Turning Interdisciplinary Brain Tumor Science into Survival; Report from the Neuro-Oncology Scientific Club Opening Session, NOSC 2012 -19 January- Tehran, IR Iran

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Abstract: On the 19[Th] January 2012, the opening session of the interval meetings of the Neuro-Oncology Scientific Club (NOSC-THN) was held in Tehran, Iran. The NOSC is a newly established scientific forum which currently has formed provincial steering boards in the country and is expected to be turned to the national NOSC in its future perspective. The interdisciplinary nature of this club provides a multifaceted approach for diagnosis, treatment and follow-up of brain tumor patients. Participants utilized this transparent and unbiased round table to contribute to discussions and decisions. All comments were open to debate, with interdisciplinary team work for brain tumor patients' health and quality of life at the center. This paper summarizes the communicated insights (neurosurgery, radiodiagnostics and radiochemotherapy) and the suggested strategies during the first NOSC-Tehran meeting hoping to let readers further perceive the significance of the interdisciplinary approach as a practical model in CNS tumor patients' care. [Haddad P, Zali A, Tabatabaeefar M, Nikoofar A, Hadizadeh Kharazi H, Ghadyani M, et al. **Turning Interdisciplinary Brain Tumor Science into Survival; Report from the Neuro-Oncology Scientific Club Opening Session- NOSC 2012 -19 January- Tehran, IR Iran**. Report and Opinion, 2012;4:(2):42-53] (ISSN: 1553-9873). http://www.sciencepub.net/report. 7

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1. Introduction

The role of multidisciplinary care in treating cancer is well recognized. Having a team of expert physicians from various allied disciplines in cancer treatment would help more favorable results. For CNS tumors it has also been well evident that fostering a working team spirit in treating patients, will result in more individualized and focused managements and hence optimized outcomes [1].

By allied disciplines in brain tumor care we mean neurosurgery, neuropathology, neuroradiology, radiation oncology, medical oncology, neurology and other related specialty care health professions. We initially formed the NOSC concept, since we believe that linking all different aspects of CNS tumors clinical care and related fundamental science not only helps arriving at novel therapeutic options, but also selecting most practical measures in maximizing patient care's outcome. To let this happen, neuro-oncology experts from almost all universities and oncology research academies in Tehran were invited to take part in the NOSC opening session.

Following the NOSC opening session in Mashhad, Iran, we were the second team who took steps towards this club's establishment in Tehran. The need for sharing insights, round table approach in problem solving, and having a specialized neuro-oncology tumor board encouraged us to take NOSC as an opportunity for the goal oriented exchange of ideas.

The NOSC-Tehran plenary and round table discussions tried to elaborate on the long term goals and the mission it would pursue. After communicating recent updates in neurosurgery, imaging and chemo-radiotherapy of brain tumors, the session went on to agree upon some conclusive remarks which will be outlined at the end of this report. We begin with the discussed scientific insights and then turn to strategic discussion evolved during this event.

2. Surgical management of CNS tumors

Surgery plays an indisputable role in both diagnosis and treatment of brain tumors. Glial brain tumors and specifically high grade glioma is our focus here. The current knowledge which justifies the

benefits of surgical resection is shown to have an impact on patients' outcome [2, 3]. Available data (subject to modification) suggest that in Iran, CNS malignancies are in third place in terms of cancer burden i.e. wasted life time of early death and morbidity. Therefore we are facing a malignancy of really a high burden [4].Our local brain tumor data almost conform with those of other countries [5,6]. The incidence of glioma in our community is roughly 7.5/100000 per year. The most prevalent solid malignancy in pediatric population is the brain tumor. Focusing on glial brain tumors, 76% of all adult glial brain tumors are within the category of malignant gliomas. Taking all types of brain tumors together, gliomas comprise 46% of primary brain tumors. This is followed by meningiomas which accounts for 27%. Among gliomas, astrocytomas account for 40% of tumors, oligodendroglioma for 5% and the remaining 1% are categorized as other glial cell tumors [7].

When high grade glioma patients (mainly glioblastoma multiforme) do not undergo surgery and are only dependent on adjunct therapies including radiotherapy, despite beneficial effects of these measures only 3% of patients stay alive within a 3 year follow up [8]. This signifies the role of surgery as an important component of the multidisciplinary management in brain tumors. The recent conceptual advances have highlighted the advantage of radical surgery while conserving the eloquent areas of the brain. The installation of chemotherapy wafers such as biodegradable BCNU implants (Gliadel®) has also been approved by FDA and is shown to offer benefits [9]. Recently applied modalities in radiotherapy are also proven to have notable advantages [10]. Chemotherapy with Temozolomide (TMZ) is demonstrated to provide survival benefits in long term follow up studies [11].

There are 3 surgical management options for malignant gliomas. These include palliative, biopsy and debulking with or without wafer installation. Palliative option is for the advanced patients with no chance for surgery. Presence of co-morbidities, especially in elderly cases makes palliative care a more preferred option. With new neurosurgical advances, debulking, surgical decompression and installation of wafers for interstitial chemotherapy are turned to be the surgical management of choice in many patients. Except for instances where radical resection or surgical debulking is by no means possible, Biopsy alone, is not recommended. The importance of patient selection is strongly being re-emphasized in Today's practice standards [12].

Stereotaxis role in brain tumor surgery is well acknowledged. This technique is specially of value for surgical planning for deep seated tumors and tumors nested in eloquent cortical and subcortical areas. Stereotaxis can also be a great tool for intra-tumoral seeding, brachytherapy (e.g. with phosphorus) and cytoaspiration. The main shortcoming of stereotaxis is the very minimal tumoral cytoreduction it serves [13].

Tumor debulking in presence of the possibility for total resection of the tumor, is by no means warranted [13]. Debulking alone cannot eliminate the tumor mass effect which is the main cause for mortality and morbidity. Figure-1, illustrates imaging of a patient who has a glial tumor with a cortical involvement. Tumor decompression (diminishing mass effect) and reducing tumor bulk by 90% has relatively become possible through modern techniques. This allows the resection cavity to be a bed for implantable wafers.

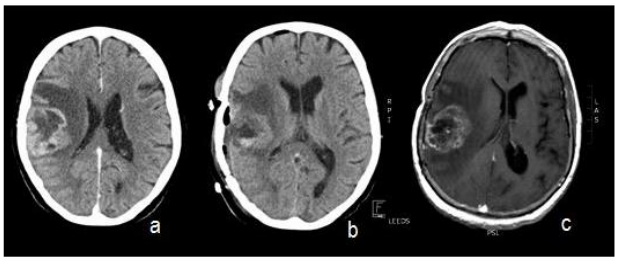

Figure-1 Illustrates the imaging of a patient with a glial tumor with cortical presentation, midline shift and sulci effacement (a). The minimal debulking of the tumor seating adjacent to the skull (b) failed to result in elimination of the pressure effect and edema. This patient could possibly receive a total resection rather than just debulking surgery(c). Adapted from [13]

Functionally eloquent brain cortices and white matter tracts which are for motor, sensory or neuro-cognitive functions, should not be injured or removed during tumor surgery. This has been made possible through pre-operative image guided planning (fMRI, PET, SPECT, DTI and QEEG) as well as intra-operative electrocorticography and fluorescence guided debulking. Having the awake surgery setting available would allow the real time assessment of the cortices in awake patients under brain surgery, hence minimizing the risks to patients' eloquent brain [13,14]. Electric Cortical Stimulation (ECS), Tractography and functional MRI will assist surgeons to define the surgical approach and trajectory to avoid functional areas while doing the brain surgery.

One of the other the other useful techniques to increase the precision in brain surgery is the fluorescence-guided surgery using 5-ALA. As illustrated in Fig.3, by this technique tumor borders, mass and necrotic areas will be delineated (Figure-2) [15, 16].

Tractography displays all anatomically important subcortical tracts and their relation to tumor and its mass effect. fMRI in turn would allow us to map functionally eloquent brain areas with relation to tumor location [17].

There raise a question whether debulking makes any significant difference in patients survival. To

answer this, the glioma outcome project was implemented in USA which reported survival of 21 and 45 weeks for closed biopsy and craniotomy, respectively. Median survival of patients with glioblastoma multiforme (GMB) was reported 11.3, 10.4 and 6.6 months in total resection, partial resection and biopsy alone group, respectively. This denotes a statistically significant difference in median survival favoring total and partial resection vs. biopsy ($p<0.0001$ and $p<0.001$, respectively) [18]. Stummer et al, continued to assess the outcome impact that surgical resection could have in GBM patients. They did a retrospective study reviewing the post operative imaging data to stratify the 243 patients into complete vs. incomplete resection groups, matched for age and eloquent areas. The results showed 16.7 vs. 11.8 months survival in complete vs. incomplete resection groups ($p<0.0001$) [19].

In a multicenter double-blind, randomized, placebo controlled phase 3 trial in patients with primary malignant glioma, complete resection and implantation of Carmustine wafers has resulted in favorable survival outcomes [20].

Other than providing diagnosis, the goals of surgery for malignant glioma include relieving symptomatic mass effect, setting up externally (post operative) or locally delivered therapies and prolonging survival through cytoreduction [21].

Providing diagnosis

Since we are dealing with a wide spectrum of overlapping signs in imaging (i.e. vascular distribution, infarction, local encephalitis, demyelinating disease or brain tumor) definite diagnosis often may not be made through imaging alone and this mandates surgery.

Given the fact that gliomas are notoriously heterogenous, more extensive resections more frequently provide higher grade diagnosis. One of the prognostic indicators is to identify what percentage of the gliomas are mixed and specifically contain the oligo component (Oligoastrocytoma or oligidendroglioma). Presence of oligo cells of high turnover and hyper metabolism makes the tumors sensitive to chemoradiotherapy [21,22].

Having a chemical shift imaging (Magnetic Resonance Spectroscopy) from the region of interest which we plan to take stereotactic biopsy from, will help obtaining biopsy from the most presumably malignant area. This leads to the more precise diagnostic report from pathology [23].

Relieving mass effect

Neurosurgical experience shows obvious and frequent success in relieving neurological symptoms from mass effect. Surgical decompression also provides possible increase in Karnofsky Performance Status (KPS) in malignant glioma and relieved medically intractable seizures in low grade glioma [24,25].

Prolonging survival

In both univariate and multivariate analysis on post operative adjuvant radiation efficacy data, results show predicted better imaging response to radiotherapy following more extensive surgical resections. The rate of response to chemotherapy is also increased following gross extensive resections. In summary, many multivariate analyses of survival after resection of GBM (non-randomized) now provide evidence that extent of resection is an independent prognostic factor for survival (independent of age and KPS). The results from the glioma outcome project also confirmed that resection was favorable prognostic factor (compared to biopsy). This has been after correction for age, KPS and after omission of patients with multifocal disease [26].

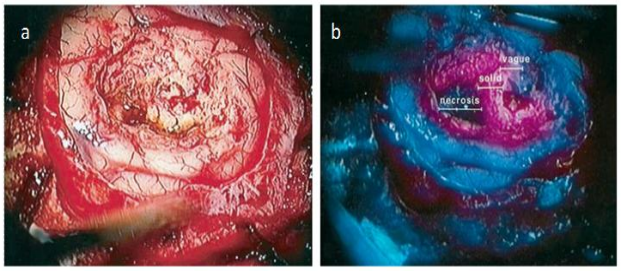

Figure-2 Tissue marginal to tumor in a patient after prior administration of 5-ALA. Inconspicuous appearance under conventional illumination(a). Vivid red fluorescence marking delineating necrosis from mass and vague. Adapted from [16]

Resectability

The complex concept of respectability is frequently a subject for debate among surgeons. There is a wide display of factors influencing rate of resection. Patient related (age, KPS, marital status), tumor related (size, location i.e. non eloquent, near eloquent or eloquent brain involvement, fuzziness of boarders) and provider dependent (volume of practice, experience, professional incentives) may all affect the extent of resection. Furthermore, resectable and non-resectable tumors may have well different pathology features [24].

Reoperation

There are distinct patients who may benefit from reoperation in GBM. These patients more likely benefit when recurrence is symptomatic. Results of a study evaluating the KPS after second resection in GBM patients showed that 28% of patients had improved,49% stable and 23% declined (by 10-30points) KPS, post second surgery [27].

3. The value of state-of-the- art imaging techniques in high grade gliomas

Magnetic Resonance Spectroscopy (MRS) is a

measurement providing a map of biochemicals in the brain. Proton (1H) constitutes almost 80% of the brain mass therefore is the most common nuclei used as the reference in MRS, Producing a high signal to noise ratio. MRS is used in a variety of instances such as stroke, epilepsy, metabolic disorders, infections, neurodegenerative diseases and demyelinating processes; however our focus in this review is the brain tumors [28].

We can do MRS with single box or multi-box 2D or 3D, and our voxel size is usually 2x2x2 cm^3. Two main issues which result in false negative results in MRS include lesion size and scale factor. The spectrum of very small lesions (subcentimetric) can appear normal due to the partial volumetric effect. Furthermore, when one single metabolite dominates the spectrum, the other metabolites will be displaced as smaller peaks because of the scale factor [28, 29].

In order to have optimal quality MRS for interpretation, we should avoid areas know to contain fat, necrotic tissue, blood and blood products, air (negative susceptibility artifact), metal (positive susceptibility artifact), calcium (paramagnetic effect) and bone (bone marrow).

MRS could by no means substitute conventional MRI. The two modes of MRS imaging should usually be applied. They are Stimulated Echo Acquisition Mode (STEAM) with three 90 degree pulses and Point Resolved Spectroscopy (PRESS) with one 90 degree and two180 pulses. The above 2 modes are T1 and T2, applied to evaluate products of short and long relaxation times (TR), respectively [30].

We can use both "with" and "without" IV gadolinium MRS. In IV Gd MRS, although individual peak areas may alter, the overall interpretation of the spectra remains unchanged. Should we have the single voxel MRS for brain tumor as the only available option, we must have voxel positions in abnormal regional cerebral blood volume (rCBV) areas (obtained from perfusion weighted images). In multiple box mode we do not need perfusion assessments prior to MRS. For localization purposes, T2 signals will be used [30].

In two dimensional graphs of MRS, the vertical axis represents integral concentrations of metabolites. Each metabolite would peak at a level which is maximally affected by the magnetic field (e.g. choline peaks at 3.2 ppm). Long TR products (NAA, Choline and Creatine) should solely be assessed by T2 and PRESS mode MRS, whereas for short TR elements such as lipids, STEAM is the preferred mode.MRS multi-box imaging is usually producing over 15 graphs to cover the whole region of interest (these apply to both STEAM and PRESS modes) [28].

Referring to metabolite ratios, the optimal NAA/Cr, NAA/Cho and Cho/Cr ratios are considered to be 2, 1.6 and 1.2 . Corresponding ratios of <1.6, <1.2 and >1.8 will be taken as abnormal, respectively [31].

What MRS can really offer in neuro-Oncology routine practice?

1. MRS can provide dependable data on significant changes within lesions compared to contra- lateral normal brain tissue (except for gliomatosis cerebri).
2. MRS shows decreased NAA/Cr and Cr/Cho ratio in all intra axial CNS tumors.
3. In extra axial tumors where there will be no NAA peak, MRS shows a notably decreased creatine, increased alanine (particularly in meningiomas) and increased lipids in metastases.
4. To differentiate abscesses and cysts from necrotic tumors, a concomitant diffusion map other than MRS is needed. The rCBV is significantly higher in the wall of necrotic tumors compared to abscess walls [31]

Increased lactate will be seen when a distinct brain region faces oxygen depletion. Lactate is a sign of hypoxic tissue. Lower oxygen supply as seen in vascular insults, or increased oxygen demand (neoplasm), would produce a peak in lactate level in MRS.

Lipid peaks should not be seen unless there are destructive processes in the brain including necrosis, inflammation or infarction (Figure-3).

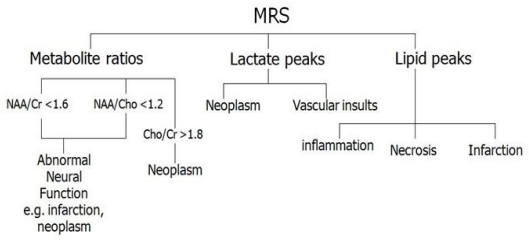

Figure 3 MRS helps to detect neurochemical concentrations at a distinct voxel of interest. The metabolite ratios are suggestive for pathologies. Analyzing MRS data from an area suspected for tumor progression, would partly help differentiating pseudo from true progression of a given tumor. Adapted from [29].

Some major shortcomings of MRS [32]:

1. MRS can neither delineate a significant difference between different intra-axial tumors nor provide any data for grading.
2. The concentration level of lactate reported in MRS, has no correlation with histologic tumor grading.
3. No tumor type differentiation is made by MRS. Cho/Cr ratio in all tumors is usually higher than 1.

MRS, however is currently utilized as a useful tool in differentiating glial tumor progression from pseudo progression. This should be interpreted with MRI with and without contrast. To differentiate the radiation necrosis from tumor progression, with the current available facilities in our local setting, treating physician should request a set of imaging. These include

a CT scan without contrast (to detect calcification or hemorrhage), MRI with and without gadolinium and MRS. Reports would contain data on possible presence or absence of tumor progression. Post radiation demyelinated components, granular tissue, necrosis and often hemorrhage should be well differentiated from tumoral progression. This is possible through MRS provided the voxel size is more than 1 cm^3 (Figure-4).

When conventional MRI fails to guide us toward detection of true vs. pseudoprogression (radiation necrosis for instance), MRS would provides a clue whether a voxel of interest (in questionable zone for true progression of tumor) has a malignant component or not [33] . Should MRS failed to provide conclusive data in this respect, as per the most recent Canadian guideline, continuation of adjuvant chemotherapy and re-imaging after three cycles is recommended. Figure-5 demonstrates an example for the current application of MRS in delineating pseudo from true tumor progression (Figure-5). PET scan is also considered as an optimal imaging modality for the above purpose (Figure-6) [1]

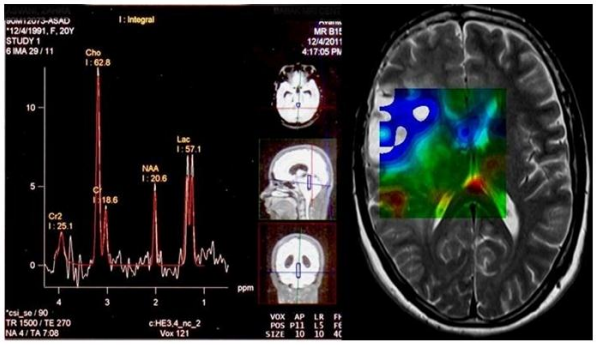

Figure 4 In addition to the MRS graphs, chemical shift maps serve a facility for a short review. Map scales guide us to have an overview of metabolites concentrations; however graphs are used for comprehensive analyses. *Courtesy of H.Hadizadeh*

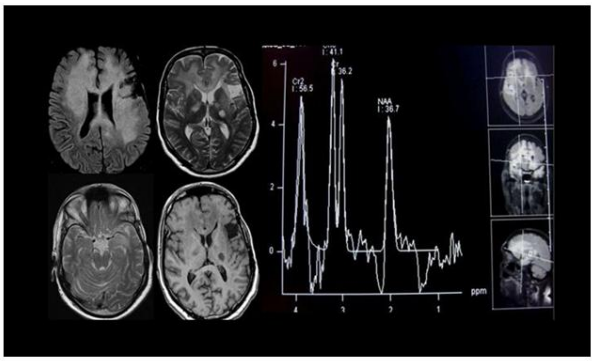

Figure 5 The MRI slices show diffuse signal intensity in bilateral frontal lobes involving the cortex and white matter. There is the tumor resection site. This patient underwent post resection radiation therapy. The question is whether the signal intensities represent recurrence or not? Conventional MRI is inconclusive so MRS is obtained showing Cho/Cr ratio of 4, high lactate and decreased NAA. The pattern is suggestive for tumor progression. *Courtesy of H.Hadizadeh*

4. High grade glioma treatment; past, present and future

In 1978 walker and Anderson published the results of their studies evaluating the benefits of adding adjuvant radiotherapy in treating GBM. They used 5000-6000 cGy whole brain radiotherapy post GBM resection. Even by whole brain RT, this showed survival benefits compared to surgery alone. Later, the whole brain radiotherapy was modified to limited field radiotherapy. When we look at the High grade glioma (HGG) management from historical point of view, it is of note that until 2004 (i.e. almost 30 years after addition of adjuvant RT) no significant advances were made in its management [34].

They used to stratify patients to those aged<70 with Performance status (PS) of 0-1 or young patients with PS>1 and patients aged >70 with WHO PS>1. The management strategy was to administer 30 sessions RT (60 Gy), short course or "palliative RT" and supportive care for corresponding above stratified groups, respectively [34,35].

Technological advances offered accelerators, 3D and IMRT plans. Given its fall off dose effect, proton nuclei was used to help less irradiate intact areas of the brain compared to photons. None of these technological advances as well as dose modifications could increase the survival rate in HGG patients.

In 2005, the results of a pivotal phase III randomized trial of newly diagnosed patients with GBM was published by Stupp et al. The outcome of this study introduced a breakthrough alkylating chemotherapeutic agent known as Temozolomide (TMZ) to be the standard regimen for GBM who have a favorable PS.

They used TMZ with radiotherapy concomitantly for 42 consecutive days followed by 6 cycles of adjuvant (maintenance) TMZ. This became the standard regimen of choice for GBM since then [36].

In Stupp trial, the randomization was made to compare the overall survival of patients who received the defined chemoradiation protocols vs. patients on RT alone. The two groups were well balanced.

The treatment protocol of Stupp et al. in their phase III study on new GBM with RT, with or without TMZ is summarized in (Figure-7).

In 573 examined patients, the 2 year Overall survival (OS) rate improved from 10.4% with RT alone to 26.5% with RT+TMZ. During this investigation, 78% of patients in RT+TMZ arm started adjuvant TMZ. Median number of cycles was 3 (0-7). 47% of patients completed the 6 cycles. The main reason (39%) of discontinuation of adjuvant TMZ was disease progression. This analysis was not confined to a 2 years follow up. The final 5 year survival data of primary Stupp et al. investigation got published in Lancet 2009. This reported the 5 year survival of 10% vs. 2% in

TMZ+RT vs.RT alone arms, respectively. Having TMZ included in the treatment armamentarium of GBM resulted in a significantly improved survival rate in 2,3,4 and 5 years [11,36] (Figure-8).

One of the endpoints of Stupp trial was to assess TMZ safety profile. No grade 3 or 4 hematological toxicities were seen in radiation only group and the rate of severe infection during the radiation period was not significantly different in RT alone and RT+TMZ arms. TMZ was considered safe and well tolerated [11].

Alternative schedules of adjuvant TMZ have not been assessed in randomized trials and evidence based data dose not strongly warrant TMZ alternative treatment protocols. The only so far recommended regimen protocol is only what established by the registration trial of TMZ which led to its FDA approval [37,50].

To date, there are no randomized trials comparing TMZ with nitosourea- based combination regimens. However, the BR-12 trial has compared the efficacy and safety of TMZ vs. nitrosourea- based regimen in *recurrent* grade III and IV astrocytic tumors. This study evaluates whether PCV is as effective as TMZ in recurrence setting. Furthermore, the standard 5/28 vs. dose dense regimen of TMZ were compared. Results showed no significant difference between TMZ and PCV in *recurrence* setting of chemotherapy naïve patients. Secondly, dose dense vs. conventional TMZ regimens demonstrated no difference in terms of response. The biomarker analysis from these patients is ongoing [38].

Although some studies tried to assess the efficacy and safety of the standard vs. dose dense TMZ regimens, the currently available data and the clinical experience does not warrant the use of any alternative TMZ regimen (including the dose dense protocol) outside the established protocol on its label [39-41].

Although the duration of adjuvant therapy with TMZ was recommended to be 6 months [11,36], due to the presence of residual microscopic disease despite surgery, continuation of treatment for the visible disease should be termed as “maintenance”. Prolonged maintenance therapy with cytotoxic chemotherapy agents has not been shown to confer a benefit in many diseases. Never the less, and short of class 1 evidence, prolongation of maintenance for up to 12 cycles is considered and practiced in some centers. This specifically can be considered for patients demonstrating continued tumor response on MRI and have a favorable clinical evolution [41].

The O6-Methylguanine-DNA-Methyl-Transferase (MGMT) is a repair enzyme causing resistance to DNA alkylating drugs. Methylated status for MGMT is proven to cause TMZ sensitivity. In a study done by Hegi et al. MGMT gene silencing through its promoter methylation predicted a better outcome in GBM patients treated with TMZ.

For two main reasons, MGMT methylation status is not recommended to be routinely assessed [41].

1) This test required DNA extraction, and stereotactic biopsy can hardly provide sufficient specimen for such an assay.
2) Since we are short of an alternative strategy for unmethylated MGMT tumors, routine MGMT gene promotor methylation status test would serve little benefit.

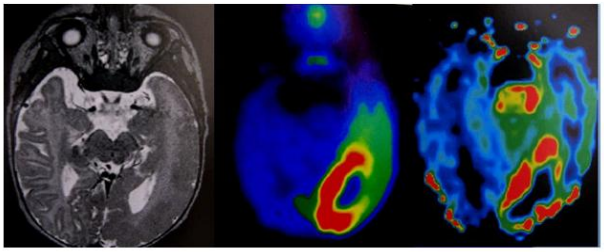

Figure 6 PET scan utilizes radiotracers mainly glucose (FDG) to suggest metabolic areas with glucose uptakes. The minimal thickness of slices is 6 mm. Regions with high metabolite concentrations will be apparent in the given color scale. PET scans and more recently ASL (Arterial Spin Labeling) perfusion scans are used to differentiate true and pseudoprogression in glial brain tumor imaging assessment.

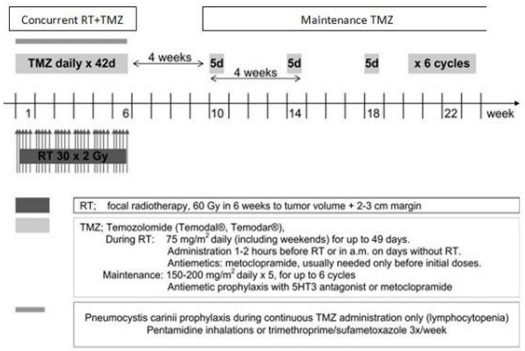

Figure 7 The standard protocol widely used for the treatment of GBM. This constitutes a concurrent TMZ+RT followed by the adjuvant TMZ phase. As recommended *pneumocystis carinii* prophylaxis with Trimethoprime-sulfametoxazole should be considered during the concomitant phase. There is a 4 week between concurrent and maintenance treatment phases. Adapted from [36].

Glioblastoma; a highly vascular tumor

Microvascular proliferation and hypoxia are pathophysiological hallmarks of GBM. Vascular Endothelial Growth Factor (VEGF-A and VEGF-R2) levels correlate with histological grade of glioma. Other than anti VEGFs, there are number of angiogenesis targeting agents for glioblastoma which are in phase I/II studies. Based on the results of ongoing phase II trials, Cilengitide (anti-integrin) and Cediranib (Thyrosine Kinase Inhibitor) are expected to render further helps to specific patients in the future.

Bevacizumab is being evaluated as a component of

the initial combination approach in patients with newly diagnosed GBM [42]. Since some GBM cells have stem cell characteristics (CD133+), and meanwhile are nested next to the vascular endothelium, targeting VEGF has opened new spectra of neuro-oncology research realm [43].

5. Whom to choose for chemotherapy and beyond in management of glial tumors; the RPA concept

Despite the notable technical advances in therapy for malignant gliomas, improved patients' survival has not been clearly documented. This can partly be attributed to the non-selective approaches in high grade glioma chemotherapy. The pretreatment prognostic factors are shown to influence outcome more than minor modifications of therapy in HGG. Age, performance status (PS) and tumor histopathology have been identified as the pretreatment variables most predictive of survival outcomes. Different prognostic factors for survival in adult patients with malignant glioma are incorporated into a model based on RPA (Recursive Partitioning Analysis) [44].

Recursive partitioning is a statistical method for multivariate analysis. This provides a decision tree that strives current classification of patients based on several dependent variables. For brain tumors, the variables taken into the RPA approach include factors associated with an increased risk of death. These factors are increased age, lower Karnofsky Performance Scores (KPS), initial histology of GBM, use of corticosteroids, shorter time from original diagnosis to recurrence, surgery background and tumor location [44,45].

The RPA concept is not related to a particular drug. It can be applied to clinical trials helping the investigators to select more homogenous population and hence more reliable results. In neuro-oncology routine practice, the RPA concept allows physicians to be realistic in treatment outcomes expectations. This prevents us from jumping to conclusions about a certain drug of modality inefficacy. Figure-9, summarizes the interplay of these factors which results in stratification of HGG patients into RPA class III, IV and V (Fig-10) [44].

For chemo-radiotherapy with TMZ vs. RT alone, patients of different RPA classes show significantly different survival outcomes. The rate of response and survival has an incremental pattern from RPA III to RPA V patients [11].

Given the above data, it can be concluded that RPA retains its prognostic value in patients receiving RT with or without TMZ for newly diagnosed GBM particularly in class III and IV. In other words,patients in RPA III and with methylated MGMT benefit most from RT+ TMZ regimen[11].

6. The role of chemotherapy in the treatment of malignant gliomas

To date cumulative data support the fact that recent advances in treatment of GBM have significantly prolonged the median OS and increased the number of long-term survivors [46].

TMZ is the most widely used chemotherapeutic agent attacking the glioma cells. TMZ molecule was discovered in 1978 following the works in Aston university in Birmingham, UK. At first, TMZ was not considered the best candidate for a new cancer medication however, other compounds failed to show comparable benefits in clinical trials [47].

TMZ is in fact a second-generation alkylating agent. It converts to its metabolite MTIC (5,3-Methyl Triazen 1-yl- Imidazole 4-Carboxamide) at physiologic pH. For TMZ, no hepatic or renal metabolism is required; therefore, drug levels are not altered by anticonvulsants use. MTIC methylates DNA, thus the cellular mechanisms cannot adjust. This leads to DNA damage and ultimately results in apoptosis. Therefore, high levels of MGMT (The DNA repair enzyme) play a primary role in TMZ resistance [49].

Myelosuppression is the only dose limiting adverse event which is though not cumulative and resolved within 2 weeks. Prior to dosing patients must have an absolute neutrophilic count (ANC)$\geq$1.5 x 10^9/L and Platelet count $\geq$ 100 x 10^9/L. The dose can be then adjusted according to nadir neutrophil and platelet counts [50].

The only drug which its co-administration decreases the clearance of TMZ by 5% is the Valproic Acid. TMZ is also shown to have some impact in terms of HGG patients' seizure control [50].

TMZ yields additive cytotoxicity in combination with radiation. Minimally cytotoxic doses of TMZ produce radiosensitization in human HGG regardless of MGMT expression. Presumably this effect involves an inhibition of DNA repair leading to an increase in mitotic catastrophe [51-53].

The results of the study conducted by Yung WKA et al [54], with regard to evaluation of the effect of TMZ in anaplastic glioma, led to the accelerated FDA approval of TMZ for refractory anaplastic astrocytoma (AA). This was due to TMZ's meaningful benefits over existing treatments.

The data led to TMZ FDA approval for newly diagnosed GBM patients, is mainly derived from Stupp et al. registration trial which was outlined earlier in this paper [11].

Significant improvement in HGG survival [11,54], providing a measurable response, acceptable safety and tolerability profile of TMZ [11] have resulted in its wide acceptance and use by the neuro-oncology field treating physicians now in 77 countries worldwide. However, risk-benefit evaluation and important safety information should meticulously be considered when

using a treatment option [see 50].

There are recent compelling reasons for safe handling of TMZ capsules which have encouraged the manufacturer to let TMZ now be available in individually packed capsules in sachet form rather than amber glass bottles [55-57].

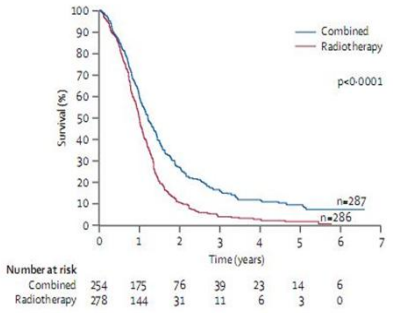

Figure 8 The overall survival by treatment group, shown in Stupp et al. trial final analysis showing a significant survival benefit in RT+TMZ arm compared to RT alone. Adapted from [11]

7. Neuro-Oncology Scientific Club (NOSC) and the National Iranian Brain Tumor Registry (NIBTR); the interface

The preliminary draft of the national brain tumor registry software proposal was communicated during NOSC meeting. Participants interactively took part in making comments (anonymous polling sheets) to improve the quality standard of this primary version of registry system to be used as a valid tool for brain tumor data gathering and analysis in national scope. Below is an outline of what communicated in this respect.

Defining a clinical data gathering system would help categorizing patients' data in a useful, accurate and ordered manner. For brain tumors, apart from North America and UK, and few other European countries, there hardly are comprehensive and organized national registries worldwide .There has always been a room to apply well designed data registry software which is endorsed by Iranian neuro-oncology experts and is applicable for brain tumor registry purpose nationwide. As an initial important step, during the NOSC meeting (Neuro-Oncology Scientific Club) January 2012 in Tehran, the project entitled the NIBTR (National Iranian Brain Tumor Registry) was launched. There are defined constituted committees to ensure acceptance standards for all patients' data incorporated into NIBTR software. There also are provincial committees as well as a national one to ascertain the accuracy of the inputs.

The registry items were defined based on obtained experts' opinions (interdisciplinary) nationwide and following a thorough search in electronic databases including Medline, Scopus, Cochran Central Register of Controlled Trials and ISI for different combinations of "brain tumor" and "registry". These items include the patients' clinical information, the presenting complaints and symptoms, brain tumor related information, imaging data, CSF analysis, pathology reports, surgery data, radiotherapy and chemotherapy protocols and experienced side effects. An additional post mortem section will have the data from those registered patients who die within the 6 month to 1 year follow up period, and have a post-mortem examination. For some cases this may be the only laboratory examination of the brain (thereby substituting for a biopsy as a means of diagnosis).

The expected practical implications of NIBTR would include epidemiologic data gathering, brain tumor patients' treatment and side effects data and follow up results. This leads to elucidation of efficacy and safety of any of the applied treatment strategies in our setting as well as sub-analyses based on recorded and analyzed qualitative and quantitative parameters.

8. NOSC Plenary and round table discussions, conclusive remarks

The participants at the NOSC-Tehran opening session(Figure-10) kept on sharing ideas and running debates to arrive at a common place for the vision, mission and forthcoming plans of their newly established scientific club in neuro-oncology (NOSC). Based on the quote that "even most challenging journeys begin with the *first* mile", they believe that the *first* step in establishing NOSC has been successfully taken.

Within the NOSC, members aim to establish a stronger spirit for a team work in diagnosis, treatment and follow up of brain tumor patients. To reach this, other than the communicated scientific insights, below decisions were made during the meeting:

1) This scientific club not only helps strategizing for maximal outcome in treatment of brain tumors but also is a scholarly forum which all can benefit. Everyone agrees on its rationale, vision and mission.
2) NOSC above all aims at improving our brain tumor patients' health and quality of life through an interdisciplinary team work.
3) Participation of expert physicians from all allied disciplines should be further encouraged.
4) The preliminary constructive steps towards the National Iranian Brain Tumor Registry (NIBTR) are taken. This should be refined as per the participants inputs (already obtained) and quality standards of the national cancer registry, steered by the MOH. NIBTR as a focused section of this registry will be an optimal approach for brain tumor data gathering.
5) Once the final format of the NIBTR-Software (endorsed by the experts and authorities) is out, the

process for installation and commencement of data gathering will be switched on.

6) NOSC will contribute to organization and conduction of "CNS tumor boards" in either Tehran University of Medical Sciences , Shahid Beheshti Medical University or as joint activities.

7) The outcome of the meeting as a scientific report publication will appear in an internationally accessible journal.

The next Tehran NOSC meeting is planned to be held in Late May 2012.

RPA Class	AGE	HISTOLOGIC TUMOR TYPE	MMSE	PS	TREATMENT STATUS
III	<50	AA	Abnormal		
III	<50	GBM		WHO PS 0	
III	<50	GBM		KPS 90-100	
IV	<50	GBM		KPS<90	<3m from time of first symptom to start of treatment
IV	≥50	AA		KPS 70-100	<3m from time of first symptom to start of treatment
IV	<50	GBM		WHO PS 1,2	Complete/partial surgical resection
IV	≥50	GBM	≥27		Complete/partial surgical resection
V	≥50	GBM	Neurologic Function which inhibits ability to work	KPS 70-100	Surgical resection or Bx only followed by at least 54.4 GR RTx
V	≥50	GBM	<27		Biopsy Only
V	≥50	GBM	Normal	KPS<70	

Figure 9 The prognostic factors contributing to RPA classification is incorporated in a multivariate table. Redrawn from [44]. RPA: Recursive Partitioning Analysis, PS: Performance status, KPS: Karnofsky Performance Status, MMSE: Mini-Mental State Examination

Figure-10 NOSC members, contributors and collaborators

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11. Competing Interests

NOSC (The Neuro-Oncology Scientific Club) is a professional forum for the exchange of experts' experience and updates on brain tumors in an interdisciplinary fashion. NOSC plans to act as a working team and further as a guideline definition group in Tehran and meanwhile has no competing interest to disclose.

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