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Current and Future Perspective of Glioblastoma, Molecular Heterogeneity with Clinical case

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Abstract

Background: Glioblastoma multiforme is a highly vascular most common primary brain tumor which is extremely narcissistic in its character and function. It has high rates of recurrence despite neurosurgery, chemotherapy targeted therapy and radiotherapy. It is diligent endeavor of neurosurgeon and neurooncologist to make decision for patients who present with recurrence of this evil disease many times. This article is an attempt to delineate clinical spectrum molecular types character of this disease with a clinical experience of professionals dealing with this glioblastoma.

Methods: We have clinically examined patients in Neuro oncology department and Neurosurgery Department and provided best possible service to patients according to current evidence-based medicine. The modern guidelines have been followed in practice. We have been conducting meticulous discussion regarding glioblastoma and getting help from international experts for decision making and treatment planning of individual patients. A case was discussed by corresponding author in European School of Oncology live session.

Results: Majority of patients are returning back to Neuro physicians Neurosurgeons with recurrence of brain tumor with worsened health and debilitating morbidity.

Conclusion: Brain tumor scientific knowledge needs to be upgraded with biomarkers, new approach and newer drugs and surgical protocols.

Keywords: Glioblastoma; Tumor heterogeneity; Molecular classification; Molecular heterogeneity; Primary brain tumor; Glioma

Abbreviations: OS: Overall Survival; PFS: Progression Free survival; EOR: Extent of Resection; IDH: Isocitrate dehydrogenase; ATRX: ATP-dependent X linked helicase; P53: A tumor protein; EGFR: Epidermal growth factor receptor; CCRT: concurrent chemo radiotherapy; MGMT: O [6]-methylguanine-DNA methyltransferase; MRI: Magnetic Resonance Imaging; GBM: Glioblastoma multiforme

INTRODUCTION

Glioblastoma is a tumor that originates from star shaped glial cells of brain and spinal cord. Gliomas begin in the gluey supportive cells (glial cells) that surround neurons and help to function. It is a fast growing highly invasive tumor that born from brain cells, astrocytes and oligodendrocytes. It encroaches surrounding tissues expeditiously. Glioblastoma multiforme is also known as Grade IV astrocytoma. It was estimated that approximately twenty-three thousand plus people in USA would be diagnosed with primary tumor of brain and spinal cord and these account for 85 to 90% of all CNS tumors in 2020. CNS tumors are 10th leading cause of death. Apart from this, secondary brain tumors are those which metastasize from other cancers like breast, lung, lymphoma, kidney, bladder cancer etc. [1] Worldwide research has shown an annual incidence rate of 0.59 to 5 per 100,000 persons approximately; however, there have been studies indicating an increase in incidence rate of brain tumors. [2]

In past retrospective study showed no statistically significant difference in the progression-free and overall survival in IDH1, WT-1, p53 and ATRX expression analysis. The OS and PFS in radiotherapy and chemotherapy was found statistically significant difference. There was no statistically significant in PFS and OS with surgical treatment. [3].

MR spectrometry is used to identify IDH mutant metabolite. It is noninvasive detection of the grade or sub-type of glioma. It is used for evaluating responses to treatments against IDH mutant tumors. IDH1 mutation may be useful as a biomarker for treatments and prognosis. [4]

Tumors like glioblastoma might be set to continuous immune-editing, either under selective pressure from the patient's own immune system or during active immunotherapy.

EGFR v III expression may be lost at recurrence, suggesting immunologic escape after a period of progression-free survival. [5]

Treating recurrent glioblastoma is one of the ultimate challenges in neuro-oncology and therapy design must consider knowledge on the biology of primary as well as recurrent glioblastoma. [5]

Complications like stroke due to infiltration or occlusion of cerebral arteries by glioma can present with severe, subtle to no symptoms. Difference in tumor-related and cerebrovascular brain infarction is obscure. MRI with diffusion and perfusion imaging with gadolinium contrast, are useful in diagnosis. This is incorporated in the diagnostic protocol of stroke with the slightest signs of brain tumor. Patients who have glioblastoma presenting with ischemic stroke have high chances of complications after surgery. [6]

Recurrent Glioblastoma

Use of advanced surgical tools have caused improved survival for patients with glioblastoma compared to surgeries performed decade ago. Now, majority of patients with operable tumor are living with good functional ability, despite development of recurrence. Glioma tumors have poor prognosis in spite of advanced surgical and chemotherapeutic anticancer treatment. repeat craniotomy for recurrent gliomas has been suggested by latest research. Repeat resection of tumor has shown a benefit in overall survival and patients' quality of life. The EOR (Extent of Resection) should be adequate threshold (about 80%) during repeat craniotomy, to harness this benefit for patient. Chemotherapy and radiotherapy constitute nonoperative treatments of glioma recurrence as well. Additionally, novel drugs and immunotherapy are being used that offer valuable option for improving outcomes in patients. Immunotherapy causes target immune responses against gliomas by creating tumor antigens and delivering them halt tumor progression. [7].

Neuro scientist have observed inter- and intra-tumor heterogeneity in glioblastoma based upon genetic profiles. This heterogeneity directs biological behaviors of tumor and underlying characteristics. The genetic and molecular characters render susceptibility of these tumors to both chemotherapy and targeted therapies, although no real prognostic value of subclassification of tumor types has shown promising single therapeutic module.

Numerous heterogenous somatic events and replications within the primary tumor and metastatic brain lesions, and glioma stem cells make it difficult for the use of these molecular information in treatment of patients. It is likely that implementation of any therapeutic approach for glioblastoma, heterogeneity will be considered.

The complexity of over- and under expressed genes, mutated genes do not correspond individually to each patient and cancer types. This limits feasibility of generally applicable treatment protocol. The molecular pathways suggest that one single therapeutic approach may give brief success in handful number of patients. The tumor cell population undergoes repeated alteration, even during chemotherapy and radiation and thus is not a single cancer clone, but it is heterogeneous population of neoplastic cells with genetic aberrations that let them survive during treatment [8].

Currently, the concomitant surgery and adjuvant chemotherapy with temozolomide in addition to radiotherapy is new standard in treatment of the glioma. It has shown improved survival rates result [9]. Most brain tumors are not homogeneous masses of cancer cells. They contain tumor microenvironment and ecosystem and supportive stroma. Heterogenicity of tumor cells based on genetic and epigenetic changes as well.

Immune system plays important role in regulating tumor biology. Tumor-associated macrophages stimulate maintenance and tumorigenicity. IDH wild-type gliomas show high immune infiltration and leukocyte chemotaxis compared to Low-grade IDH mutant gliomas, suggesting that separate immune activation between various grades of tumors. Glioblastomas facilitate overall T-cell deficiency systemically and accumulation of ineffective T

cells inside bone marrow. These T cells are not capable of stopping or destroying cancer cells. Glioblastomas also generate both local and systemic immunosuppression [10].

The best treatment of glioblastoma is excision, radiotherapy, and chemotherapy altogether. The goal of initial operation is maximal tumor excision, then by radiotherapy and chemotherapy. Long-term survival is seen in female gender, location of tumor, aggressive surgical resections, younger age, and a good KPS at the time of diagnosis [11].

Bevacizumab is chosen usually after first or second relapse of glioma, but disease recurrence is soon. Usually comes back within 6 to9 months of first diagnosis. Salvage therapies may only control disease growth for next 4 to 6 months. Several molecular biomarker-driven tests are used for diagnostic purpose, like driver alterations PDGFRA, EGFR, PTEN, MET/CDK6, CDKN2A/ CDKN2B, PIK3CA, NF1, RB1, TP53, CDK4/MDM2, PDGFRA. Cancer cells are in highly proliferative state. They require elevated energy and biomolecules for propagations.

In these translations metabolic alterations occur due to oncogenes, onco-suppressors, and cellular environment. Biomarker in gliomas has been tested by metabolomics, like oncometabolite 2-hydroxyglutarate in IDH1 mutated gliomas. The progression of malignant gliomas is due to altered metabolic homeostasis. Tumor tissue and serum metabolomic studies in glioma patients has revealed prognostic and diagnostic information, allowing for patterns that distinguish different grades of glioblastomas from oligodendrogliomas [12].

Highly malignant tumors are made up of more diverse cell types and contain immature astrocytes or oligodendrocytes or both cell types in the same tumor bed. Malignant gliomas are characterized by active anaplasia, neoplastic transformation, proliferation, and invasiveness. Anaplastic astrocytomas and multiform glioblastomas are highly malignant tumors of the brain. The prognosis for these tumors is very poor. Usually, patients die after 12 to 15 months of diagnosis. Some types of gliomas are less sensitive to radiotherapy and are highly chemo-resistant, and this usually leads to tumor relapse after surgery.

Gliomas are highly radioresistant. Despite this radiotherapy is a prime modality of treatment and it is most efficient nonsurgical method implied for glioblastomas. These tumors are positive for CD133 positive TSCs. Expression of CD133 and MGMT together is associated with an increased resistance of glioblastoma to radiotherapy. Gliomas can effectively repair of radiation caused damage to DNA and can live even after radiation therapy [13].

Adjuvant Chemotherapy with temozolomide together with radiotherapy, administered after tumor excision, has increased median survival of 14.6 months compared to 12.1 months with RT alone to. PFS and the response to temozolomide are not good in recurrent Gliomas. Gliomas are highly vascular tumors with varied molecular and genetic heterogeneity. An appropriate treatment should challenge molecular heterogeneity, stop angiogenesis, and drug should cross the blood-brain barrier, without significant systemic toxicity [14].

Many of the gene expression studies of cancer to date have demonstrated that morphologically different tumors have distinct transcriptional profiles. Some patterns of gene expression correlate with increasing grade of malignancy in gliomas, for example, low-grade glioblastomas, oligodendrogliomas and astrocytomas have special gene expression set, which are clearly separable from each other and from normal brain tissue. They are also morphologically distinctive gliomas with different underlying biology [15].

Glioblastomas originate within a range of pathways in response to different signals to emerge into specific cancer phenotypes. Distinct subtypes with origin and developmental neuro-biology has been revealed by transcript-based analysis revealed. Growth dysregulation and leading to cascade of events during the neoplastic transformation process has been proven by scientists [16].

Physiological Mechanism of Necrosis in Glioblastomas. Necrosis is hallmark sign of glioblastoma. Its presence is in about 85% of cases. Cellular ATP depletion and electron transport chain collapse and subsequent decreased oxidative phosphorylation leads to necrosis in glioblastoma tumor. This lack of ATP leads to failure of ATP-dependent channels leading to cell swelling. Increased Na+ K+ ATPase causes cellular swelling and disruption of cells. Cell membrane ruptures, the contents of the cell are released into the extracellular space. protease activation and a localized inflammatory response causes of necrosis at the center of tumor [17].

Management of Recurrent Glioblastoma: Surgery, Bevacizumab or Chemotherapy?

Most of the time the choice between surgery, bevacizumab medicine, or surgery followed by bevacizumab treatment is challenging. Several studies have attempted to define

the role of surgery in the management of recurrent glioblastoma.

This is very important question which occurred to me as an oncologist as I come across several cases of glioblastoma recurrence, frequently. One representative case I discussed with expert panel in European School of Oncology, is given here.

Few studies have suggested no additional benefit of surgery after recurrence, indicating that PFS at 6 months and overall survival were comparable with and without resection at the time of tumor progression. Other studies have demonstrated that there is a survival benefit with surgery at progression, given that a minimum extent of resection is done [18].

Case Presented by corresponding author of this article Samim Akhtar, MD in European School of Oncology (ESO) on 2020-12-11

https://www.e-eso.net/sessions.do?methodcall=details&idegrandround=1931

Neuro Oncology Multidisciplinary Management of Adult Brain Tumor

Glioblastoma Multiforme Right Temporal Lobe Recurrence

55 years /male Diagnosis: Glioblastoma Multiforme Right Temporal Lobe Recurrence

2015- 07 Onset: Patient presented with headache 10 days + projectile vomiting few episodes 2 days. GTCS 1 episode.

Preoperative CECT Brain and MRI Brain: showed 2.6 cm ring enhancing lesion in right temporal lobe with edema

2015-08-12: Craniotomy, tumor excision with Duraplasty and bone flap removal was done.

2015-08-16: Histopathology of Brain Tissue: Section fragments of highly cellular glial polygonal to elongated tumor cells with moderate amount of pale eosinophilic cytoplasm and round to irregular nuclei. Tumor cells showed show marked pleomorphism with scattered large giant cells. Mitosis was seen. Necrosis with pseudopalisading of tumor cells and microvascular proliferation. Glioblastoma WHO Grade IV.

EGFR, IDH-1 and MGMT methylation studies were advised.

2015-09-10 to 2015-10-27: received CCRT Temozolomide 120 mg + Radical brain irradiation 60Gy/30Fr + 200cGy/Fr 3D VMAT module.

2015-12-08 MRI Brain: Post Surgery GBM. Interval resolution of T1 hyperintensity due to hemorrhage within surgical cavity. No abnormal enhancement along the margins of surgical cavity or adjoining parenchymaT2W Flair Hyperintensity is seen in right temporal lobe showing mild interval increase since the previous MRI causing no mass effect likely post-surgical and treatment related changes.

2017- 02-21 MRI Brain: No evidence of recurrence or residual disease.

2018- 02-22 MRI Brain: Small heterogenous nodular enhancing area 9mm in anterior superior aspect of right temporal lobe suggestive of recurrence.

2018- 07-24 MRI Brain: 2.9 × 11.2 × 6. 8 mm heterogenous enhancing nodular lesion in anterior superior aspect of right temporal lobe with elevated level of choline level in MRS s/o recurrence.

2019- 08-14 MRI Brain: Post-surgical changes in right temporal lobe as well as right temporal skull with gliosis in right temporal lobe. Meningeal enhancement in the region of prior craniotomy. Interval increase in size of previously noted heterogenous enhancing nodular lesion 42 × 5O × 2O mm previously 2.9 × 11.2 x ×6. 8 mm s/o recurrence.

2019-08-16 Patient presented with aphasia; “unable to speak, each lasting half hour, 2 episodes”. Proper history and examination reviewed. CT scan brain was done. He was diagnosed with recurrence. Patient was admitted in ward and his condition stabilized. Planned for craniotomy.

2019-08-18: Craniotomy with tumor excision was performed. During his post-operative period his vitals were monitored routinely, managed conservatively with IV fluids, antibiotics and analgesics, PPI supportive method.

On 1Oth postoperative day he was discharged with oral medications and advised for chemotherapy (Figures 1 and 2).

Glioblastoma Post surgery Post CCRT then relapsed disease post 20# CCRT till 2O19-10-18

2019-10-18: Patient was planned for concurrent re-irradiation with chemotherapy Temozolomide followed by adjuvant Temozolomide.

2020-03-11: presented with vomiting 1 episode, difficulty in swallowing since 1day and abnormal movement of limbs 1episode.

Physical examination:

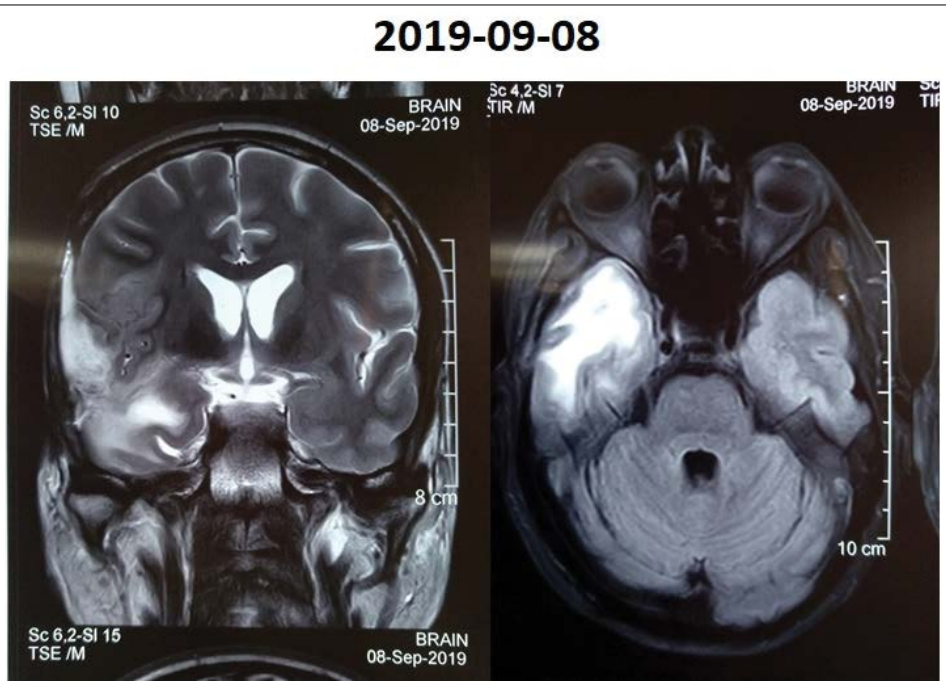

Figure 1: MRI Scan.

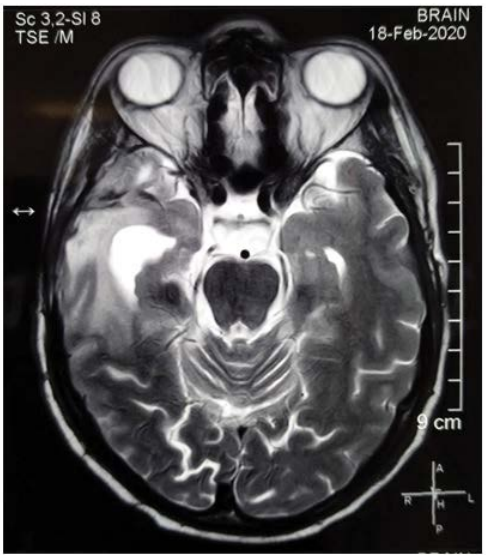

Figure 2: MRI Scan.

BP: 120/80 mmHg Pulse:78 bpm Resp: 20/min T: 98 °F SpO2: 96%

CNS Examination: GCS 15/15, both pupils equal, reacting to light and accommodation. CNS examination was unremarkable.

Chest, cardiovascular, abdominal and locomotor examinations were unremarkable.

CT Scan Brain: Right sided craniotomy with removal of the bony flap. Low attenuation of white matter parenchyma involving the frontal and temporal lobes. Bilateral in keeping with oedema causing minimal effacement of right lateral ventricle

He was treated with dexamethasone, levetiracetam, clobazam, sodium valproate etc.

Consulted with Medical Oncologist for chemotherapy

2020-09-20: Patient cries at night with hallucination. Haloperidol started.

2020-10-18: Patient came in follow up after 6 months. He is feeling weakness from last 6 months.

We planned to do CT scan Brain with baseline blood tests

Patient has completed 6 cycles of chemotherapy post CCRT (Figure 3).

Questions for discussion with Expert panel

1. What further treatment options should be explored and implemented for this patient?

2. Can 3rd time craniotomy and excisional surgery be advisable and beneficial for this patient, since he has already undergone two surgeries?

3. Can we administer Bevacizumab or Nivolumab immunotherapy for this patient? How much clinical benefit will be harnessed?

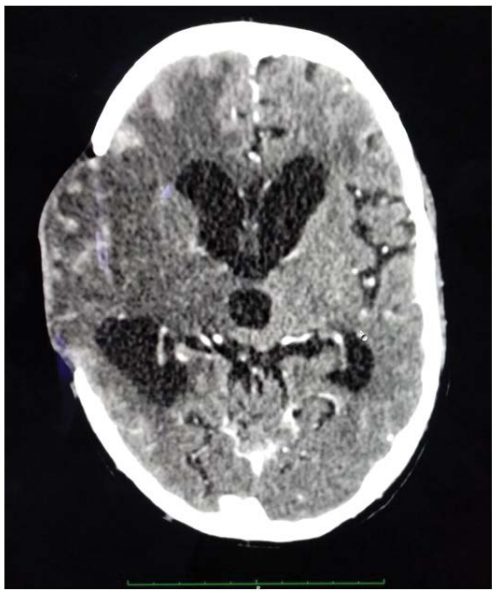

Figure 3: MRI Scan.

With meticulous discussion over this case in Neuro Oncology session it was decided by the consensus of expert panel, that surgical resection of the brain tumor for third time is the best option.

Molecular studies reveal different IDH1 mutations types in glioblastomas. Glioblastomas have been grouped on the basis of cDNA expression profiles, with distinct proneural, neural, classic, mesenchymal, and proliferative patterns. Glioblastomas without IDH1 mutations have been identified as, neural, proneural, classical and mesenchymal. Secondary glioblastomas are a rather homogeneous those which metastasize from other primary tumors of human body. But primary glioblastomas are heterogeneous, with several distinct expression. Typical proneural signatures are seen diffuse astrocytomas, oligodendrogliomas and oligoastrocytomas signifying that these neoplasms share common neural progenitor cells. Proneural glioblastomas are characterized by alteration PDGFRA and mutations in IDH1 and TP53, sharing gene expression features with lower-grade gliomas and secondary glioblastomas. Many abnormalities overlap between the transcriptional subclasses [19,20].

CONCLUSION

Glioblastoma is heterogenous group of cancer genetically and phenotypically. Researchers, Neuro surgeons and Neuro oncologist need to think out of box, discover new way to study and devise future therapies and perform various scientific research together to break the vicious cycle of this disease. Biomarker's development and discovery of novel surgical interventions, newer efficient targeted drugs may provide better out comes for Glioblastoma patients.

Take Away Message from a Neurosurgeons view:

Malignant Glioma patients are heterogeneous genetically, even though they have similar histopathology.

Immunohistochemistry, epigenetic changes and molecular markers will soon take center stage in providing a tailor made, personalized treatment for patients with malignant glioma.

Request to Neuro- pathologist- Desired Molecular markers for

1) LGG- IDH mutation, 1p19q co-deletion.

2) HGG- MGMT methylation, EGFR vIII amplification/ over expression, PTEN deletion, LOH of Chromosome 10

Request to Oncologist, Radiologist and other allied services dealing with neuro-oncology.

Kindly consult with neurosurgeon before ordering a brain imaging.

Need of the hour

MR spectroscopy

PET scan (especially 18Fluoro- Deoxy glucose)

SPECT scan

REFERENCES

1. https://www.cancer.net/cancer-types/brain-tumor/statistics
2. Grech N, Dalli T, Mizzi S, Meilak L, Calleja N, Zrinzo A. Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population. Cureus. 2020;12(5):e8195.
3. Gülten G, Yalçın N, Baltalarlı B, Doğu G, Acar F, Doğruel Y. The importance of IDH1, ATRX and WT-1 mutations in glioblastoma. Pol J Pathol. 2020;71(2):127-137.
4. Agnihotri S, Aldape KD, Zadeh G. Isocitrate dehydrogenase status and molecular subclasses of glioma and glioblastoma. Neurosurg Focus. 2014;37(6):E13.
5. Campos B, Olsen LR, Urup T, Poulsen HS. A comprehensive profile of recurrent glioblastoma. Oncogene. 2016;35(45):5819-5825.
6. Chen H, Cebula H, Schott R, Dietemann JL, Froelich S. Glioblastoma multiforme presenting with ischemic stroke: case report and review of the literature. J Neuroradiol. 2011;38(5):304-307.
7. Osorio JA, Aghi MK. Optimizing glioblastoma resection: intraoperative mapping and beyond. CNS Oncol. 2014;3(5):359-366.

8. Eder K, Kalman B. Molecular heterogeneity of glioblastoma and its clinical relevance. Pathol Oncol Res. 2014;20(4):777-787.

9. Gautschi OP, Cadosch D, Collen TD, et al. Glioblastoma multiforme--Neue Hoffnungen dank moderner Therapieansätze [Glioblastoma multiforme--new hope due to modern therapeutical approaches]. Praxis (Bern 1994). 2010;99(5):295-308.

10. Gimple RC, Bhargava S, Dixit D, Rich JN. Glioblastoma stem cells: lessons from the tumor hierarchy in a lethal cancer. Genes Dev. 2019;33(11-12):591-609.

11. Khalatbari MR, Hamidi M, Moharamzad Y. Glioblastoma multiforme with very rapid growth and long-term survival in children: report of two cases and review of the literature. Childs Nerv Syst. 2011;27(8):1347-1352.

12. Katsila T, Matsoukas MT, Patrinos GP, Kardamakis D. Pharmacometabolomics Informs Quantitative Radiomics for Glioblastoma Diagnostic Innovation. OMICS. 2017;21(8):429-439.

13. Koshkin PA, Chistiakov DA, Chekhonin VP. Role of microRNAs in mechanisms of glioblastoma resistance to radio- and chemotherapy. Biochemistry (Mosc). 2013;78(4):325-334.

14. Michelakis ED, Sutendra G, Dromparis P, et al. Metabolic modulation of glioblastoma with dichloroacetate. Sci Transl Med. 2010;2(31):31ra34.

15. Mischel PS, Nelson SF, Cloughesy TF. Molecular analysis of glioblastoma: pathway profiling and its implications for patient therapy. Cancer Biol Ther. 2003;2(3):242-247.

16. Ng K, Kim R, Kesari S, Carter B, Chen CC. Genomic profiling of glioblastoma: convergence of fundamental biologic tenets and novel insights. J Neurooncol. 2012;107(1):1-12.

17. Noch E, Khalili K. Molecular mechanisms of necrosis in glioblastoma: the role of glutamate excitotoxicity. Cancer Biol Ther. 2009;8(19):1791-1797.

18. Castro BA, Aghi MK. Bevacizumab for glioblastoma: current indications, surgical implications, and future directions. Neurosurg Focus. 2014;37(6):E9.

19. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013;19(4):764-772.

20. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA. 2013;310(17):1842-1850.