A Connect-Approach in High-Grade Glioma Management; Position Statement from the Neuro-Oncology Scientific Club (NOSC), Shiraz, Iran

Mansour Ansari[1], Ahmad Mosalaei[1], Niloufar Ahmadloo[1], Alireza Rasekhi[2], Bita Geramizadeh[3], Ali Razmkon[4], Mohammad Afarid[5], Ali Dadras[5,6], Leila Nafarieh[5], Mohammad Mohammadianpanah[1], Hamid Nasrolahi[1], Seyed Hasan Hamedi[1] , Shapour Omidvari[1], Mohammad Nami[5,7*]

[1]Department of Radiation Oncology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Radiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Neurosurgery, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Behestan Medical Scientific Committee (BMSC), Behestan Group, Tehran, Iran
[6]Institute of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran
[7]Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

***Correspondence:** M. Nami MD, PhD. Assistant Professor of Neuroscience, Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz 71348-14336 Iran. Email: torabinami@sums.ac.ir

Abstract

Portraying a robust working-team model in the practice of neuro-oncology requires continued interdisciplinary efforts. The Neuro-Oncology Scientific Club (NOSC) initiative is an interdisciplinary clinical forum promoting the connect-approach across involved disciplines in the management of CNS malignancies. With its provincial founding-panels and national steering board; NOSC has been operational in Iran since 2011. This initiative has pursued its mission through interval strategic meetings, tumor-boards, case-discussions as well as publishing neuro-oncology updates, case study periodicals and newsletters. A provincial meeting of NOSC in Shiraz, put together insights from international practice guidelines, emerging evidence and expert opinions to draw a position statement on high-grade glioma management in adults. The present report summarizes key highlights from the above clinical forum.

Keywords: Neuro-oncology; Interdisciplinary; High-grade glioma; Position Statement; Shiraz

1. Interdisciplinary Care in Neuro-oncology; Five years with NOSC

The Neuro-Oncology Scientific Club (NOSC) has been an ongoing interdisciplinary initiative fostering team-work in optimal management of brain tumors across Iran since 2011. Over the past five years and under the NOSC umbrella, experts and practitioners from the disciplines involved in brain tumor care have come together to bridge science-, knowledge- and practice-gaps through research endeavors, educational forums and concurrence on clinical pathways in brain tumor management,

respectively (Amouheidari et al., 2013; Ansari et al., 2012; Anvari et al., 2014; Anvari et al., 2011; Anvari et al., 2012; Anvari et al., 2016; Faranoush et al., 2013; Haddad et al., 2015; Haddad et al., 2012; Torabi-Nami, Hejazi Farahmand, & Mohammadzadeh, 2012).

The NOSC comprises provincial and nation-wide steering boards through which its educational and clinical activities are scheduled, planned and implemented. The provincial NOSC founding panel in Shiraz, Southern Iran, hosted an interactive clinical forum entitled: "setting standards for optimal care to high grade glioma patients through interdisciplinary efforts" where over 50 experts and professionals from related disciplines including neurosurgery, radiation oncology, pathology, neuroradiology, neurology and clinical neuroscience participated to discuss the most updated evidence.

Discussions during this NOSC forum revolved around: 1-the significance of connect approach upon diagnosis, treatment and follow-up in CNS malignancies, 2- updates on the molecular pathogenesis of GBM, 3- advanced imaging technologies in high-grade gliomas, 4-novel surgical approaches in glioma and 5- non-surgical management of high-grade gliomas (HGGs).

The present report highlights the communicated insights during the above NOSC meet-up and summarizes the agreed position by Shiraz-NOSC's expert panel on 'optimizing interdisciplinary care to HGGs'.

2. Malignant gliomas and the unsettled clinical burden

The diagnosis, morphological classification and efficiently treating HGGs are regarded as challenging clinical encounters. The clinicopathological data are often insufficiently satisfactory to realize the biology of tumors and to timely identify the therapeutic implications as well as the prognosis (Kim, Satter, Reed, Fadell, & Kardan, 2016; Stupp et al., 2014).

The primary glioblastoma multiforme (GBM) predominantly feature astrocytic differentiation while its secondary types may result from astrocytic, oligodendroglial or mixed tumoral transformation of glial cells.

According to the world health organization (WHO) classification, GBM is regarded as the most common primary brain tumor with preponderating astrocytic differentiation. GBM is basically identified through atypial, mitotic and pleomorphic glial cells together with necrosis, vascular thrombosis, micro-vascular proliferation(Alcedo-Guardia, Labat, Blas-Boria, & Vivas-Mejia, 2016; Evans & Evans, 2016).

HGGs comprise a large number of primary brain neoplasms. Though we have started epidemiological surveys using the NOSC brain tumor collaborative registry (BTCR), the prevalence record for HGGs in Iran is yet to be established (Torabi-Nami et al., 2012). In general, GBM is known to account for up to 15% and 60-70% of the intracranial and astrocytic tumors, respectively (Baldi, Huchet, Bauchet, & Loiseau, 2010; Burton, Ugiliweneza, Woo, Skirboll, & Boaky, 2015; Darefsky, King, & Dubrow, 2012).

Similar to a population-based study conducted Europe which showed that the incidence of GBM peaks at almost the age of 60, and over 80% of the cases were older than 50 years, interim results from our BTCR suggest a comparable trend (Baldi et al., 2010; Haddad et al., 2015). In agreement with the above study, our so far records confirm that GBM is more common in males than females (Haddad et al., 2015).

Given the infiltrative nature of HGGs and their interference with critically-functional and eloquent brain regions, they are typically not amenable to total resection. With a high capacity for micro-infiltration, spreading and rapid progression; GBM's survival tends to be below one year in almost half of the patients (Carlberg & Hardell, 2014; Kong et al., 2014).

Upon confirmation of the primary of secondary GBM diagnosis, the overall survival (OS) is roughly similar. However in secondary GBM, OS depends on the grade of the original pathology which transformed to GBM (Stupp et al., 2009).

When the genetic aspects of the tumors are studied, a large number of mutations may be observed. In many instances, while proto-oncogenes are fortified, oncogene-protecting factors are suppressed. Studies have suggested a long list for gene mutations both for the primary and secondary GBM (Franceschi et al., 2016; Lohkamp et al., 2016; Sarmiento et al., 2016).

In terms of the GBM location, they may appear in any subcortical region of either hemispheres. When almost in two third of the cases GBMs are found in temporal and parietal lobes, they are observed in frontal and occipital lobes in almost 25% and 16% of the cases, respectively. The fronto-temporal presentation of HGGs and GBM in particular is also frequent (Paldor, Drummond, & Kaye, 2016; Tuovinen et al., 2016).

Tumors may infiltrate via the white-matter tracts and through the corpus callosum to conquer the contralateral hemisphere. In children, the presence of HGGs in striatum and the thalamic region is not uncommon. Some infrequent or exceptional locations of the tumor include the ventricles, brainstem, cerebellum and spinal cord (Akbari et al., 2016).

The clinical manifestations of GBM cases may largely vary. In fact, many of the symptoms suggestive for the pathology (including headache, nausea and vomiting, and clouding of consciousness) may root in the increased intracranial pressure or mass effect through invasion, compression and edema. Symptoms arising from the latter may include seizures, focal neurological deficit and altered cognitive functions (Anvari et al., 2012; Haddad et al., 2015).

GBM is generally regarded among most common primary CNS tumors. Though this neoplasm is currently categorized more histologically, genetic studies will soon be positioned as an integral part of the diagnosis, disease profiling and prognostic assessments (Ansari et al., 2012; Anvari et al., 2012).

In practice, treatment approaches are pursued based on the patient's age, performance status and baseline neurocognitive status. In many instances, the standard care comprise surgical resection followed by chemoradiation and adjuvant chemotherapy in cognitively-competent patients younger than 70 years old. In elderly subjects however, radiotherapy and palliative care is perhaps all that is sought (Weller et al., 2014).

Despite the best possible care today, GBM prognosis has remained poor given the aggressiveness nature of the tumor. As such, it is crucial to ensure not only an extended progression-free survival but also an acceptable quality of life is provided through treatments. In terminal cases where treatments are withheld, best supportive or palliative care has to be provided to ameliorate symptoms as much as possible (Weller et al., 2014).

3. Clinical assessment and follow-up of patients with GBM

The general, neurological and cognitive examination constitute the key imperatives while evaluating a case with GBM. When baseline measures are established, an improvement in patients' clinical status can be witnessed, in terms of intracranial hypertension, focal neurological signs or cognitive

profile. The assessment of the patients need to be dynamic based on the response to treatment (Stupp, Tonn, Brada, Pentheroudakis, & Group, 2010; Weller et al., 2014).

As the clinical status improves, evaluation of the patient may advance to more sophisticated tests including neuropsychological evaluations, language assessment, neurocognitive profiling and rehabilitation or studies where the patient's cooperation is definitional including the functional magnetic resonance imaging (fMRI) of functional near infra-red spectroscopy (fNIRS) (Ashjazadeh et al., 2014).

The functional status of patients is usually reported by the Karnofsky performance status (KPS) core or Eastern Cooperative Oncology Group (ECOG) scale, where patients with KPS of 70 and above, or ECOG score of 0 to 1 have maintained their autonomy and can actively engage in activities of daily living (Janinis et al., 2000; Jones et al., 2009).

Other than comprehensive neurological examination, patients would need to be assessed for neurocognitive performance and their quality of life. As such pre- and post-treatment quality of life and neurocognitive manifestations would be comparatively measured as a part of clinical evaluations and follow up (Stupp et al., 2014; Weller et al., 2014). Some validated tools which are used for neurocognitive assessment include test batteries such as Addendrook's Neurocognitive Examination (ACE), Repetitive Battery for the Assessment of Neuropsychological Status (RBANS), trail making test and the multilingual aphasia examination (Ashjazadeh et al., 2014).

4. Treatment protocols and approaches

The choice of treatment is essentially determined by the patient's age, general medical condition, KPS, characteristics of the lesion, extent of surgical removal, survival benefits against risks and patient's willingness (Weller et al., 2014).

The open surgery, navigation-guided or stereotactic biopsy taking can be done to provide histopathological sample to confirm diagnosis. Selection the site for biopsy is crucial since taking samples from necrotic, edematous areas and areas near the subarachnoid space with the potential of bleeding may be life-threatening. A multidisciplinary neuro-oncology group may best decide on the most appropriate site to be biopsied (Haddad et al., 2012).

Moreover, the surgical resection of the lesion done to help decompressing the cerebral tissue, especially when the compressive effects threats patient's life or function. Compared to biopsy only, surgery is known to improve patient's condition and contribute to extended survival (Anvari et al., 2014; Haddad et al., 2012). The improved condition of patients following surgery may enable their access to further treatment measures and the opportunity to respond (Anvari et al., 2014).

To minimize the post-surgical sequellae, functional surgery and awake craniotomy setting have been employed in some centers. To maximize the functional outcome, proximity to eloquent areas (motor, language, sensory, visual), baseline focal neurologic signs and deep location of the tumor (basal ganglia, ventricles, brainstem) need to be well considered upon surgery (Anvari et al., 2012; Haddad et al., 2015).

Baseline neuropsychological assessments and brain-mapping measures for surgical planning would provide useful baseline information. Furthermore, stereotactic radiosurgery or safe maximal resection will be done for which the latter includes intraoperative recording through electrocorticography or somatosensory evoked-potentials where applicable. The setup has already been established in two well-equipped neuroscience laboratories in Shiraz (Ashjazadeh et al., 2014).

4.1. Primary and complimentary treatments in GBM

The choice of treatment in patients younger than 70 years with a KPS of 70 and above is based on the latest EANO guideline (Weller et al., 2014). Maximal surgical excision is in fact the practice at first place. Although years ago, the prognostic impact of surgery was questioned, different studies confirm that, in high grade gliomas, extensive surgery is related to a more favorable prognosis (Badhiwala, Nassiri, & Almenawer, 2016; Krivosheya, Prabhu, Weinberg, & Sawaya, 2016; Pessina et al., 2016; Satoer, Visch-Brink, Dirven, & Vincent, 2016; Sun et al., 2016)

The treatment in this patient category is based on the results from an international, multi-center open-labeled, randomized controlled phase III, where patients who were randomized to undergo radiotherapy (RT) alone or concurrent chemoradiation with temozolomide (TMZ) at 75 mg/m^2 followed by 6 cycles of TMZ at 150-200 mg/m^2 where compared in terms of overall survival (OS) (Stupp et al., 2009).

According to Stupp's study, a larger two-year OS rate was observed in cases receiving RT+TMZ than RT alone (26% vs. 10%). In an extension follow-up investigation on the same study population, 9% of GBM patients who followed this treatment survived up to 5 years, while this was only 1% in RT alone arm. This led the choice of this treatment as the standard of care thus far. Additionally, the impact on OS was superior in patient with positive methylation status in the O6-methylguanine-DNA-methyltransferase (MGMT) promoter (Stupp et al., 2009).

More recently, further possible treatments targeting to arrest angiogenesis have also been experienced in clinical setting. For instance, in a multi-center, international, randomized phase III trial known as AVAglio, an anti-angiogenic therapy provided survival benefits in newly-diagnosed GBM patients (Chinot et al., 2016; Sandmann et al., 2015). This study randomly assigned patients into two arms whereby the first underwent standard protocol by Stupp et al., plus placebo while the second followed the similar standard treatment plus a concurrent dose of bevacizumab at 10 mg/kg i.v., with the treatment continued for 3 additional weeks. Results of the above investigation indicated an improved progression-free survival (PFS), and quality of life in concurrent treatment arm. This could have largely been due to a reduced use for steroids secondary to the add-on therapy using bevacizumab. This study however failed to demonstrate improvement in OS (Chinot et al., 2016).

In the current practice of neuro-oncology, bevacizumab is particularly indicated in recurrent GBM setting. The regimen is normally administered at 10 mg/kg i.v. biweekly, or 15 mg/kg i.v. every 3 weeks (Stupp et al., 2014; Weller et al., 2014).

Other alternative chemotherapeutic regimen to consider include the procarbazine, lomustine and vincristine (PCV) combination protocol (Weller et al., 2014)

In recurrent GBM setting, some challenging cases who fail to respond to the above, may be enrolled in investigational setups including immunotherapy (PD-1 or IL4 receptor antagonists) (Lamano et al., 2016; Platten, Bunse, Wick, & Bunse, 2016).

4.2. Treatment follow-up

In controversial cases, an interdisciplinary neuro-oncological assessment would help determining the most advisable therapeutic and follow-up approaches.

In fact, a crucial component in patients' treatment is proper follow up through interval clinical, imaging and laboratory assessments. The follow-up is normally pursued with the post-operative control

MRI, allowing to define the extent of residual lesion following surgery. In addition, patients undergo non-multimodal imaging using MRI to assess their tumor behavior as well as response to treatment (Amouheidari et al., 2013; Haddad et al., 2015).

Moreover, on-treatment laboratory assessments also become warranted to clinically evaluate patients for possible chemotherapy-induced side effects prior to each treatment cycle (typically, every 4 weeks) (Weller et al., 2014).

In case of uncertainties with regard to tumor behavior in regular MRI, multimodal MRI scans comprising diffusion- and perfusion-sequences with apparent diffusion capacity (ADC) maps would provide additional information on the extent of the lesion and regional cerebral blood volume (rCBV). To elucidate whether true- or pseudo-progression has occurred, uncertain areas might be evaluated using the magnetic resonance spectroscopy (MRS). Other than the above and when accessible, using Positron Emission Tomography (PET) scan with fluorothymidine or methionine would provide useful data on the metabolic activity of the lesion. Such imaging assessments would clarify contrast enhancement or hyper-intensity signals in T1 and T2 sequences, respectively (Stupp et al., 2014; Weller et al., 2014).

4.3. Control MRI schedule

Post-operatively, the first MR scan is recommended at 48 hours. Further to regular follow-up imaging upon treatment, a diffusion-weighted MRI might be required to define the presence any subacute contrast enhancement which might be mistaken for progression while in fact resulted from radiation necrosis in typical instances (Stupp et al., 2014).

While the need for control MRI upon completion of radiotherapy treatment is a matter of debate, the first control MRI is strongly advised following the 2nd or 3rd cycle of adjuvant chemotherapy. Control MRIs would be then taken every 8-12 weeks to evaluate the patient's responses to therapy (Stupp et al., 2014; Weller et al., 2014).

4.4. Neuroimaging technical characteristics and considerations

The control and follow-up MRI need to be practiced using the same equipment, acquisition protocol, contrast and topographical references, to technically allow comparable data (Bagheri, Ahmadloo, & Rezaian, 2013).

The sequences applied to follow-up MR scans include the T1 3D and Gadolinium-contrasted T1 3D spoiled gradient recalled (SPGR) images providing three-plane reconstruction and size calculation through segmentation as well as T2 or T2 fluid-attenuated inversion recovery (FLAIR) with thin cuts (Bagheri et al., 2013).

In practice, CT scans have no position in follow-up assessment of patients with CNS tumors unless complications including hydrocephalus or hemorrhage are doubted (Evans & Evans, 2016).

4.5. Response Assessment in Neuro-oncology (RANO) criteria

The RANO criteria, based on the MRI scans, are currently referenced for response assessment in neuro-oncology. The radiological response to a given therapy is evaluated after measuring baseline tumoral dimensions before and after the treatment. It should always be noted that radiological response assessment particularly upon permeability changes after treatment with anti-angiogenic therapies is challenging. Thus, confirmatory imaging needs to be considered 4 weeks following a radiological response (Huang et al., 2016; Jaspan et al., 2016).

With respect to the radiological response, key terms including complete response (CR), partial response (PR), stable disease (SD) and progressive disease are applied. Disease progression is usually considered when T2/FLAIR non-enhancing lesions are increased in size on stable or increased corticosteroid doses compared to baseline or earlier assessments (Huang et al., 2016).

When following-up the disease, the possibility of pseudo-progression needs to be taken into account. In other words, early tissue reactions within first few months should be differentiated similar effects which are in fact resulted from true progression. Some factors to consider when labeling true progression include: 1- contrast enhancement beyond 12 weeks after the completion of radiotherapy, 2-contrast enhancement in a non-irradiated zone, 3-an increase in non-enhancing and hyper-intense signals on T2/FLAIR, 4- excluded underlying causes (ischemia, post-radiotherapy changes, seizure activity, infection or demyelination) explaining the changing T2/FLAIR signals and 5-Altered T2/FLAIR signals indicating tumor infiltration outside the radiation field(Huang et al., 2016).

5. Conclusions

In line with the mission statement of the neuro-oncology scientific club in Iran, and in order to draw an updated clinical pathway for the interdisciplinary practice of neuro-oncology, and treatment of high-grade gliomas in particular, the panel of experts from Shiraz NOSC concurred that following the clinical suspicion, conventional/functional neuroimaging are taken after which stereotactic biopsy would be taken to ensure pathological diagnosis. The specimen is then assessed for molecular markers. Patients will initially undergo baseline neuropsychological assessments and further brain-mapping measures for surgical planning. Stereotactic radiosurgery or safe maximal resection will be done for which the latter includes intraoperative recording through electrocorticography or somatosensory evoked-potentials where applicable.

Post-operatively, the newly-diagnosed HGG patients would undergo Stupp et al protocol of chemo-radiation and adjuvant chemotherapy with TMZ. Seizure control and optimized steroid use are to be considered.

In recurrent HGG patients, those with poor performance status receive best supportive care, whereas patients with fair to favorable performance either receive targeted/re-challenge therapy (anti-angiogenic agent, TMZ re-challenge/metronomic dosing, radiosurgery, re-irradiation or TMZ+anti-angiogenic agent) or enter the investigational setups including immunotherapy (PD-1 or IL4 receptor antagonists).

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7. Competing Interest

The present report outlined the communications and experts' opinions during the NOSC meet-up 2015, Shiraz, Iran. The authors declare no competing interest upon data review, talk delivery during the meeting, interactive discussions and preparation of the present report. MN provided medical consultancy to Behestan Medical Scientific Committee, Behestan Group, Tehran, Iran.

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