



NEUROLOGICAL OUTCOME OF GLIOMAS;

BY MEASURING KARNOFSKY SCORE BEFORE AND AFTER SURGERY

mrshah@hec.gov.pk

1. Resident Neurosurgeon,
Department of Neurosurgery,
PIMS, SZABMU, Islamabad.
2. Resident Neurosurgeon,
Department of Neurosurgery,
PIMS, SZABMU, Islamabad.
3. Assistant Professor,
4. Professor and HOD,
Department of Neurosurgery,
PIMS, SZABMU, Islamabad.

Correspondence Address:

Muhammad Khalid
Resident Neurosurgeon,
Department of Neurosurgery,
PIMS, SZABMU, Islamabad.
mrshah@hec.gov.pk

Article received on:

07/08/2016

Accepted for publication:

30/11/2016

Received after proof reading:

00/00/2016

Muhammad Khalid¹, Umer Farooq Raina², Dr. Ejaz Ahmad³, Dr. Khaleeq UZ Zaman⁴

ABSTRACT... Background: Mostly Primary brain tumors are derived from neuroglial cells, neuronal or primitive bipotential precursors or neuroepithelial cells and they are called gliomas. These comprise of 45-65% of intracranial tumors. We aimed to conduct a study to determine the neurological outcome of patients with gliomas on the basis of karnofsky score who are managed with craniotomy and excision of tumor. **Study Design:** Descriptive case series. **Setting:** Neurosurgery Department, PIMS, Islamabad. Patients reporting to OPD accident and emergency department and those admitted to neurosurgery unit or referred from other units were enrolled. **Period:** July 2014 to April 2015 in duration of ten months. **Methods:** 140 gliomas patients which were diagnosed on CT/MRI with contrast. Patients with low grade glioma, those with post radiation necrosis diagnosed on MRI and MR spectroscopy brain, children having glioma and those gliomas patients having co-morbidities were excluded from this study. The outcome of this study was determined as neurological outcome of patients with glioma according to karnofsky score after craniotomy plus excision of tumor. **Results:** The patients' average ages were 37.4 + 11.2 years. Male gender was in dominance with 83 (59.2%) cases compared to 57 (40.7%) females. Of the total 140 patients of gliomas, 24 (17.1%) had neurological deficit. The mean Karnofsky score was 70.0 + 10.0 before surgery and after surgery it improved to 90.0 + 10.0 and this difference in mean karnofsky score between before and after surgery was found statistically significant (p-value = 0.001). The mean Glasgow coma scale was 12.0 + 2.0 before surgery and 14.0 + 1.0 post operatively. Post operatively it was observed that, of the 24 patients with neurological deficit, 18 (75.0%) improved completely whereas 6 (25.0%) patients could not improve. **Conclusion.** There is a significant improvement in neurological outcome which is measure through the karnofsky score of gliomas patients whose undergoing craniotomy and excision of tumor.

Key words: Neurological outcome, Resection of Gliomas, Karnofsky score

Article Citation: Khalid M, Raina UF, Ahmad E, Zaman K. Neurological outcome of gliomas; by measuring karnofsky score before and after surgery. Professional Med J 2016;23(12):1513-1521. DOI: 10.17957/TPMJ/16.3662

INTRODUCTION:

Mostly Primary brain tumors are derived from neuroglial cells, neuronal or primitive bipotential precursors or neuroepithelial cells and they are called gliomas.¹ Gliomas are the most common intracranial tumors comprising of 45-65% of all brain tumors. Gliomas are named according to the glial cells from which it originates.² There are three main types of gliomas: astrocytomas, Oligodendrogliomas and ependymomas. According to their grades of malignancy Gliomas are classified, such as low and high grade gliomas. Gliomas can be classified anatomically according to whether they are above or below the tentorium as supratentorial, Infratentorial gliomas.³ Gliomas

considered as 30% to 40 % of all the intracranial tumors and 80% of all malignant brain tumors.⁴

The symptoms of gliomas depend on the location of the brain or spine which is affected. Glioma patients can present with raise intracranial pressure symptoms such as headaches, nausea, vomiting, seizures, and also affect the cranial nerve disorders. Gliomas can spread via the cerebrospinal fluid and cause drop metastases to the spinal cord.⁵

Despite recent advances in glioma treatment, patients' outcome remains poor. 15 months is the median overall survival of glioblastoma multiforme

which is the most aggressive type of glioma.⁶

Gliomas are diverse in pathology, location and prognosis. Gliomas are broadly divided in two groups, low grade and high grade gliomas. Low grade gliomas (LGGs) account for 15% of primary adult brain tumors diagnosed, in adults they mainly occur in supratentorial areas, particularly in the insular and supplementary motor areas.⁷

LGGs comprise astrocytomas, oligodendroglioma and Oligoastrocytomas. Factors such as age less than 40, KPS greater than 70 and GCS 15/15 are associated with better prognosis for LGGs. Extent of a surgical resection probably correlates with a better survival for LGGs, but resection must be tempered by their location close to the eloquent area. Postoperative radiotherapy is often used for LGGs.⁸

High grade gliomas (Malignant gliomas, GBM) may arise in progression from low grade glioma (secondary GBM) or as de novo lesions (primary GBM). There are distinct genetic differences between two groups of tumors.⁹

Factors such as younger age group, lower histological grade and high KPS score are associated with good prognosis for malignant gliomas. The aggressive resection of gliomas has an influence on outcome. Both radiotherapy and chemotherapy significantly increase survival time of these patients.¹⁰

Brainstem gliomas are divided in five types, 1) tectal gliomas 2) Cerebral peduncle gliomas 3) pontine glioma 4) glioma of medulla oblongata 5) cervicomedullary junction glioma.¹¹

In medical oncology, current active status of the patients is an attempt to quantify cancer patient's quality of life, needed primary treatments such as surgery and other palliative treatments such as radiotherapy or chemotherapy.¹² There are different scoring systems. The most common one which is used are the Karnofsky score and the Zubrod score. For children the Lansky score is used.¹³

The Karnofsky score runs from 100 to 0, where 100 is perfect health and 0 is death. This scoring system is named after Dr. David A. Karnofsky.¹⁴ Although practitioners occasionally assign performance scores in between standard intervals of 10. There is no substantiated rationale for this and prognostication is not improved.

By using the Karnofsky score we can determine the neurological outcome and treatment options in glioma patients and can compare our study with international studies thus generating local statistics for our department.

MATERIAL AND METHODS

A current study was done to determine the functional outcome of patients in terms of Karnofsky score after surgery in patients presenting with gliomas to the Neurosurgical department at Pakistan Institute of Medical Sciences, SZABMU and Islamabad.

A total of 140 patients having glioma diagnosed on CT/MRI brain with contrast were included in the study. Patients with low grade glioma, post radiation necrosis diagnosed on MRI and MR spectroscopy brain, children having glioma and those patients with glioma who also had co-morbidities like diabetes mellitus, cardiac disease, renal disease etc were excluded from the study.

Common presenting symptoms include progressive headache, double vision, nausea, vomiting, seizures, and weakness.¹⁵ The LGGs patients usually presenting with seizures because tumor directly infiltrate the parenchyma. Clinical presentations depend on the tumor location. Unsteady gait, difficulty in swallowing, dysarthria, drowsiness, may be seen due to brain stem gliomas.¹⁶ Cerebellar pilocytic astrocytoma presenting with headache, vomiting and gait ataxia. Optic glioma common presentation is visual loss.¹⁷

Physical examination is according to the history. Symptoms and signs of gliomas depend on location or part of brain or spinal cord

which is affected. Common clinical finding for supratentorial gliomas are Epilepsy, hemiparesis if on motor strip. Aphasia if gliomas involving the Broca’s or Wernicke’s area, papilledema may be seen.

Clinical presentation of Infratentorial gliomas are cranial nerve deficits, ataxia, long tract signs, headache, vomiting and Papilledema. Cerebellar astrocytoma patients had cerebellar signs positive. Optic nerve glioma usually present with visual loss.¹⁸

Spinal cord gliomas usually present with pain, weakness, in the extremities. Gliomas can cause spinal sign and symptoms as arise from spinal cord as primary tumor or as a drop mets.¹⁹

MRI brain with contrast is the diagnostic test of choice. MRI will help us to see the location of the tumor, surrounding structure, approaches and more accurate radiological diagnosis as compare to CT scan brain. MRI brain will help us to counsel the patient and patient relatives about the surgery, outcome and complications.²⁰

With the help of MRI, we can localized the tumors site, size, numbers, characteristics, important surrounding structure, with help of these radiological finding we can make a best strategy and preplanning for surgery.²¹

The best management for gliomas patients is to individual patient takes into account the tumor location, their symptoms and signs and potential advantages versus risks of the different treatment options (modalities). Treatment for a glioma is customized to the individual patient and may include surgery, radiation therapy, chemotherapy, observation.²²

Follow-up neuroimaging with MRI or CT scan (unless contraindicated) is recommended after 72 hours of surgery and every 2-3 months to see response to therapy and progression of disease. This should be considered standard care for these patients.

RESULTS

In this study a total of 140 cases with gliomas were enrolled. The average age of patients was 37.4 + 11.2 years ranging from 19-54 years. There were 7 (5.0%) cases having age of up to 20 years while majority of the patients 133 (70.0%) were between 21 and 50 years. There were 28 (20.0%) patients of 51 or above age. (Table-I)

	Number of patients	%age
Age categories (years)		
Up to 20	7	5.0%
21 to 30	28	20.0%
31 to 40	42	30.0%
41 to 50	35	25.0%
51 or above	28	20.0%
Mean + SD	37.4 + 11.2	
Range (min – max)	19-54	

Table-I. Age of study patients (n=140)

In this study male gender was in dominance with 83 (59.2%) cases compared to 57 (40.7%) females.

The mean Glasgow coma scale was found to be 12.0 + 2.0 before surgery whereas post operatively. It improved to 14.0 + 1.0 and this difference in mean GCS was found statistically significant (p-value = <0.001). Similarly, the mean Karnofsky score was 70.0 + 10.0 before surgery and after surgery it improved to 90.0 + 10.0 and this difference in mean karnofsky score was also found statistically significant (p-value = 0.001). (Table-II)

	Before surgery	After surgery	p-value
GCS			
Mean + SD	12.0 + 2.0	14.0 + 1.0	<0.001
Karnofsky score			
Mean + SD	70.0 + 10.0	90.0 + 10.0	<0.001

Table-II. Comparison of GCS and Karnofsky score in patients before and after surgery (n=140)

Further analysis was done according the stratification of GCS and Karnofsky scores in the

study. It was observed that before surgery, 87 (62.1%) patients had GCS level of 15/15 which remained constant in these patients after surgery. Moreover, 23 (16.4%) cases had GCS level of 12 – 14 before surgery, whereas after surgery it improved to 15/15 in 21 cases whereas in 2 (1.4%) cases it remains constant.

In 30 cases, the GCS was found to be 11-12 before surgery which improved to 15/15 in 26 cases whereas it remained constant at this level in 4 (2.8%) cases. It was found out that out of total 140 cases, 40 (28.5%) patients had karnofsky score of 90-100 before surgery and it remained 90-100 postoperative. In another 40 (28.5%) cases karnofsky score was between 80-90 before surgery, out of which 5/40 (12.5%) cases improved to 100 post-operatively and other remained constant at pre-operative score. Similarly, 60 (42.8%) patients had karnofsky score of 70 -80 before surgery which improved 100 in 25/60 (41.6%) cases and to 80-90 in 5/60 (8.3%) cases where the other half 30 (50.0%) remained constant at the pre-operative karnofsky score of 70 - 80. (Table-III)

	Before surgery	After surgery
GCS/15		
15	87 (61.1%)	97 (69.2%)
12-14	23 (16.4%)	2 (1.4%)
11-12	30 (21.4%)	4 (2.8%)
Karnofsky score/100		
90-100	40 (28.5%)	70 (50.0%)
80-90	60 (42.8%)	30 (21.4%)
70-80	40 (28.5%)	40 (28.5%)

Table-III. Stratification of GCS and Karnofsky scores in the study (n=140)

The post-operative karnofsky score findings of the current study were compared with other studies on this topic. In this study 70 patients had karnofsky score of 90-100, 30 patients had 80-90 whereas 40 patients had score of 70-80. Comparatively, in the study by Malstrom et al, 342 patients had postoperative karnofsky score of 60-100. Similarly, Uzuka et al reported that 79

patients in their study had post-operative score of 60. Wick et al witnessed 584 patients having karnofsky score of 60. Minniti et al reported that 32 study patients had karnofsky score of 80. (Table-IV)

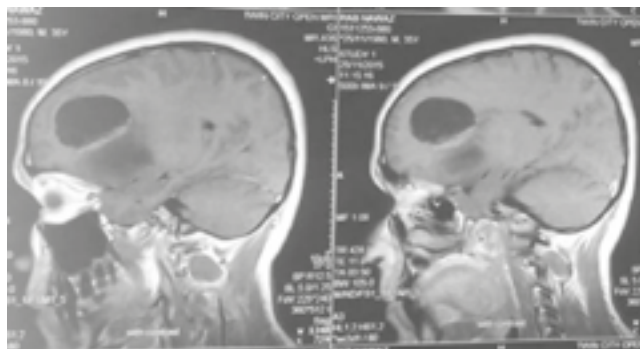
	Number of patients	Karnofsky score
Current study		
	70	90-100
	30	80-90
	40	70-80
Malmstrom et al		
	342	60-100
Uzuka et al		
	79	60
Wick et al		
	584	60
Minniti et al		
	32	80

Table-IV. Comparison of karnofsky score after surgery with other studies

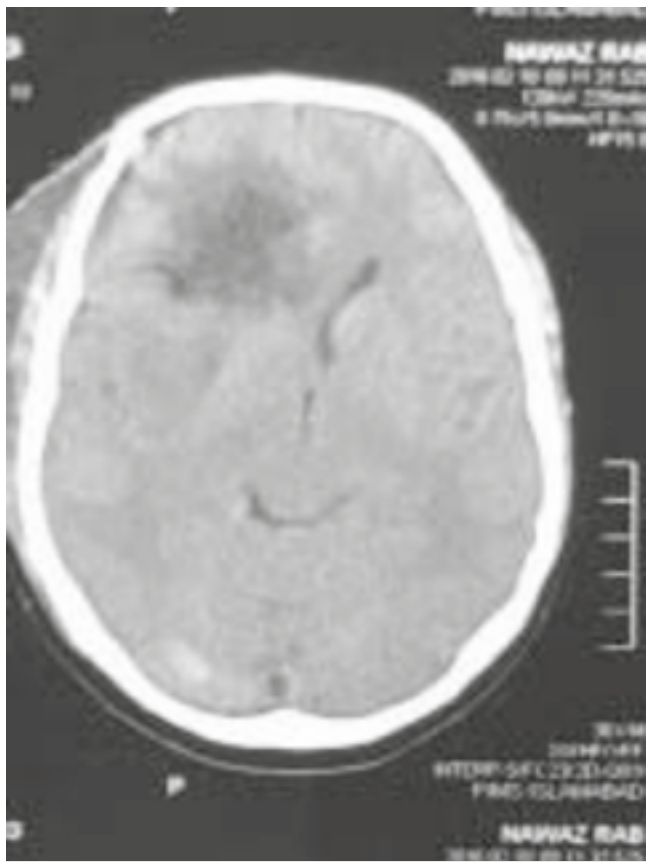
Post operatively it was observed that, of the 24 patients with neurological deficit, 18 (75.0%) improved completely whereas 6 (25.0%) patients could not improve. (Table-V)

	No of patients (n= 24/140)	%age
Improved	18	75.0%
Not improved	6	25.0%

Table-V. Neurological outcome of patients post operatively (n=24)



Pre Op MRI Brain with Contrast



Post op CT Scan Brain with contrast
Figure-1. Images after Surgical resection of glioma

DISCUSSION

Gliomas account for 80% of primary malignant brain tumors. Is glioblastoma multiforme is a common type of malignant glioma which has a very poor prognosis. and due to this severity the epidemiology on gliomas should be focused not only on identifying the factors associated with gliomas but also on different therapies like radiotherapies and inherited mutations of highly penetrant genes associated with rare syndromes.²³

Surgical treatment with craniotomy is the first line therapy for gliomas, however, functional recovery after surgery varies.²⁴ As the gliomas from low grade are any how known to progress to malignant gliomas with passage of time, thus, a better understanding of the natural history of gliomas can lead to an early detection and treatment.²⁵ However, the decision for resection in a patient with low grade glioma depends on

a number of factors including age, performance status, location of tumor and patients preference.²⁶

In a Retrospective study, surgical outcome of glioblastoma including elderly and less than 70 KPS patients, and analyzed the prognostic factors using the medical records of 107 patients, male: female ratio 59:48 aged from 21 to 85 years. 71 out of 107 patients have high-risk patients with age >70 years and KPS <70%. Based on the extent of resection, the patients were classified into 3 groups: more than subtotal resection (subtotal, n = 44), partial resection (partial, n = 29), and biopsy only (biopsy, n = 34). Median overall survival of all 107 patients was. 13.5 months. Median OSs was 15.8, 12.8, and 12.1 months in the subtotal, partial, and biopsy groups, respectively.^{27,28}

The median postoperative KPS score tended to be better than the preoperative score, even in the high-risk group. We recommend maximal safe resection for glioblastoma patients, even those with advanced age and/or with low KPS score. In outcome of gliomas patients two factors, Age and KPS score before surgery is a good predictor. A retrospective study was done in which the average age of patients was noted to be 37.4 + 11.2 years. A study by Tanaka T and colleagues on wax pile method for glioma surgery utilizing intra operative magnetic resonance imaging noted average age of 50.9 years.²⁹ Another study by Yu H and colleagues on hemiparesis after operation of astrocytoma grade II in adults: effects of acupuncture on sensory motor behavior and quality of life reported the average age of 44.0 years ranging from 20 to 65 years in their study.³⁰ These ages are comparable to our results as they have also been conducted on adult population with gliomas.

In this study male gender was in dominance with (59.2%) proportion. In the study by Tanaka T et al the male gender also found to be predominant with 56.2% proportion. However, Yu H et al reported a contrastable finding on gender with females presenting in majority in their study with 66.6% proportion.³¹ So the gender has a less effect on outcome as compare to KPS.

Our study findings are also continuous with national level data from US where they found out 3.9 males per 100000 populations suffering from glioblastoma compared to 2.4 females per 100000 population.³² The overall demographic characteristics are not much different in terms of gender in patients less than 20 years of age.

The overall rate of neurological deficit was 17.1% in this study. Yu H et al reported that 65.6% of the patients with neurological deficit had right sided hemiparesis.²² Tanaka T et al also found out right sided hemiparesis in majority of cases where they witnessed 56.2% proportion.³³

In the current study the mean Glasgow coma scale was found to be 12.0 + 2.0 before surgery whereas post operatively it improved to 14.0 + 1.0.

Similarly, the mean Karnofsky score was 70.0 + 10.0 before surgery and after surgery it improved to 90.0 + 10.0. It was observed that before surgery, 87 (62.1%) patients had GCS level of 15/15 which remained constant in these patients after surgery. Moreover, 23 (16.4%) cases had GCS level of 12 – 14 before surgery, whereas after surgery it improved to 15/15 in 21 cases whereas in 2 (1.4%) cases it remains constant. In 30 cases, the GCS was found to be 11-12 before surgery which improved to 15/15 in 26 cases whereas it remained constant at this level in 4 (2.8%) cases.³⁴

It was found out that out of total 140 cases, 40 (28.5%) patients had karnofsky score of 100 before surgery and it remained 100 postoperative.^{35,36} In another 40 (28.5%) cases karnofsky score was between 80-90 before surgery, out of which 5/40 (12.5%) cases improved to 100 post-operatively and other remained constant at pre-operative score. Similarly, 60 (42.8%) patients had karnofsky score of 70 -80 before surgery which improved 100 in 25/60 (41.6%) cases and to 80-90 in 5/60 (8.3%) cases where the other half 30 (50.0%) remained constant at the pre-operative karnofsky score of 70 - 80.

In the present study 70 patients had karnofsky

score of 90-100, 30 had 80-90 whereas 40 patients had karnofsky score of 70-80. When compared with other international studies similar findings of post-operative karnofsky score were found. In a systematic review outcome of karnofsky score was found comparable with the current study findings³⁷ (Hindawi review ref). Malstrom et al, revealed that 342 patients were found to have postoperative karnofsky score between 60-100. Uzuka et al reported that 79 patients in their study had post-operative karnofsky score of 60. Wick et al witnessed 584 patients having karnofsky score of 60. Minniti et al reported that 32 study patients had karnofsky score of 80.

In the current study it was observed that, 24 patients with neurological deficit, 18 (75.0%) improved completely after surgery whereas 6 (25.0%) patients could not improve.^{38,39}

Along with GCS and other predictive scores of patient outcome, karnofsky score is equally successful. The patients with karnofsky scores less than 60 at presentation have a less chance of getting successful neurological outcome.⁴⁰

The current study has many advantages firstly, it is one of the very few studies in which neurological outcome of patients with gliomas has been assessed with karnofsky score. A reasonable number of cases i.e.140 has been studied.

There were some limitations of the study as well which are mainly related to the scope of the study. A detailed data collection could not be done due to time restraints. Moreover, data regarding long term outcome of patients with gliomas could not be collected in the current study as the overall outcome of patients was out of the study scope.

Cognitive functioning of brain tumor patients is an increasingly important outcome measure, because cognitive impairments can have a large impact on self-care, social and professional functioning. Many factors contribute to the cognitive and neurological outcome such as direct and indirect tumor effects, seizures, medication and oncological treatment modalities.^{41,42} It can

be suggested that further research should be focused on these factors with detailed information regarding outcome of these patients.

CONCLUSION

Based on the results of current study it can be concluded that there is a significant improvement in the karnofsky score of patients with gliomas undergoing craniotomy and excision of glioma. The neurological outcome after surgery was found improved in three forth of these patients.

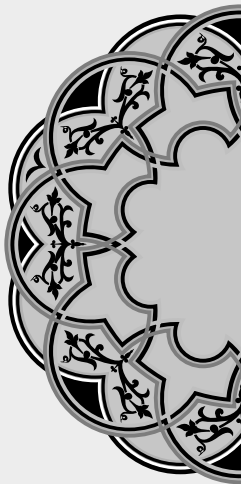
Before generalization of the findings of current study, more, trials on this topic on a larger scale with rigorous methodology would be mandatory.

Copyright© 30 Nov, 2016.

REFERENCES

- Karnofsky D, Abelman W, Craver L, Burchenal J. **The use of nitrogen mustards in the palliative treatment of carcinoma.** *Cancer.* 1948; 1: 634-656.
- Karnofsky DA, Burchenal JH. **The clinical evaluation of chemotherapeutic agents in cancer.** In: MacLeod CM. *Evaluation of chemotherapeutic agents.* Columbia Univ Press. 1949; pp 196.
- Hart MG, Grant R, Metcalfe SE. Hart, Michael G, ed. **Biopsy versus resection for high grade glioma.** *Cochrane Database Syst Rev* 2000; (2): CD002034.
- Glantz MJ, Cole BF, Forsyth PA. **Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors.** Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000, 54: 1886-1893.
- Stewart L, Burdett S; Glioma Meta-analysis Trialists Group (GMT). **Stewart, Lesley, (eds). Chemotherapy for high-grade glioma.** *Cochrane Database Syst Rev* 2002; (3): CD003913.
- <http://www.ncbi.nlm.nih.gov/pubmed/23099483>.
- Tutt AN, van Oostrom CT, Ross GM, van Steeg H, Ashworth A. **Disruption of Brca2 increases the spontaneous mutation rate in vivo: synergism with ionizing radiation.** *EMBO Rep.* 2002; 3 (3): 255–60.
- Mandonnet E, Delattre JY, Tanguy ML, Swanson KR, Carpentier AF, Duffau H et al. **Continuous growth of mean tumor diameter in a subset of grade II gliomas.** *Ann Neurol* 2003; 53:524-28.
- Kanner AA, Staugaitis SM, Castilla EA, et al: **The impact of genotype on outcome in oligodendroglioma—validation of the loss of chromosome 1p as factor of importance in clinical decision making.** *J Natl Cancer Inst.* 2003, submitted.
- Stupp R, Mason WP, van den Bent MJ. **Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.** *New Engl J Med* 2005; 352:987-96
- Ohgaki H, Kleihues P. **Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas.** *J NeuropatholExp Neurol.* 2005; 64 (6): 479–89.
- Donaldson SS, Laningham F, Fisher PG. **Advances toward and understanding of brain stem gliomas.** *J ClinOncol* 2006; 24; 1266-72.
- Griffin CA, Burger P, Morsberger L, et al.: **Identification of der (1;19)(q10;p10) in five oligodendrogliomas suggests mechanism of concurrent 1p and 19q loss.** *J NeuropatholExpNeurol* 2006; 65:988–994.
- Hegan DC, Narayanan L, Jirik FR, Edelmann W, Liskay RM, Glazer PM. **Differing patterns of genetic instability in mice deficient in the mismatch repair genes Pms2, Mlh1, Msh2, Msh3 and Msh6.** *Carcinogenesis* 2006; 27 (12): 2402–8.
- Mamelak AN, Jacoby DB. **Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601).** *Expert Opin Drug Deliv* 2007; 4 (2): 175.
- Schiff D, Brown PD, Giannini C: **Outcome in adult low-grade glioma: the impact of prognostic factors and treatment.** *Neurology* 2007, 69:1366–1373.
- O'Hagan HM, Mohammad HP, Baylin SB. **Double strand breaks can initiate gene silencing and SIRT1-dependent onset of DNA methylation in an exogenous promoter CpG island.** *PLoS Genet*2008; 4(8) e1000155.
- Cuozzo C, Porcellini A, Angrisano T, Morano A, Lee B, Di Pardo A. **DNA damage, homology-directed repair, and DNA methylation.** *PLoS Genet* 2007; 3 (7): e110.
- Altekruse S, Kosary C, Krapcho M, Neyman N, Aminou R, Waldron W, et al. (eds). **SEER Cancer Statistics Review, 1975-2007, National Cancer Institute.** Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site, 2010.
- Porter K, McCarthy B, Freels S, Kim Y. **Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology.**


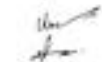

- Neuro-Oncology 2010; 12:520-527.
21. IARC classifies radiofrequency electromagnetic fields as possibly carcinogenic to humans. (Press release). IARC. 31 May 2011.
 22. Goodenberger ML, Jenkins RB. **Genetics of adult glioma.** *Cancer Genet* 2012; (doi:10.1016/j.ancergen.2012.10.009).
 23. Smoll N, Gautschi OP, Schatlo B, Schaller K, Weber DC. **Relative Survival of Patients with Supratentorial Low Grade Gliomas.** *Neuro-Oncology*. 2012.
 24. Goodenberger ML, Jenkins RB. **“Genetics of adult glioma.** *Cancer Genet* 2012; 205: 613–21.
 25. Cohen AL, Holmen SL, Colman H. **IDH1 and IDH2 mutations in gliomas.** *CurrNeurolNeurosci Rep* 2013; 13 (5): 345.
 26. Wang P, Dong Q, Zhang C, Kuan PF, Liu Y, Jeck WR et al. **Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hyper methylation targets with glioblastomas.** *Oncogene* 2013; 32(25): 3091–100.
 27. Mojarad EN, Kuppen PJ, Aghdaei HA, Zali MR. **“The CpG island methylator phenotype (CIMP) in colorectal cancer”.** *GastroenterolHepatol Bed Bench* 2013; 6 (3): 120–128.
 28. Benson, Victoria; Kristin Pirie; Joachim Schüz; Gillian K Reeves; Valerie Beral; Jane Green. **Mobile phone use and risk of brain neoplasms and other cancers: prospective study.** *Int J Epidemiol* 2013; 42 (3): 792–802.
 29. Tanaka T, Ishii T, Kato N, Arai T, Akasaki Y, Yamamoto Y et al. **Wax pile method for glioma surgery utilizing intraoperative magnetic resonance imaging: a technical note.** *Neuroscience Discovery* 2013; (doi:10.7243/2052-6946-1-6).
 30. Yu H, Schroder S, Liu Y, Li Z, Yang Y, Chen Y et al. **Hemiparesis after operation of astrocytoma grade II in adults: effects of acupuncture on sensory-motor behaviour and quality of life. Evidence based complementary and alternative medicine.** 2013; Volume 2013; Article ID 859763 (doi.org/10.1155/2013/859763).
 31. Bernstein C, Prasad AR, Nfonsam V, Bernstein H. **DNA Damage, DNA Repair and Cancer, New Research Directions in DNA Repair, Prof. Clark Chen** (Ed.), 2013; ISBN 978-953-51-1114-6, InTech, <http://www.intechopen.com/books/new-research-directions-in-dna-repair/dna-damage-dna-repair-and-cancer>.
 32. Efirid, Jimmy T.; Davies, Stephen W.; O’Neal, Wesley T.; Anderson, Ethan J. (2014). **“Animal viruses, bacteria, and cancer: a brief commentary”.** *Frontiers in Public Health* 2014; 2: 14.
 33. Ostrom, Quinn T.; Bauchet, Luc; Davis, Faith G.; Deltour, Isabelle; Fisher, James L.; Langer, Chelsea Eastman et al. **The epidemiology of glioma in adults: a “state of the science” review.** *Neuro-Oncology* 2014; 16 (7): 896–913.
 34. Adel Fahmideh M, Schwartzbaum J, Frumentio P, Feychting M. **Association between DNA repair gene polymorphisms and risk of glioma: A systematic review and meta-analysis.** *Neuro-oncology* 2014; 16 (6): 807–14.
 35. CDC - Women’s Safety and Health Issues at Work: Job Area: Agriculture - NIOSH Workplace Safety and Health Topic. www.cdc.gov. Retrieved 2015-06-20.
 36. **PRETEST pediatrics pg 224.**
 37. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science (New York, N.Y.)* 2014; 343(6167): 189–193. 2014. doi:10.1126/science.1239947. Retrieved 17 June 2015.
 38. **Recurrent Brain Cancers Follow Distinctive Genetic Paths.** University of California Santa Cruz. University of California San Francisco. Retrieved 17 June 2015.
 39. Article online at URL: <http://www.neurology.org/cgi/content/abstract/54/7/1442> (Accessed 15-08-2015).
 40. Article online at URL: <http://www.dipgregistry.org/patients-families/basic-facts/> (Accessed 15-08-2015).
 41. Uzuka T, Aoki H, Natsumeda M, Takahashi H, Fujii Y. **Effectiveness of maximal safe resection for glioblastoma including elderly and low Karnofsky performance status patients: retrospective review at a single institute.** *Neurol Med Chir (Tokyo)*.2012; 52(8):570-6.
 42. Farina P, Lombardi G, Bergo E, Roma A, Zagonel V. **Treatment of Malignant Gliomas in Elderly Patients: A Concise Overview of the Literature.** *BioMed Research International* 2014; 2014: Article ID 734281, 9 pages. doi:10.1155/2014/734281.



*“It’s difficult to follow your dream.
It’s a tragedy not to.”*

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Muhammad Khalid	Main Script writer + Data collection + Main Surgeon	
2	Umer Farooq Raina	Help in data analysis and write up	
3	Dr. Ejaz Ahmad	help in write up, surgeon	
4	Dr. Khaleeq UZ Zaman	help in writing, surgeon	