of survival prediction, and old treatment paradigms are slowly being reformulated to take advantage of this new understanding. Currently, maximal safe resection followed by RT with or without marker-based chemotherapy is the standard of care to improve quality of life and survival. Future prospective randomized trials addressing the role of tumor histology, potential molecular markers, and adjuvant therapies will inform treatment strategies and ultimately improve outcomes in patients with LGG.

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