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Commentary

Recurrent Glioblastoma: Nuances and Insights

We reviewed with interest the article entitled as "*The impact of surgery on the survival of patients with recurrent glioblastoma*" in this issue of AJNS. This case–control study evaluates the impact of surgery on the survival of the patients with recurrent glioblastoma over a 5-year period. One hundred and fifty-seven cases of recurrent glioblastoma are enrolled, and the baseline characteristics and survival of the patients who had at least one new tumor resection followed by chemotherapy (reoperation group, n = 59) are compared with those who received only medical treatment for recurrence (no-reoperation group, n = 98). The study concludes that repeated surgery for those patients with recurrent glioblastoma who have a good functional status (the WHO performance status of 0 or 1 and KPS score > 70) helps achieve prolonged survival with an acceptable complication rate given the overall poor prognosis of glioblastoma multiforme (GBM).

The treatment of recurrent glioblastoma is one of the most challenging issues in neuro-oncology practice. Patients with recurrent GBM usually face a rapid decline in performance status, quality of life, neurocognitive adverse effects from previous treatments, and median overall survival <1 year.[1] Several studies have confirmed a role for performance status, age, focal versus multifocal disease, smaller preoperative tumor size, and favorable tumor location with a greater likelihood of complete and safe resection as predictors of improved survival.[2-4]

Although re-radiation, repeated resection, antivascular endothelial growth factor (VEGF) agents, and chemotherapy are still the most common used therapies for treating recurrent glioblastoma, the clinical benefit from these treatments is still not well established and is limited due to retrospective study designs and lack of randomization.[5]

There is a growing body of evidence suggesting that a personalized therapeutic approach for the stratification of glioblastoma patients to novel treatment regimens is necessary to improve survival rates for glioblastoma patients. Indeed, genetic profiling of glioblastoma samples has revealed aberrant expression of several potential therapeutic targets including a number of receptor tyrosine kinases (EphA3, EGFR, VEGF, platelet-derived growth factor receptors, and MET),[6,7] however, there has been variable and limited success rates for clinical application of inhibitors of these targets as anticancer therapy have been reported. This elucidates that a better understanding of the basic biology of GBM is required so that additional targets can be identified. The heterogeneity in glioblastoma is both intertumoral and intratumoral, with each tumor presenting a complex heterogeneous setting of cell biology. The resistance of GBM to current aggressive chemoradiotherapy can be attributed to the tumor's extensive cellular heterogeneity and the presence of multiple subclonal populations that invariably either respond to or escape therapy, regenerating treatment-refractory recurrent tumor. Current models for the study of GBM fail to directly address the problem of GBM recurrence and continue to focus efforts on understanding primary, treatment-naive tumor biology. New models of GBM must address both spatial and temporal intratumoral heterogenicity. A detailed understanding of the evolutionary dynamics of tumor progression will provide insight into the associated molecular genetic mechanisms underlying GBM recurrence.

Despite the promising outlook for personalized therapeutic approaches to treating GBM patients, identification of therapeutics that can cross the BBB, while maintaining therapeutic concentrations, still remains a challenge. Furthermore, although targeted therapies show limited efficacy as single agents, the combination of several targeted therapies may be of benefit to GBM patients. Thus, further studies are required both to identify new therapeutic targets and to design novel therapeutic strategies for the treatment of glioblastoma.

The identification of pathways governing therapy resistance in clonal subpopulations will allow clinicians to offer patients therapeutics that selectively target the specific subclonal populations that drive GBM recurrence in each individual patient, leading to improved prognosis and outcomes.[8]

Last but not least, an interdisciplinary dedicated team, including neuro-oncology, radiology, radiation oncology, and neurosurgery, is needed to manage the patients who suffer from glioblastoma recurrence, a multifaceted problem that needs multidisciplinary management. We would encourage constituting institutional dedicated teams within referral centers for a deep understanding and handling of recurrent glioblastoma.

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Conflicts of interest

There are no conflicts of interest.

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