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Prognostic Factors and Treatment Outcome in Glial Brain Tumors; Data from the Third Neuro-oncology Scientific Club's Input Forum, 2013, Mashhad, Iran

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Policy Article

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ABSTRACT

Management of the central nervous system malignancies are among the evolving areas of research and clinical practice requiring a well-coordinated interdisciplinary approach. The neuro-oncology scientific club (NOSC) has tried to cross the links between various disciplines' experts involved in brain tumor care in Iran since 2011. The NOSC's structured collaborative brain tumor registry (BTCR) and the support received from its steering committee and provincial boards have been the key elements for its success and growth so far. This scientific community not only has helped to optimize brain tumor care but provided interdisciplinary research opportunities to its members across Iran. Mashhad's NOSC has been the pioneer in the above. During the 3rd Mashhad's NOSC meeting held in November 21st 2013, the interim results from some important local neuro-oncology studies were presented. Some potential opportunities to improve the coordinated interdisciplinary brain tumor care within the province were discussed by neurosurgery, neuroradiology and radiation oncology faculty at this provincial NOSC meeting. Clinical outcome, survival data and prognostic factors in adult and pediatric gliomas over the past several years in Mashhad, the association between methyl guanine methyl transferase (MGMT) methylation status (determined by MSQP or methylation specific quantitative polymerase chain reaction) where among the main studies outlined during this event. We realize that optimized brain tumor management and productive research in neuro-oncology can only be achieved through an integrated approach and strong team work. This is what the NOSC pursues.

Keywords: Neuro-oncology; consensus development; brain tumor management; interdisciplinary; Mashhad; Iran.

1. INTRODUCTION

The Neuro-Oncology Scientific Club (NOSC) was established in 2011 based on the necessity to augment coordination within and between the neuro-oncology health care professionals across Iran. This Iranian scientific club started to be recognized as a promising community serving all specialties involved in neurological malignancies' treatment and research across the country [1-5].

The third NOSC meeting in Mashhad was held on 21 Nov. 2013. NOSC-3 hosted around 50 local experts and academics from various brain tumor-allied disciplines. Apart from the provided updates and discussions on the minimally invasive brain tumor surgery, the

intraoperative image-guided surgery in CNS tumors, the standard of care in high-grade gliomas and some interdisciplinary practical discussions, part of the meeting was dedicated to updating the members with the interim results of the neuro-oncology clinical investigations and ongoing brain tumor trials conducted in Mashhad. Finally, issues such as: 1-how to further strengthen our interdisciplinary approach to improve challenging brain tumor patients' care? Role of the NOSC platform and the collaborative brain tumor registry (BTCR), 2-unmet needs in neuro-oncology practice in our local setting and 3- role of the Cancer Research Center of Mashhad University of Medical Sciences in our prospective neuro-oncology research strategies, were dealt with upon conclusion. The present report outlines the strategic discussions during the above event as well as the results of some recent concluded projects within NOSC-Mashhad.

2. ADVANCED SURGICAL APPROACHED FOR MAXIMAL SAFE RESECTION OF BRAIN TUMORS

2.1 Current Approaches in Functional and Minimally-invasive Brain Tumor Surgery

Considering the aggressive nature of high-grade gliomas (HGGs) and glioblastoma multiforme (GBM) in particular, these tumors are associated with a dismal prognosis [6]. Hence, it has been shown that maximal safe resection plays a critical role in improving such poor prognosis [7]. The issue of "safe resection" is a practical dilemma since without knowing the functional status of a distinct area of the involved cortices in the brain, the risk of serious damage to the eloquent brain areas upon surgery remains high [8]. There are fortunately some techniques generally referred to as functional brain surgery helping to minimize such post-operative sequellae [8].

The fluorescence-guided surgery for brain tumor using 5-aminolevulinic acid (5-ALA), is a technique to mark tumor margins upon excision [2]. With respect to the use of 5-ALA in brain tumor surgery setup in Mashhad, although we had some experience with this method in some centers, cost and infrastructure barrier (the dye itself and the optical devices) has prevented us from contemplating such application as a common practice. We however consider the fluorescence-guided surgery a setup to be installed in our centers, the soonest possible.

2.2 Awake Brain Surgery

Awake brain surgery is an attempt which depends on intraoperative brain mapping. This setup is not widely accessible in our region and there are very few centers in Iran having started to run a pilot setup for such surgery. In this setting, surgical procedures on the brain are performed while the patient is under sedation but still awake. This approach enables the neurosurgeon to remove the tumors which would be otherwise inoperable. Some deep-seated or critically positioned tumors are too close to the brain areas controlling motor functions, vision or speech. In addition, some tumors such as HGGs spread throughout the brain and lack a clear visible margin [8,9]. In such instances, non-functional surgical procedures carry a remarkable risk for post-operative functional catastrophes [10]. Some real-time auxiliary tools are employed to localize eloquent areas during high-risk surgical procedures on brain tumors. The intraoperative neurophysiological monitoring (IONM) encompasses techniques which enables the brain surgeon to reserve the functionality of the nervous system while excising the tumor [8]. Such techniques include intraoperative

magnetic resonance imaging (MRI) [11], intraoperative brain mapping, image-guided stereotactic surgery, intraoperative navigation[9]. Moreover, some other neurophysiological monitoring tools such as somatosensory evoked potentials (SSPE), electro corticography (ECoG) to map the motor and sensory cortex adjacent to the lesion, brainstem auditory evoked potentials (BAEP) may be used to ascertain the safety of the functional cortices upon tumor resection [8,9,12,13].

2.3 Image-guided Stereotactic Surgery

2.3.1 Intra-operative MRI

The intraoperative MRI (iMRI) facility provides a real-time vision on the brain and the operative area allowing neurosurgeon to recognize the tumor margin and remove the lesion as safely and effectively as possible [11]. A more precisely done operation under iMRI is shown to minimize the need for redo surgeries in many cases and also reduce the rate of post-operative complications [11,14]. Such sophisticated operating rooms are technically equipped with high-quality MRI machines with very fast image sequences through which neuro-navigational systems can be simultaneously applied. The system may enable navigating the brain upon surgery without causing an insult to functional brain areas [11]. By this, the surgeon may determine if the whole tumor is excised. If not, they can use iMRI cues to maximally remove the tumor tissue with no or as minimally as possible harm to the critical cortical or subcortical regions [15].

2.3.2 Stereotactic radiosurgery

Stereotactic radiosurgery is a technique especially suitable for deep-seated tumors in the brain and depends on advanced computer 3D-reconstruction of the brain tumor through which irradiation is delivered to the tumor site in a well-focused manner. The cyber knife is an example of stereotactic radiosurgery [16]. This technique allows focused radiation beams to be delivered to a distinct tissue volume and enables multiple beams for fractionated treatment [16,17]. Using the intersecting multiple beam irradiation in this technique, a high dose of radiation can be delivered to the targeted tissue and meanwhile, the surrounding tissue is exposed to radiation at a benign level [16]. Stereotactic radiosurgery is done through gamma knife (using the cobalt-60 source for irradiation, with multiple beams targeting a tissue), linear accelerator- (LINAC) based systems (using high-energy X-ray and fractionation, known as X-knife) and cyber-knife (a LINAC-based system installed on a robotic arm, using fractionation) [18]. The above techniques are shown to provide reasonable efficacy and safety when employed as the part of management of CNS malignancies such as gliomas, meningiomas, hemangioblastomas, craniopharyngiomas, pituitary adenomas and even metastatic brain tumors [19].

2.4 Minimally-invasive Brain Surgery

There are strong trends towards minimally invasive brain surgery techniques using endoscopy through minimal incisions. Moreover, recent techniques has extensively employed computerized 3D visualization and model construction to improve surgeon's dexterity, provide visual feedback, and quantitatively integrate information both for preoperative planning and intraoperative execution with optimized outcome [20,21]. Robotic surgery is also an evolving trend offering hopes for more favorable outcome in brain surgery [22].

Having shared these perspectives and discussed the practical challenges and realistic measures at this stage, Mashhad NOSC decided to proceed to equip neurosurgery operating rooms with the intraoperative ultrasound (iUS) equipment at this stage. This facility provides low-cost real-time imaging that is simple and rapid to use [23]. In close collaboration with the radiology faculty at Mashhad's NOSC, the use of iUS is expected to provide a practical value during brain tumor resections in our setting.

2.5 Our Current Status with Regard to Technological Advances in Brain Tumor Care

Due to infrastructure and funding barrier in developing countries including Iran, many advanced surgical/ treatment setups are not readily available. Nevertheless, for the purpose of maximal safe resection in brain tumors, some advanced techniques including brain mapping for surgical planning using functional MRI, and awake craniotomy with electrocorticography (EcoG) and somatosensory evoked potentials (SSEP) recording are of limited use in our practice. The intra-operative MRI is not currently available in our setting. Stereotactic radiosurgery is being done in some centers in Iran while not widely accessible in all provinces including Mashhad. We fortunately have some facilities with intensity modulated radiotherapy (IMRT) setup and some centers are being equipped with the multi-leaf collimator (MLC) linear accelerators. With all current limitations, we need to consider establishing new technologies as much and early as possible.

3. SO FAR ACCOMPLISHED RESEARCH AND ONGOING PROJECTS WITHIN MASHHAD'S NOSC

Within the past two years, Mashhad's NOSC faculty has concluded number of neuro-oncology studies and are currently involved in some other ongoing research projects. The interim analysis of some of these projects as well as the summary of ongoing research was communicated during this meeting.

3.1 A 12-year Retrospective Analysis to Assess the Prognostic Factors and Treatment Outcome in Adult Patients with Glial Brain Tumors in Mashhad

In this study, the prognostic factors and treatment outcome of a total of 415 patients [median age of 43 years (ranging 16 to 84) and M/F ratio= 252/163 (1.54)] with glial brain tumors who referred to the oncology departments of Omid and Qaem hospitals in Mashhad (1999-2011) were evaluated. Grade I to IV astrocytoma were found in 40 (9.6%), 88 (21.2%), 71 (17.1%) and 216 (52%) patients, respectively.

The median follow up time for low- and high-grade gliomas were 37 (ranging from 3 to140) and 13 (ranging from 1 to 91) months, respectively.

The 5-year survival in grade I to IV gliomas was 92.1%, 69.1%, 49.2% and 9.6%, respectively. Following the standard-of-care protocol [24], mainly over the past years, our reported long-term survival data were comparable to those stated by the Central Brain Tumor Registry of the United States (reporting an overall 5-year survival rate of 94%, 48%, 35% and 8% for pilocytic astrocytomas, fibrilary astrocytomas, anaplastic astrocytomas and GBM, respectively) [25]. Across the evaluated cases, sex had no significant impact on overall survival. Tables 1 and 2 demonstrate the correlation between the prognostic factors

and survival rates in patients with low- and high-grade astrocytomas using log-rank and cox-regression analyses.

Our findings in this study demonstrated that optimal surgery and favorable performance status were associated with more favorable survival in both low and high grade astrocytomas. In high grade astrocytomas, patients younger than 43 and those who received standard of care chemotherapy had better overall survival.

3.2 Prognostic Factors and Treatment Outcome in Pediatric Brain Tumors in Mashhad; over 10-year Cumulative Data

In another study which was done under Mashhad NOSC's umbrella, we retrospectively assessed the treatment outcomes and prognostic factors in pediatric non-brainstem astrocytomas.

Evaluated cases were children with non-brainstem astrocytic tumors referring to the radiation oncology departments of Omid and Qaem Hospitals in Mashhad between 2000 and 2010. Inclusion criteria were: 1-age equal to or less than 16 years, 2-pathologically confirmed astrocytoma, 3-patients with tumor in non-brain stem region confirmed by imaging. Exclusion criteria were unavailable pathological report and/or incomplete medical records (n=12).

Evaluation of the survival curves and potential prognostic factors was done in 87 cases [median age of 10, ranging from 2 to 15 years with a boy/girl ratio of 43/44 (0.97)] for a follow up duration of 38 (6-110) and16 (4-100) months in low- and high-grade astrocytomas, respectively Fig. 1. All tumors were located in supratentorial compartment and many were associated with significant neurological deficit which reflects aggressive nature of these tumors.

We recorded 28 death during follow up which was significantly higher in cases with high grade tumors. Survival was inversely correlated with the tumor grade. Glial tumors were the most common primary brain tumor in our hospital-based survey.

According to our study, cases with grade I astrocytoma (pilocytic astrocytoma) had the most favorable outcome and only one out of 20 patients (5%) experienced failure. The prognosis was worst among patients with grade IV astrocytoma. Surgical resection was not optimal in a significant number of high grade cases especially for those with grade IV tumors. In our analysis, for all cases with pediatric non-brainstem astrocytoma, tumor grade had a dramatic influence on their survival. Gross total resection is believed to be crucial in achieving favorable outcome in both low grade and high grade cases. We also demonstrated that major motor deficits upon presentation and disease progression was associated with less favorable survival outcome. Results of this retrospective analysis are summarized in Tables 3, 4, 5, 6, 7 and 8. Fig. 1 illustrates the survival curves in patients with non-brain stem astrocytoma and different tumor grades.

Table 1. The correlation between prognostic factors and survival rates in patients with low-grade astrocytomas

Factor	Number	Death N (%)	5-year survival Mean (%)± SEM	Log-rank *p* value	cox- regression *p* value
Grade					
I	40	3 (7.5)	92.1±4	0.01	0.01
II	88	26 (29.5)	69.1±5.1		
Sex					
Male	71	14 (19.7)	79.8±5	0.4	-
Female	57	15 (26.3)	69.9±7		
Age-year					
≤ 30	54	11 (20.3)	79.8±5.9	0.6	-
>30	74	18 (24.3)	72.8±5.8		
Surgery					
Optimal resection	79	9 (11.4)	86.1±7.7	<0.001	0.001
Biopsy	49	20 (40.8)	59.3±4.4		
Performance					
Ambulatory	71	8 (11.2)	88.2±4.3	<0.001	0.01
Non-ambulatory	57	21 (36.8)	60.2±7.2		

Table 2. The correlation between prognostic factors and survival rates in patients with high-grade astrocytomas

Factor	Number	Death N (%)	5-year survival Mean (%)± SEM	Log-rank p value	cox- regression p value
Grade					
III	71	33 (46.6)	49.2±6.6	<0.001	<0.001
IV	216	199 (92.1)	9.6±4.4		
Sex					
Male	181	124 (68.5)	24.9±3.7	0.8	-
Female	106	75 (70.7)	18.5±5.1		
Age-year					
≤ 50	144	90 (62.5)	29.6±9.7	<0.001	<0.001
>50	143	109 (76.2)	14.6±3.7		
Surgery					
Optimal resection	113	58 (51.3)	39.4±5.9	<0.001	<0.001
Biopsy	174	141 (81.1)	10.5±3.1		
Adjuvant Chemotherapy					
Yes	197	131 (66.4)	23.7±3.8	0.02	<0.001
No	89	67 (75.3)	18.7±4.8		

Table 3. The prevalence of various type pediatric primary brain tumors in our retrospective analysis

Primary tumors	Number (%)
Non-brain stem astrocytoma	87 (52.1)
Brain stem tumor	26 (15.1)
Medulloblastoma	26 (15.1)
Pineoblastoma	1 (0.6)
Ependymoma	11 (6.5)
Oligodendroglioma	7 (4.2)
Craniopharyngioma	4 (2.4)
Meningioma	3 (1.8)
Choroid plexus papilloma	2 (1.2)
Total	167 (100)

Table 4. Tumor grades

Tumor grade	Patients (%)
Grade I	20 (23.0)
Grade II	34 (39.1)
Grade III	20 (23.0)
Grade IV	13 (14.9)
Total	87

Table 5. Performance status in patients with high and low grade tumors

Tumor grade	Performance		Tumor grade
	Ambulatory	Needing aid	
Low grade	50	4 (7.4 %)	54
High grade	19	14 (42.4 %)	33
Total	69	18	87

Table 6. Two- and five-year survival rates in patients, based on the tumor grades

Grade	Total number	2-year survival Mean (%)± SEM	5-year survival Mean (%)± SEM	Number of events (%)
I	20	100	90.9±7.6	1 (5)
II	34	84.7±6.1	73.9±8	8 (23.5)
III	20	60±10.9	60±10.9	8 (40)
IV	13	10.8±10	Not reached	11 (84.5)

Treatment of brain tumor in children remains challenging [26]. A number of strategies have been devised in an attempt to minimize the long-term effects of treatment for pediatric brain tumors. Some almost necessary measures include: 1- daily anesthesia for children younger than age 4 or 5 years, requiring a skilled pediatric anesthetist since the anesthesia is administered at a different environment lacking all the normal supports available in an operating room, 2-improved immobilization techniques (e.g., rigid casts or a stereotactic frame for small-volume focal radiotherapy for all or part of the treatment) that allow the use of reduced margins around the target volume, 3-avoidance of RT altogether (e.g., in patients with low-grade astrocytoma for whom surgery alone may be a good option), 4-delay to RT

for young children (i.e., those younger than age 3 to 8 years) by the use of chemotherapy, 5- use of focal rather than extended-field radiotherapy when evidence suggests that extended field (whole-brain, craniospinal) radiotherapy does not influence survival (e.g., ependymoma) and 6 - use of image-based treatment planning using CT–magnetic resonance imaging (MRI) or combined CT–MRI–positron emission tomography (PET) imaging [26,27].

Table 7. Potential prognostic factors in patients with low-grade non-brain stem astrocytomas

Characteristics	Number	5-year survival Mean (%)± SEM	Log-rank p value	Cox-regression p value
Grade				
grade I	20	90.0±7.8	0.04*	0.25
Grade II	34	73.9±8.3		
Age-years				
<10	34	81.3±7	0.69	-
≥10	20	76.7±13		
Performance				
Ambulatory	50	84.2±6.4	0.001*	0.01*
Non-ambulatory	4	25±21.6		
Resection				
Total/sub-total	41	94.9±3.5	0.001*	0.001*
Biopsy alone	13	24.4±18.8		

Table 8. Potential prognostic factors in patients with high-grade non-brain stem astrocytomas

Characteristics	Number	5-year survival Mean (%)± SEM	Log-rank p value	Cox-regression p value
Grade				
grade III	20	60.0±10.9	0.003*	0.5
Grade IV	13	Not reached		
Age-years				
<10	8	33.1±18	0.7	-
≥10	25	39±9.9		
Performance				
Ambulatory	19	56.7±11.6	0.003*	0.38
Non-ambulatory	14	Not reached		
Resection				
Total/sub-total	17	70.1±11	<0.001*	0.001*
Biopsy alone	16	Not reached		

To avoid excluding the patients from analysis only due to insufficient records in our future reports, the NOSC's dedicated brain tumor registry system (the brain tumor collaborative registry or BTCR) is being installed and utilized in Mashhad and other main provinces across Iran. Following the installation of the BTCR, currently, the patients' clinical information, the presenting complaints and symptoms, brain tumor related information, imaging data, CSF analysis, pathology reports, surgery data, radiotherapy, chemotherapy protocols and experienced side effects and post mortem data (for those registered patients who died within 6 month to 1 year follow up period, and had a post-mortem examination) are carefully recorded. We expect to have more comprehensive records of our patients' data within

NOSC's BTCR and our prospective trials and cohorts are not expected to exclude patients from analysis only due to the missing data. The content validation report of this registry was presented in 10th European Association of Neuro-Oncology (EANO) meeting, September 2012.

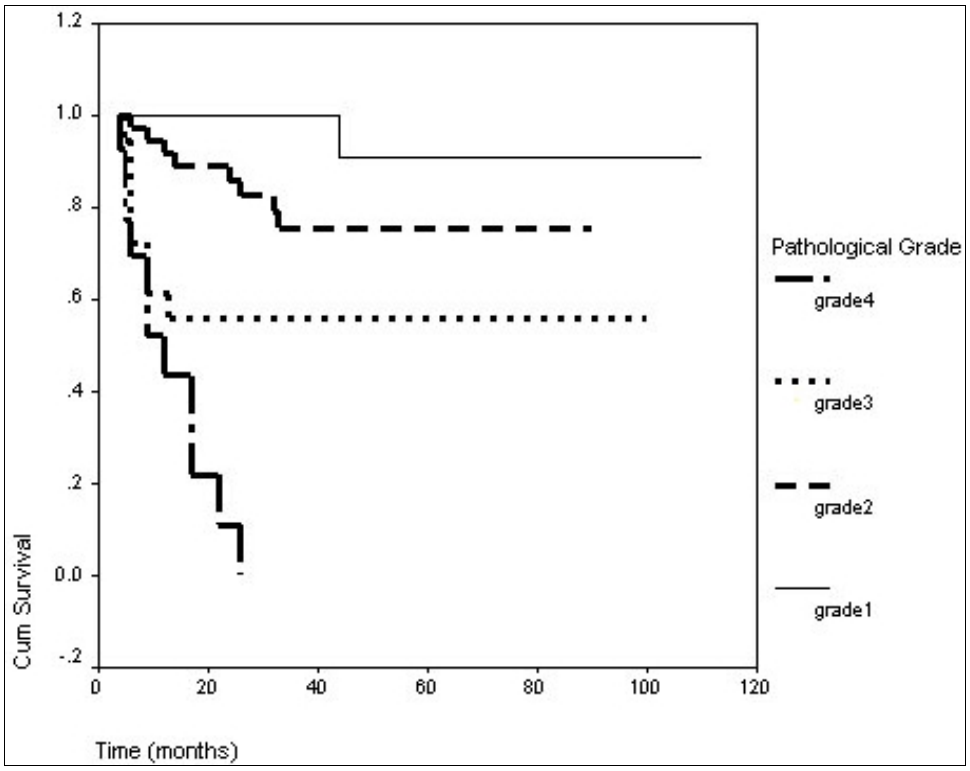

Fig. 1. Survival curves in patients with non-brain stem astrocytoma and different tumor grades

3.3 The Association between MGMT Methylation Status (Measured by MSQP-Methylation Specific Quantitative Polymerase Chain Reaction) and Treatment Outcome in Patients with GBM.

Currently, the standard care in GBM comprises maximal safe surgical resection of the tumor and chemoradiotherapy with temozolomide (TMZ) followed by adjuvant chemotherapy with TMZ [24]. Studies have shown that not all patients equally benefit from the above therapeutic regimen and molecular markers such as the methylation of MGMT gene promoter can play a role in response [24].

Similar to nitrosureas, TMZ is a DNA-alkylating agent functioning on the O_6 position of guanine. In the subsequent DNA replication, the methylated guanine, couples with thymidine rather than cytosine and the resultant cytotoxic effect results in the apoptosis of the tumoral cells [28].

MGMT gene (located on the chromosome 10q26) expresses MGMT as one of the main contributors to DNA repair. Demethylating function of this enzyme on O_6 guanine site

promotes the DNA repair process by which the cytotoxic effects of alkylating drugs are abrogated. On the other hand, when a chemotherapeutic agent such as TMZ methylates the gene promoter of MGMT, DNA repair enzyme is not produced secondary to MGMT gene deactivation. This results in proliferation control of the tumoral cells translated to extended survival in GBM patients treated with TMZ [29]. The available methods used to determine the MGMT methylation status include methylation-specific polymerase chain reaction (MSP)[30], mRNA expression (only applicable on freshly obtained tumor tissue) and immunohistochemistry (IHC) using the anti-MGMT antibody[31]. None of the studies including the largest clinical trials could substantiate any conformity between IHC and MSP results with regard to MGMT methylation [31].

This study which evaluated the MGMT methylation status in 78 GBM patients (56 males and 22 females with the mean age of 51 years old) demonstrated a significantly more favorable response to chemo-radiation and adjuvant chemotherapy with TMZ in MGMT-methylated (QMSP method) group. Figs. 2 and 3 illustrate the expression of MGMT methylation status in QMSP protocol and the outcome of chemo-radiotherapy with and without TMZ in patients with methylated and un methylated MGMT status, respectively.

All patients underwent partial resection of the tumor and received the median dose of 60 Gy irradiation. 29 patients were treated with Stupp's protocol [24] and the remaining received nitrosurea-based chemotherapy regimens. Patients were followed up for the median duration of 12.5 months. By the end of the follow-up period, 49 patients (62.8%) had deceased due GBM progression.

According to our results, the median overall survival (OS) and progression free survival were 13 and 10 months, respectively. The 1 year, 2 year survival rates were 57.2% and 31.5%, respectively.

59 cases (75.6%) had methylated and 19 (24.4%) had un methylated status of MGMT gene promoter. Log-rank test results indicated that methylation of the MGMT gene was significantly correlated with prolonged survival ($p < 0.001$). Moreover, multivariate analysis using the cox-regression analysis revealed that MGMT methylation was an independent factor influencing survival ($p = 0.001$). Favorable response to chemo-radiation was observed in 75% and 54.5% of MGMT methylated GBM patients who received TMZ and other nitrosurea-based chemotherapy regimens, respectively Figs. 3 and 4.

Evaluation of methylation status is not recommended in routine practice basis due to the lack of alternative chemotherapy regimen (other than TMZ) for non MGMT-methylated GBM. Moreover, the use of conventional IHC techniques to assess MGMT methylation is not validated. Meanwhile, until more research data is available, it would not be prudent to apply other techniques to define the methylation of this enzyme. We suggest conduction of larger scale studies to validate the practical feasibility of MSQP to determine the MGMT methylation status and whether this enzyme in less methylated amongst Iranian patients afflicted with high-grade gliomas.

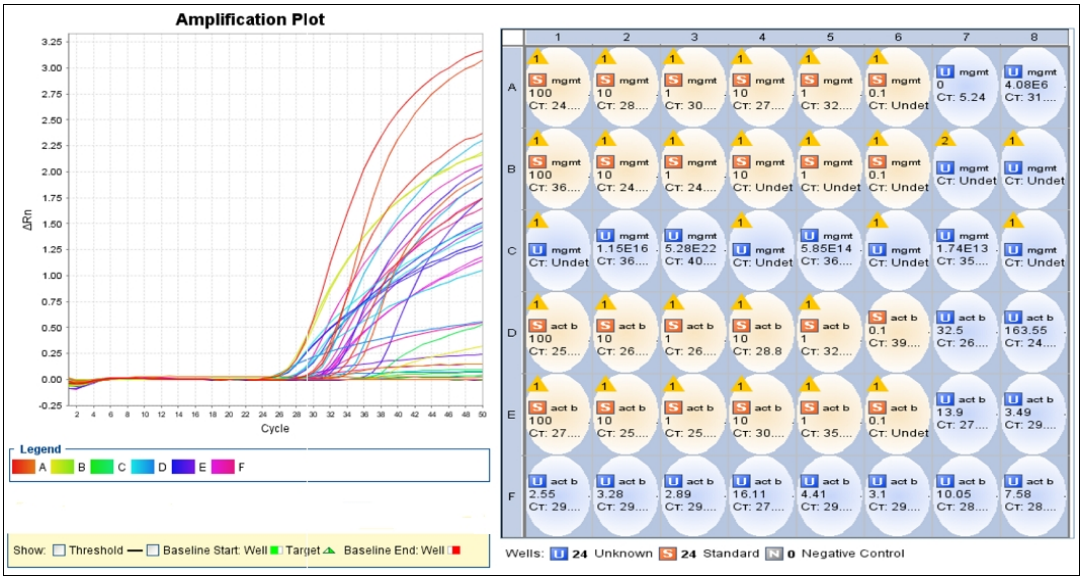

Fig. 2. Plate setting graph illustrating expression of methylated and unmethylated status of the MGMT gene as well as beta-actin in a plan of methylation specific quantitative polymerase chain reaction (MSQP)

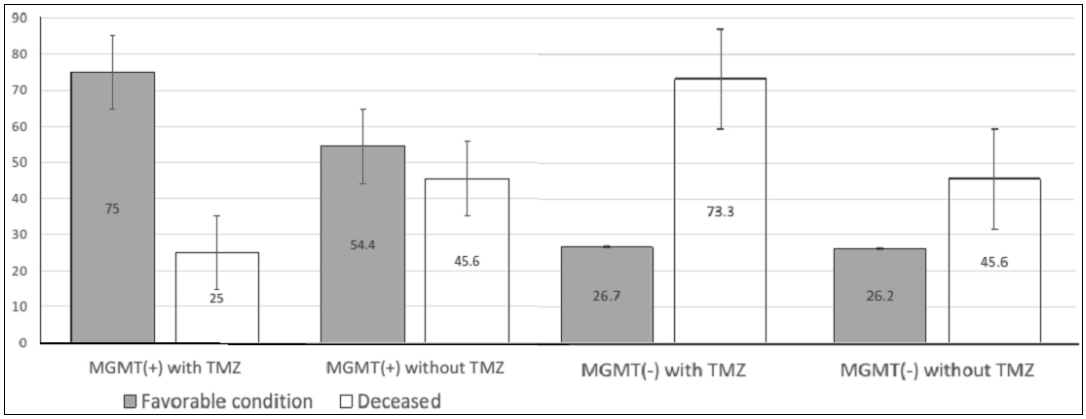

Fig. 3. The outcome of chemo-radiotherapy with and without TMZ in patients with methylated and un methylated MGMT status in a 2-year follow up

3.4 Ongoing Neuro-oncology Research within Mashhad's NOSC

There are number of interdisciplinary research works currently being conducted by a number of Mashhad's NOSC faculty and members. The preliminary results of these projects are expected to be communicated during the forthcoming NOSC meeting in 2014. Some major ongoing projects under Mashhad NOSC's roof include: 1-Assessment of re-irradiation outcome in recurrent brain gliomas using a 3D-conformal planning system, 2- Expression analysis of Cancer/ testis antigens (GAGE, MAGE-E1, SOX-6) in glioblastoma patients using IHC, 3-analysis of HORMAD1, FTHL17 and ADAM29 cancer/testis specific genes expression in glioblastoma using PCR and 4- IHC detection of isocitrate dehydrogenase-1

(IDH-1) mutations (R132H, R132S) in patients with astrocytoma. Mashhad's NOSC has tried to cross-link basic, translational and clinical brain tumor science for collaborative research projects of which some are already published or currently under review.

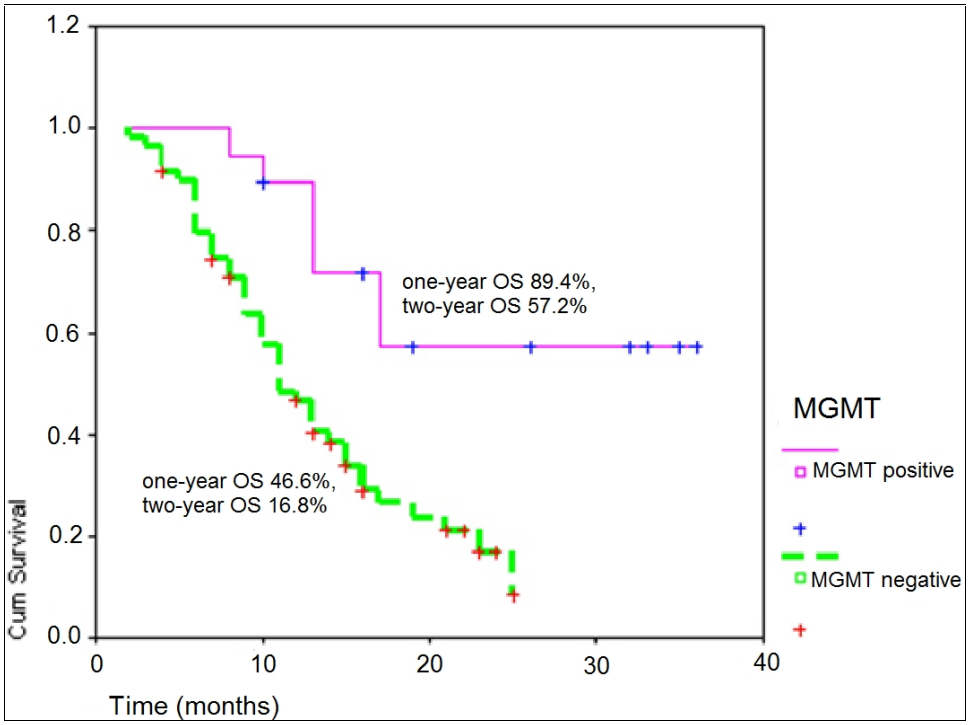

Fig. 4. The log-rank analysis showing that MGMT methylation status was positively correlated with survival (p<0.001). Based on the multivariate cox-regression analysis, MGMT methylation status was an independent factor significantly affecting the survival outcome

4. CONCLUSION

Mashhad's NOSC faculty and members discussed further opportunities and potential challenges for upcoming projects and so far achievement versus shortcomings in clinical care provided to brain tumor patients. Members decided to further utilize the NOSC's collaborative brain tumor registry at more centers across the province to unify data collection. Installation of the intraoperative ultrasound (iUS) equipment in neurosurgery operating rooms was decided. Contributors agreed to submit the final analysis of the implemented projects for possible publication soon and share the interim reports of the ongoing works during the next NOSC meeting in Mashhad which will be held mid July 2014.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that the presented retrospective studies were examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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