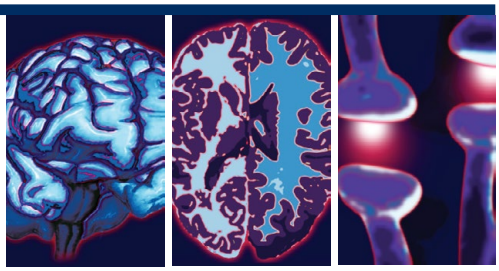
Opinion



What is Making News in Neuro-oncology?

Suhag V[1]*, Sarin A[2], Dutta V[1], Sunita BS[1], Dubey AP[1], Purkayastha A[1]

Central nervous system neoplasms include diverse group of tumors with a wide spectrum of morphologies, tissues of origin, histologic subtypes and molecular abnormalities. Despite their relatively rare occurrences, these tumors can result in considerable mortality as well as morbidity. Depending on their tissue of origin, these neoplasms can be broadly divided into glial and non-glial tumors. Primary glial neoplasms constitute a major group of CNS tumors and incorporate entities like astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. Non-glial tumors are relatively uncommon and may be derived from diverse structures like pineal gland, meninges, germ cells, hematopoietic cells, metastases etc. Gliomas are the commonest primary CNS tumor, comprising about 80% of all brain tumors. Glioblastoma multiforme, the commonest histology, is quite aggressive with a 5-year relative survival of less than 5%. The treatment options essentially include maximal safe resection of the tumor followed by concurrent chemoradiation and adjuvant chemotherapy depending on the histological features, molecular studies, quantum of residue and other risk factors. Over the last 2 decades, advances in the fields of neurosurgery, radiation delivery techniques, imaging modalities, molecular and translational research, chemotherapy and immunotherapy have made the clinical scenario more optimistic, though this is yet to be translated into significant improvement in overall survival. Despite the multimodal aggressive treatment, the prognosis of patients with high grade gliomas remains poor; with a median overall survival of about 15 months. Relapse is quite often, commonly due to the extensive spread of tumor cells into surrounding regions of the brain, difficulties in complete resection due to eloquent locations, and relative chemo/radio resistance of such tumors [1, 2].

Imaging has got a significant role in the diagnostic workup, response assessment to chemo-radiation and follow-up of brain tumors. The characteristic anatomical features of CNS neoplasms imaging include the presence of contrast enhancement, hemorrhage, calcification and macroscopic necrosis. Locally advanced tumors may result in mass effect, edema and herniation which can be assessed via CT and MRI. According to the standard guidelines for imaging of brain tumors, Gadolinium-enhanced MRI is the imaging modality of choice for most brain tumors. Novel functional and metabolic MRI imaging provides the ability to analyze tumor tissue properties including tumor vasculature, vascular permeability, tumor cellularity, hypoxia, and tumor proliferation. Advanced physiologic MRI modalities such as MRS, MR perfusion, MR diffusion, and fMRI remain potentially useful modalities for further evaluation in selected cases, especially differentiation of tumor recurrence from post-radiation treatment effects. Similarly, PET imaging with experimental radiotracers beyond FDG, including FLT, FMISO, and multiple amino acid compounds, have shown early promise for improved characterization of brain tumor biology as compared to MRI and FDG PET alone [3].

The field of neurosurgery and skull-based surgery has witnessed significant advancements over the past two decades. The conventional large, open surgeries with their inherent morbidities have been replaced by endoscope-assisted minimally invasive neurosurgical techniques. Advantages of these novel techniques include lesser post-

[1]Army Hospital, Delhi, India

[2]Oncology Centre, Command Hospital (SC), Pune, India

[†]Author for correspondence: Lt. Col. Virender Suhag, MD DNB, HOD Radiation Oncology Army Hospital (R&R), Delhi-110010, India, Tel: +918826804584; E-mail: virendersuhag@gmail.com

operative pain, lesser need of medications, small and cosmetically better scar, prompt recovery, lesser duration of hospital stay and early return to work. The state-of-art neurosurgical centers are integrating advanced 3D imaging, computer simulation and next-generation surgical tools to perform a highly complex brain surgery through a small incision to remove deep-seated tumors which decreases the risk of the surgery and shortens the patient's hospital stay. A critical part of this surgery involves identifying the neural fibers in the brain and their orientation with restriction spectrum imaging, thereby enabling safe resection of tumor within millimeter precision and minimizing any post-surgical neurological deficit [4].

Direct cortical stimulation has got an evolving role during surgery for high-grade gliomas to successfully locate and preserve cortical areas responsible for language; and thus allows preservation of motor function. Functional localization of eloquent cortex can enable maximal safe resection without any deficit. These eloquent areas can be pre-operatively identified by functional MRI and diffusion tensor imaging fiber tracking. The help of neurophysiological methods like navigated transcranial magnetic stimulation and magnetoencephalography,can also be sought to improve functional outcome without compromising quality of life. Local drug delivery of polymers like Gliadel wafer containing carmustine (BCNU) placed in the resection cavity at surgery and availability of novel compounds that modify brain tumor biology is further likely to enhance drug delivery beyond blood brain barrier. The use of polymer wafer enables delivery of higher dose of chemotherapy directly into brain tumor tissue thereby minimizing systemic effects of chemotherapy and resulting in small survival benefit. However the rate of complications, including an increase in perioperative surgical site infection, cerebrospinal fluid leaks and intracranial hypertension, has limited their use. Though quantum improvements in imaging and management of brain tumors have been made, the infiltrating edge of the tumor and distant microscopic satellite lesions are difficult to be identified and suitably addressed, which may result in residual and recurrent disease [5, 6].

The field of radiotherapy has witnessed major leaps in advanced and précised radiation delivery techniques in the last two decades. Intensity-modulated radiotherapy (IMRT) , Image guided radiotherapy (IGRT) and volumetric-modulated arc therapy (VMAT) provide highly conformal target radiation doses, but can also expose large volumes of healthy tissue to low-dose radiation if proper planning and contouring is not done. Frameless or with-frame classical single-fraction stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy can be executed non-invasively by Gamma Knife, Cyber knife, helical tomotherapy and other advanced linear accelerators. These techniques play significant role in the treatment of cranial lesions, including primary brain tumors, brain metastases and functional disorders of cranial nerves. The recent paradigm changes in oncological practice including more individualized and focused treatment for any individual patients requires highly sophisticated infrastructures and dedicated team of radiation oncologists, medical physicists and dosimetrists. Use of SRS for metastatic lesions to brain is no longer limited to patients with 3 or fewer lesions, because data suggest that total disease burden, rather than number of lesions, is predictive of survival benefits associated with the technique. SRS is increasingly becoming an integral part of management of patients with controlled, low-volume brain metastases. There is a promising role of treating the surgical cavity with radiosurgery after resection of oligo metastases. Another newer approach is the GliaSite RTS which involves placing an inflatable balloon in the area of the brain tumor at the time of surgery. Low-dose-rate radiation is delivered through a catheter into the balloon [7, 8].

With the evolving role of novel techniques like fluorescent in-situ hybridization (FISH) and polymerase chain reaction (PCR) techniques, molecular phenotyping of brain tumors is playing a significant role in diagnosis, workup and prognostification of brain tumors. The neuropathologists are increasingly playing an important role in providing a morphological diagnosis as well as additional information on biological behavior, likely response to targeted therapies and the outcome. Molecular tumor signatures help oncologists select the best molecular and targeted therapies available. The conventional histopathological diagnosis is being increasingly supplemented with array based profiling techniques and use of molecular tests, such as **MGMT** promoter hypermethylation in glioblastomas and detection of losses of chromosome arms 1p and 19q in oligodendroglial tumors. The common molecular changes encountered in gliomas include co-

deletion of 1p19q, O6-methylguanine-DNA methyltransferase (MGMT) methylation, and Isocitrate dehydrogenase 1 (IDH1) mutation. Availability of sophisticated tumor-specific genomic or transcriptional signatures has been significantly facilitated by evolution of novel array-based profiling techniques which may serve as a valuable adjunct to the classical histological classification [9, 10].

O6-methylguanine DNA methyltransferase (MGMT) has got a role in removing DNA alkylation adducts, thus allowing repair of damaged DNA, which can potentially result in drug resistance of gliomas to alkylating agents. Approximately 50% of GBMs exhibit MGMT, these tumors is less likely to respond to temozolomide chemotherapy. IDH1 (isocitrate dehydrogenase-1), a metabolic enzyme, is known to undergo mutations that are associated with gliomas and can provide prognostic implications to the diagnosis. Mutations in IDH1 are often seen in grades II and III astrocytomas, oligodendrogliomas, oligoastrocytomas and secondary GBMs. Gliomas with mutated IDH1 and IDH2, as detected by immunohistochemistry and magnetic resonance spectroscopy, have better prognosis as compared to their wild-type counterparts [11, 12].

Cellular immunotherapy has recently shown promising role in management of malignant gliomas, based on the use of cells from the innate and adaptive immune system to mount an antitumor response. Cellular immunotherapy can specifically target brain tumor cells, thereby limiting brain damage, and can also stimulate the immune system, thereby establishing a long-term antitumor response by. For this, T cells can be used as cellular vehicles and can be modified with tumor-specific antigens to target the tumor. Another technique in T cell-based immunotherapy is the use of chimeric antigen receptors (CARs). Approaches to immunotherapy include passive immunity and active immunity. Passive immunotherapy approaches include direct administration of monoclonal antibodies or cytokines or adoptive immunity with cytotoxic T lymphocytes or lymphocyte activated killer (LAK) cells. Dendritic cell vaccines have shown encouraging results, producing clinical responses and increased progression-free survival in patients with recurrent and newly diagnosed GBM [13, 14].

An important aspect in management of CNS tumors is meticulous periodic follow up to pick up early recurrent and residual diseases, where neuroimaging and PET-CT play a vital role. FDG based PET-CT for routine imaging of brain tumors should be practiced with caution, especially in follow-up cases. 18F-fluorodeoxyglucose (18F-FDG) is the most widely used tracer for evaluation of patients with primary central nervous system lymphoma. Amino acid PET has been found useful for surgery and for planning biopsy; it has also got a role in response assessment in suspected primary brain tumors as well as metastatic lesions. Both (18) F-fluorodihydroxyphenylalanine ((18)F-DOPA) and (18)F-fluoroethyltyrosine ((18)F-FET) have been used successfully for imaging of brain tumors. It is very important to differentiate tumor recurrence from radiation necrosis, and (18)F-FDOPA PET/CT is highly useful in such clinical scenario and has been proved superior to (18)F-FDG PET/CT for this purpose. The integrated PET/MRI scanner offers certain advantages like co-registered multimodal, high-resolution data with reduced radiation exposure [15-18].

Evidence based medicine is playing an increasingly important role in management of CNS tumors. Most of the dedicated neuro-oncology centers adhere to standard guidelines like National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), and American Brain Tumor Association (ABTA) etc. However, the management of each patient need to be individualized based on the performance status, facilities available, expertise in complex surgery, financial constrains and socio-cultural considerations. In most developing and under-developed nations, facilities of molecular phenotyping and targeted therapies may not be available; and patient need to be offered the best feasible care in the form of maximal safe resection and conventional or conformal radiotherapy within existing resources.

Recently, a landmark phase 2 study of Radiation Therapy Oncology Group (RTOG) 0424 was conducted which enrolled high-risk low-grade glioma (LGG) population who were treated with temozolomide (TMZ) and radiation therapy (RT), and outcomes were compared to those of historical controls [19]. The 3-year OS rate of 73.1% for eligible patients treated in RTOG 0424 is higher than a priori specified historical controls treated with radiation therapy alone (**P**<0.001). This study has paved the way for further studies of combined chemo-radiation in LGGs and for the use of TMZ in combination

with radiation therapy to treat LGGs. Another important area of interest is role of vascular endothelial growth factor (VEGF) and other antiangiogenic agents on GBM. Early studies in the recurrent GBM setting were promising and prompted two multinational randomized phase three trials (AVAglio and RTOG 0825) investigating the effect of bevacizumab, an anti-VEGF monoclonal antibody, in newly diagnosed GBM [20]. However, the ultimate utility of antiangiogenic therapy in the management of GBM remains unclear. There is an urgent need to better understand the biology underlying angiogenesis and tumor survival, as well as mechanisms of antiangiogeneic resistance. Most of these studies are having pitfalls like selection bias, not involving patients across all spectrum of CNS tumors, lack of coordination between diagnostic and therapeutic approach and lack of uniformity among different specialists and institutions. Ultimately, multipronged approaches using functional imaging, antiangiogenic agents, targeted molecular therapy, and immunotherapy or cytotoxics will be needed to improve treatment outcomes.

To summarize, CNS tumors include a spectrum of uncommon tumors which need to be addressed multimodally by a team of neurosurgeons, radiation oncologists, medical oncologists and neuropathologists. Newer developments in field of radiation oncology, neuroimaging, molecular imaging and immunotherapy are likely to improve the prognosis in days to come. Recurrence should be picked up early and need to be addressed aggressively by re-do surgery, re-irradiation, salvage chemotherapy with agents like Irinotecan and Bavacuzimab. Enrollment in trials should be encouraged. Patients with poor performance status are best managed in palliative care centers or should be offered best supportive care at home.

References

1. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, et al. (2014) The epidemiology of glioma in adults: a "state of the science" review. Neuro Oncol 16: 896-913.
2. Punsoni M, Donahue JE, Elinzano HD, Kinsella T (2015) Updates in Molecular Pathology of Central Nervous System Gliomas in Adults. R I Med J (2013) 98: 17-19.
3. Fink JR, Muzi M, Peck M, Krohn KA (2015) Multimodality Brain Tumor Imaging: MR Imaging, PET, and PET/MR Imaging. J Nucl Med 56: 1554-1561.
4. Asthagiri AR, Pouratian N, Sherman J, Ahmed G, Shaffrey ME (2007) Advances in brain tumor surgery. Neurol Clin 25: 975-1003, viii-ix.
5. Brell M, Conesa G, Acebes JJ (2003) [Intraoperative cortical mapping in the surgical resection of low-grade gliomas located in eloquent areas]. Neurocirugia (Astur) 14: 491-503.
6. Nagpal S (2012) The role of BCNU polymer wafers (Gliadel) in the treatment of malignant glioma. Neurosurg Clin N Am 23: 289-295, ix.
7. Rajakesari S, Arvold ND, Jimenez RB, Christianson LW, Horvath MC, et al. (2014) Local control after fractionated stereotactic radiation therapy for brain metastases. J Neurooncol. 120: 339-346.
8. Balducci M, Autorino R, Chiesa S, Mattiucci G, Pompucci A, et al. (2015) Radiosurgery or Fractionated Stereotactic Radiotherapy plus Whole-brain Radioherapy in Brain Oligometastases: A Long-term Analysis. Anticancer Res 35: 3055-3059.
9. Wick W, Weller M, van den Bent M, Sanson M, Weiler M, et al. (2014) MGMT testing--the challenges for biomarker-based glioma treatment. Nat Rev Neurol 10: 372-385.
10. Qiu ZK, Shen D, Chen YS, Yang QY, Guo CC, et al. (2014) Enhanced MGMT expression contributes to temozolomide resistance in glioma stem-like cells. Chin J Cancer 33: 115-122.
11. Leeper HE, Caron AA, Decker PA, Jenkins RB, Lachance DH, et al. (2015) IDH mutation, 1p19q codeletion and ATRX loss in WHO grade II gliomas. Oncotarget 6: 30295-30305.
12. Iaccarino C, Orlandi E, Ruggeri F, Nicoli D, Torricelli F, et al. (2015) Prognostic value of MGMT promoter status in non-resectable glioblastoma after adjuvant therapy. Clin Neurol Neurosurg 132: 1-8.
13. Chung DS, Shin HJ, Hong YK (2014) A new hope in immunotherapy for malignant gliomas: adoptive T cell transfer therapy. J Immunol Res 2014: 326545.
14. Suryadevara CM, Verla T, Sanchez-Perez L, Reap EA, Choi BD, et al. (2015) Immunotherapy for malignant glioma. Surg Neurol Int 6: S68-77.
15. Karunanithi S, Sharma P, Kumar A, Khangembam BC, Bandopadhyaya GP, et al. (2013) 18F-FDOPA PET/CT for detection of recurrence in patients with glioma: prospective comparison with 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 40: 1025-1035.
16. Wardak M, Schiepers C, Cloughesy TF, Dahlbom M, Phelps ME, et al. (2014) ^{18}F-FLT and ^{18}F-FDOPA PET kinetics in recurrent brain tumors. Eur J Nucl Med Mol Imaging 41: 1199-1209.
17. Kratochwil C, Combs SE, Leotta K, Afshar-Oromieh A, Rieken S, et al. (2014) Intra-individual comparison of ^{18}F-FET and ^{18}F-DOPA in PET imaging of recurrent brain tumors. Neuro Oncol 16: 434-440.
18. Suchorska B, Tonn JC, Jansen NL (2014) PET imaging for brain tumor diagnostics. Curr Opin Neurol 27: 683-688.
19. Fisher BJ, Hu C, Macdonald DR, Lesser GJ, Coons SW, et al. (2015) Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys 91: 497-504.
20. Arrillaga-Romany I, Reardon DA, Wen PY (2014) Current status of antiangiogenic therapies for glioblastomas. Expert Opin Investig Drugs 23: 199-210.