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Is there an optimal MRI surveillance schedule for patients with high-grade glioma after standard-of-care therapy?

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See the article by Ji et al in this issue, pp. 837–847.

Predictive survival modeling is an area of growing interest in high-grade gliomas (HGGs). The natural history and survival outcomes in HGGs are heterogeneous, and the prognostic and predictive impact of molecular biomarkers such as IDH (isocitrate dehydrogenase) mutation status, O^6-methylguanine-DNA-methyltransferase (MGMT) methylation status, and CDKN2A loss have emerged more clearly over the last decade.[1] In addition, functional status, age, and treatment history, specifically extent of resection, have long been known to be important independent predictors of survival outcomes. While some of these variables can help with overall prognostication, predicting survival (and recurrence) for individual patients remains challenging. Advanced imaging or molecular prognostic biomarkers of early vs late progression in HGGs have emerged as promising areas of active research.[2]

Currently, MRI is the imaging modality of choice for treatment planning and follow-up in HGG. The current guidelines regarding how often MRIs should be performed within the clinical framework of managing gliomas are based on societal[3,4] or organizational guidelines (namely the National Comprehensive Cancer Network Guidelines),[5] rather than biomarkers of individual tumors other than histological grade. In HGG, it is broadly recommended that the first postoperative scan be obtained within 48 hours of resection, and that the following MRI should occur 2-8 weeks after chemoradiation. While this scan is used to establish a new baseline, radiation-induced effects such as pseudoprogression are common during this timeframe and may mimic tumor progression, and therefore at least one additional confirmatory scan is recommended prior to any change in therapy or additional intervention.[6] Post-radiation, and upon initiation of adjuvant therapy, a scan is recommended every 2-4 months for 3 years, and thereafter, every 3-6 months indefinitely. The Response in Neuro-Oncology (RANO) criteria in HGG have been established to provide guidance on grading response[7] and, ideally, follow-up MRIs should capture tumor progression at a point when clinically meaningful interventions can be performed.

In this issue of *Neuro-Oncology*, Ji et al. present a parametric-modeled schedule for follow-up MRI after completion of standard therapy for anaplastic astrocytoma (AA) and glioblastoma (GBM), stratified by IDH mutation status and the presence of residual tumor, based on a single institution retrospective analysis of 277 patients.[8] Separate models were created for GBM and AA, each with layered risk groups based on recursive partitioning analyses. RANO criteria were used to determine radiological progression. This study introduced a piecewise exponential model with 10% progression rate which was graphically matched to Kaplan-Meier survival curves for GBM and AA. This progression rate was arbitrarily chosen by the authors but was felt to reflect a reasonable threshold for detection of progression within real-life clinical practice. The model utilized by the authors accounts for the change in risk of progression over time and identifies the close follow-up periods as being approximately 2.3 years from diagnosis for IDH-wild-type GBM, 2.9 years for IDH-mutant GBM, and 4.6 years for all AAs. After this timeframe, the proposed model diverges from the current standard recommendations, allowing follow-up imaging to be spaced out considerably. By nature of its design, this study only included patients who were able to complete standard of care treatment with surgery and concurrent chemoradiation with temozolomide and 6 adjuvant cycles of temozolomide. As a result, all early progressors were effectively excluded, as reflected by the relatively high proportion of (1) MGMT methylated tumors and (2) patients with "no residual disease after standard treatment" within the included cohort. These long-term HGG survivors, for which this schedule is therefore best suited, may represent a distinct population with a different clinical and molecular profile than those at risk of progression during standard therapy or following the initial close follow-up phase. Despite this

limitation and the need for external validation, the authors' work should be applauded as it is one of the first studies to establish an evidence-based model for an imaging follow-up schedule in HGG.

An essential question, however, remains the clinical usefulness of earlier asymptomatic detection of recurrent disease in the surveillance stage given the absence of effective salvage strategies for HGG. Patients whose recurrent disease are detected through routine surveillance imaging appear to have similar overall survival compared to those who have symptomatic detection outside of scheduled surveillance scans.[9] While treatment strategies such as re-resection (if feasible) or bevacizumab could increase progression-free survival, overall survival at recurrence for HGG remains dire and there are currently no proven life-extending treatment options. Arguably, motivated and eligible patients may be enrolled sooner in clinical trials if disease recurrence is captured prior to the development of symptoms (and decline in functional status), and this may on a broader scale benefit clinical trial accrual and contribute to the advancement of research. On an individual level, patients may also feel reassured by the predictability of a surveillance schedule. Regardless of the advantages and setbacks of such a schedule, the question of proper resource utilization has never been more relevant as the COVID-19 pandemic has highlighted the need to re-evaluate practices in neuro-oncology. As a result, potential benefits of surveillance scans in asymptomatic patients also need to be weighed against minimizing exposure risks, health care system overloading, and general cost-effectiveness. We may thus be at a unique juncture, with the opportunity to re-evaluate current practices, aided by past evidence and the right modeling and validation tools.

Predictive analytics and artificial intelligence in health care should aim to improve the outcomes of individuals and the overall effectiveness of the systems through which they navigate. While model-generated surveillance schedules are a helpful guide to clinicians, independent external validation is key to evaluate their performance in heterogeneous patient populations and clinical care settings and to further determine their true clinical utility in the care of HGG patients.

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