

Editorial

Glioma: A continuing challenge and a mystery?

Glioma has no longer remained a primary neurosurgical disease. Recent advances in diagnostic radiology, neuropathology, and molecular biology have radically changed the current understanding of glioma. It is essentially an infiltrative disease. The entire spectrum of gliomas could be better described as 'Glial infiltrative disease' (GID). A multidisciplinary approach involving the neuroradiologist, neuropathologist, radiation oncologist, and medical oncologist, in the treatment of gliomas, has become the standard of care. The heterogeneity of gliomas is puzzling and a 'cure' for gliomas still appears out of sight. Glioma is a heterogenous tumor arising from the supporting glial cells of the brain and the spinal cord. Although no underlying cause has been identified for a majority of malignant gliomas, there appears to be an association between the immunologic factors, gene polymorphism, and sequential accumulation of genetic aberrations. It is a genetic disease, the manifestation of which is a function of time and has a wide range from birth till one becomes old. There is no method as yet that can predict the time of manifestation of glioma or the time of transformation of glioma to a higher grade. Usually, in younger patients it commences as a low-grade tumor and over a period of time evolves into a higher grade tumor. The eventual fatal outcome is almost a certainty. The time and rate of transformation into a higher grade variety is uncertain and unpredictable. They may also present as primary high-grade gliomas, especially glioblastomas occurring in patients older than 50 years, and the overall outcome is guarded in these patients in spite of the intense treatment protocols.^[1] It is well known that the average age (time for transformation) for a low-grade glioma is about 7 to 10 years and the life span of a high-grade glioma patient (glioblastoma multiforme, GBM) is about two to three years, with the best of treatment protocols.

The major stride in understanding the gross behavior of glioma has been objectively possible due to the advances in magnetic resonance (MR) imaging including special sequences, namely, perfusion studies, functional studies, and MR spectroscopy. The primary status (low or high grade) of the glioma, the extent of involvement of the critical neural structures, the presence or absence of the preoperative seedling of leptomeninges or ventricles or spread to the spinal canal can be

objectively demonstrated. T2 flair studies have been particularly informative in mapping the extent of the disease. Advances in radiology can now reasonably distinguish between treatment-related effects, namely, postoperative changes, radiation-induced change or frank necrosis and pseudoprogression of disease following temozolomide administration. The treatment paradigms have been significantly altered on a timely basis due to the significant inputs obtained from neuroradiology colleagues. The application and interpretation of neuroradiology advances such as MR spectroscopy and perfusion studies can sometimes be difficult and no definite conclusion or concrete recommendation can be derived. A high level of training and expertise is required to maintain accuracy.

In spite of the major advances in the field of neurobiology and molecular genetics, the understanding of the nature and behavior of glioma still remains a mystery. Consequently, the therapy for glioma presents a continuing challenge for the multidisciplinary team. Precise neuropathological diagnosis is paramount to achieve optimum results of the therapy. The neuropathological interpretation can have interobserver bias and requires skill, expertise, and a good understanding of the neurobiology of a glioma. A central review of the pathology is more likely to reduce the bias. Histological diagnosis is crucial and is the ultimate deciding factor for the institution of appropriate therapy. It is a formidable challenge, since with newer advances in immunohistochemistry, the characterization and categorization of glioma have changed, resulting in serial modifications and revision of the WHO classification of gliomas. The World Health Organization (WHO) has coined several newer terminologies for which there are fewer cases and information in the literature. The decision to reoperate or observe, to deliver radiation or not or to administer chemotherapy is entirely dependent on the correct histological diagnosis. In spite of the advances in immunohistochemistry, the importance of the Hand E stained slide cannot be underestimated. As advances in neuropathology unfold, many variations and subtypes of glioma, whether they are completely benign, intermediate grade or frankly malignant, have been reported. It is sometimes difficult to differentiate glioma from central nervous system (CNS) infections and demyelination.

The initial treatment of a glioma, low or high grade, is essentially surgical. It could range from a stereotactic biopsy to radical excision depending on the involvement or proximity to eloquent sites in the brain and the extent of infiltration. A safe radical excision is the goal. However, subsequent therapy is largely guided by neuropathological diagnosis and the clinical neuro-oncologist. Re-exploration for recurrence of tumor is advocated in some cases, to enhance the quality of life or as a salvage measure. The modern day neurosurgeon is blessed to have state-of-the-art neurosurgical microscopes with neuronavigation compatibility, improved anesthesia techniques with provision for awake craniotomy, advanced microinstrumentation, better three dimensional understanding of the microanatomy of the brain, stereotaxy, functional mapping, and fiber tracking technology. The primary aim of all the advances is directed at better understanding the pathology and biological behavior of glioma, thus enabling the surgeon to select the appropriate surgical strategy, trajectory, approach to the tumor, and intraoperative decision, to perform surgical excision ranging from biopsy to complete resection. Unlike surgery for extra-axial brain tumors like meningioma or neurinoma, intra-axial tumors, especially gliomas, pose a tremendous challenge for the neurosurgeon. The surgery for glioma is one of the most difficult neurosurgical problems, as the tumor cells can imperceptibly blend with the normal functioning tissue, which may not be appreciable even to the microscopic eye.

Can glioma be completely excised? The so-called 'complete excision' is suggestive of a gross total excision and not a 'radical' excision as the descriptive terminology in cancer therapy. A 3 cm margin would not be plausible in brain considering the complex anatomy and eloquent nature of the brain. Since glioma is essentially an infiltrative disease, a certain component of the tumor, low grade or high grade, is likely to remain in the vicinity of the gross bulk of the tumor. The main aim of surgery is to provide tissue diagnosis and decompression without any enhanced neurological deficit. Symptomatic relief enhances the quality of life. The safety of surgery has been improved by advanced neurosurgical technology including neuronavigation, intraoperative MRI, functional MRI, intraoperative mapping, as well as, fluorescence-guided surgery. The relationship between progression-free survival and the extent of removal of the glioma has been studied extensively by various groups. However, there is no general consensus whether the extent of surgical removal of a glioma significantly enhances the long-term survival of a glioma patient, but a modest survival advantage is reported.^[2] In recurrent malignant gliomas involving inaccessible and deep-seated areas, 'no further

treatment' is also a good option. In a majority of patients, the primary goal of surgery has been to relieve the symptoms of raised intracranial pressure and in turn enhance the quality of life for a short term.

The cure for glioma is still a distant dream. The behavior of the glioma cell and molecular genetics is not fully elucidated. The ultimate answer to glioma treatment ('glioma magic pill') will come from the geneticist. Till then, the concept of 'curability' from glioma will be a controversial topic. The overall survival for glioma has been modest in spite of recent advances in treatment. Glioma stem cells may contribute to the resistance of malignant gliomas to standard treatments.^[1] The term 'cure' should be preferably not used in the management of glioma, since the biological behavior of a glioma is still not fully understood. Radiation and chemotherapy measures have achieved considerable control rates and modern techniques have been successful in enhancing the progression-free survival rate and reducing the treatment-related toxicity to a certain extent. However, with evidence-based guidelines for treatment of low-grade and high-grade gliomas, new and more challenging issues, such as, radiation-induced necrosis, pseudoprogression following temozolomide administration, and radiation-induced benign and malignant tumors need to be addressed.

The current standard of therapy for GBM is inadequate. There is certainly a need for better therapies. There is a wide heterogeneity and complexity in the genetics of gliomas in general, particularly GBM.^[1,2] Targeted molecular therapies hold promise for the future. Activation of cell signaling pathways does matter.^[1] However, effectively targeting cell signaling pathways is not simple. Critical targets exist in the tumor microenvironment and are currently being explored. Single-agent targeted therapy does not always work and is likely to evolve resistance. Effective delivery of the targeted therapy is paramount, which includes adequate intratumoral concentration ensuring confirmed target inhibition. Clinical trials involving antiangiogenic agents that cause inhibition of VEGF and integrins have shown promising results. Glioblastoma multiforme is complex tumor to target, and selection of the right patient is vital for optimizing treatment response. Therapeutic strategies effectively targeting stem cells and overcoming their resistance to treatment will be necessary for eradication of malignant gliomas.^[1] The possibility of personalization of therapy, with better targets using gene-expression signatures, based on the patient's tumor genotype, also needs to be further explored.^[1,2]

In a country like India, the majority of the population

cannot afford the treatment expense since there is no standardization in medical insurance policy. With newer advances in molecular biology and therapeutics and novel drugs being inducted into clinical practice guidelines and standard of care, the treatment for GBM can be prohibitively expensive, even for the higher and middle income group families. They would need active support from nongovernmental social organizations. The approach to treatment of gliomas should have a philosophical inclination, primarily involving the patient and the family interests at the core, since lifelong cure is still not a certainty.

The glioma patient requires to be treated with passion and care. The recommendation for treatment should help him lead a good quality of life. Appropriate measures such as surgery, radiation or chemotherapy should be judiciously utilized. There has to be a general consensus amongst the neuro-oncology team, exercising a certain option for a glioma patient in a given clinical scenario. The spectrum of recommendation may range from observation, surgery, adjuvant treatment, resurgery or observation and palliative adjuvant therapy. The recommendations made by specialists should be according to scientific evidence, but sometimes they are more influenced by the specialty to which one belongs.^[3] The patient and his family should be apprised about the pros and cons of the treatment and their consent is necessary. Good education, counseling, and rehabilitation measures are the key factors. The neurosurgeon's opinion in the management of complex recurrent or residual malignant gliomas is vital, since re-exploration has its own risks and potential complications. The justification for surgical treatment or adjuvant therapy in small recurrent or residual gliomas, which do not

endanger the quality of life, is still difficult. Although an MR study may suggest a postoperative or radiation-induced change, pseudoprogression or recurrence, it is still an evolving subject, with recommendations being 'suggestive' and may not be necessarily 'definitive'. The changes seen on radiological imaging should be correlated with the neurological picture to decide treatment-related issues. There may be a time when an honest advice of not treating a recurrent high-grade glioma may arise or the patient and / or his family deferring further treatment needs sympathetic consideration. The role of the neurosurgeon in the management of gliomas has been primarily surgical. However, there is need for the present day neurosurgeon to be literate in molecular biology and genetics, since his role as a neurosurgeon-scientist, especially in the basic research on gliomas, is vital.

Muzumdar D

Department of Neurosurgery, Seth Gordhandas Sunderdas Medical, College and King Edward VII Memorial Hospital, Mumbai, India

Correspondence to: Dr. D.P. Muzumdar,
E-mail: dmuzumdar@hotmail.com

References

1. Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med* 2008;359:492-507.
2. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. *Neurosurgery* 2008;62:753-66.
3. Linskey ME. The emergence of clinical practice parameter guidelines in neuro-oncology: Promise of utility tempered with caution. *J Neurooncol* 2008;89:359-62.

DOI: DOI:10.4103/0019-509X.49144 **PMID:** 19346640