Neuro-Oncology
24(5), 794–795, 2022 | https://doi.org/10.1093/neuonc/noac008 | Advance Access date 10 January 2022

Balancing maximal resection and functional preservation in surgery for low-grade glioma

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The initial management of low-grade gliomas (LGG) has evolved over the past 3 decades. Early debates about the timing of surgical intervention, and in some cases, even whether a procedure to obtain tissue diagnosis should be performed for asymptomatic (incidental) lesions, have been replaced by questions relating to maximizing survival benefit from surgical resection of both symptomatic and incidental lesions suspicious for LGG. Yet, there is recognition that surgically induced impairment of basic neurological functions, such as speech, language, and motor activities should be avoided as they may diminish survival and quality of life (QOL). Fortunately, today's neurosurgical oncologists can employ specialized tools to both maximize the extent of resection and minimize the consequences of surgical treatment.

Publications from the 1990s illustrate the uncertainty that existed at that time regarding the utility of surgery, particularly for incidental lesions. Some neurosurgeons advocated surgery at the time of radiographic diagnosis of an LGG in order to obtain tissue to make a specific diagnosis and to evaluate for markers of biological aggressiveness.[1] Others advocated for delaying surgery for patients who did not require surgical intervention to resolve mass effect-related, potentially reversible neurological deficits, noting that the literature to date was largely descriptive and observational only.[2] Indeed, some studies that evaluated the timing of treatment after radiographic diagnosis appeared to demonstrate that the patients who had early or late surgery had similar outcomes.[3,4]

Yet, the evidence supporting a clinical benefit from initial surgical resection accumulated. Most studies focused on the relationship between residual tumor volume and survival in high-grade (enhancing) gliomas (HGG), which has become a generally accepted relationship. For non-enhancing tumors that are proven to be LGGs, the evidence is less robust but appears to support a similar relationship, at least in terms of delaying progression to high grade. One recent population-based parallel cohort study compared two strategies for managing LGG: early surgery vs. watchful waiting, and after matching for molecular genetic subtype found that there was an overall survival difference between the groups favoring early surgery. Could the timing of progression of LGG to HGG be impacted by the relative density of tumor cells in brain tissue due to interactions between tumor cells themselves?[5]

Despite the belief that the extent of resection provides meaningful clinical benefit, there was also recognition that major neurological complications related to surgery, which result in a drop in Karnofsky Performance Status (KPS), could provide a cost to survival. But not all deficits produce a meaningful reduction in KPS. For example, KPS is a relatively insensitive measure for loss of memory and other cognitive functions. Further, one must recognize that patients with LGG are expected to survive years, if not decades for some of the more indolent molecular genetic subtypes. Quality of survival is of paramount importance. Drawing from decades of experience with the surgical management of epilepsy, neurosurgeons introduced preoperative and intraoperative mapping and monitoring of speech, language, and motor functions into the surgical management of LGG. Mapping in the setting of LGG is in some ways different from the approach used in epilepsy surgery, which required extensive mapping of functionally active cortex to define its anatomic relationship to presumed seizure foci. For LGG, mapping could be limited to optimize the path of access to tumor tissue and intraoperative functional monitoring could be used to define the functional limit of tumor removal.[6] While the typical anatomic localization of speech, language, and motor functions and ease of assessment made it possible for their routine assessment and monitoring in the OR, there are additional aspects of neurological functioning that may be impacted by LGG and its removal.

Neurocognitive decline has been recognized as a complication of gliomas, and in some cases, changes in neurocognitive function can be detected earlier than changes on MRI that indicate overt tumor progression.[7] Further, it has

been observed in patients with LGG that cognitive functioning is associated with health-related QOL.[8] It follows, then, that preservation of not only easily measured and monitored neurological functions (speech, language, and motor) but also more diffusely localized neurocognitive functions should be achievable if early surgery is to be considered standard for LGG.

A study by Lemaitre et al[9] in this month's issue details the longitudinal assessment of neurocognitive function in patients who underwent surgery for LGG. The authors note that 86% of patients demonstrated no cognitive decline in the setting of aggressive tumor removal (mean extent of resection of 92.3%). With 82% of the patients living longer than 5 years, this high rate of neurocognitive preservation seems meaningful. But what if surgical resection had not been performed—would that have eliminated the risk of loss of neurocognitive function. Other evidence suggests not. It has been observed that progressive deterioration in the function of LGG glioma patients occurs over a period of years,[10] and this decline may be related to the use of adjuvant therapies (radiation therapy, chemotherapy) and/or tumor progression. It is worth noting, as well, that more than half of the patients in the Lemaitre study already had some cognitive impairment preoperatively. So, there is a component of functional deterioration that is tumor-dependent, and presumably unavoidable without earlier detection of LGG. Given the acute nature of a surgical intervention, it is reasonable to conclude that the Lemaitre study demonstrates that surgery itself is unlikely to be a significant factor in long-term neurocognitive decline, and it largely does not produce near-term cognitive loss.

These advances in surgical intervention also should be placed also into the context of our evolving understanding of the optimal management of non-enhancing lesions that are suspicious for glioma. We now understand that not all of these lesions are LGG; some turn out to have the molecular genetic hallmarks of glioblastoma and carry a much more severe prognosis than a true LGG. With these advances in surgical technique and biological understanding of gliomas, it becomes harder to support the approach of "watchful waiting" for surgically accessible lesions that are suspicious for LGG.

Acknowledgments

The text of this editorial is the sole product of the author and no third party had input or gave support to its writing.

Conflict of interest statement. There are no conflicts to disclose relevant to the topics discussed in this editorial.

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