REVIEW ARTICLE

Analysis of Isocitrate dehydrogenase (IDH) mutation in Gliomas: A call for neurosurgeons and pathologists in Pakistan

Muntaha Masood[1], Rana Fayyaz Anwar[2], Khalid Mehmood[3], Maham Javed[4], Tuaha Amjad[5], Nadia Naseem[6]

Abstract

Tumours of the central nervous system, though not very common, pose a serious health burden owing to their high mortality rate. Glial tumours are the commonest type of brain tumours in Pakistani population. Diagnosis of gliomas has been greatly revolutionised over the past few years with integration of immunohistochemistry and molecular subtyping in the World Health Organisation's updated 2016 classification of glial tumours. One of the major changes was incorporation of isocitrate dehydrogenase mutation detection that is considerably a significant prognostic and predictive marker. The published data on isocitrate dehydrogenase mutation in the local population is hard to find. The current narrative review was planned to briefly describe the international trends regarding frequency of isocitrate dehydrogenase mutation in gliomas, its predictive and prognostic significance and its impact on accurate diagnosis leading to a targeted therapeutic approach for patients.

Keywords: Gliomas, Isocitrate dehydrogenase 1, Mutation, Classification, Prognosis, Treatment.

DOI: https://doi.org/10.47391/JPMA.2342

Introduction

Tumours of the central nervous system (CNS), though relatively less frequent, pose a serious health burden. CNS tumours are the 18th most common neoplasms worldwide having a mortality rate of 2.5% ranking 13th among malignancies with high mortality rate.[1] Among them, gliomas are the most common primary intracranial tumours, representing almost 80% of malignant brain tumours causing significant mortality and morbidity.[2] According to the local cancer statistics, brain tumours represent the 6th most common malignancy among the top 10 reported malignancies in the country. Brain tumours form 3.5% of all malignant tumours in all age groups and both genders combined, and, among them, malignant glial tumours constitute the major bulk.[3] By differentiation, gliomas are of either astrocytic, which is the most common, or oligodendroglial origin or are of mixed type.[4] Despite its more common prevalence in Pakistani population compared to the Western world, there is very limited data available regarding frequency and spectrum of glial tumours in the local population. Astrocytic tumours are reported to be the commonest, followed by oligodendroglial tumours and glioblastoma in the Pakistani population. Glioblastoma tend to occur more frequently in older age group and in males, with an average male-to-female ratio of 2:1.[5,6]

[1,4-6]Department of Morbid Anatomy and Histopathology, University of Health Sciences, Lahore, Pakistan; [2]Department of Histopathology, Postgraduate Medical Institute / Ameerudin Medical College / Lahore General Hospital, Lahore, Pakistan; [3]Department of Neurosurgery, Postgraduate Medical Institute / Ameerudin Medical College / Lahore General Hospital, Lahore, Pakistan.
Correspondence: Muntaha Masood. e-mail: muntahamasoodkhaliq@gmail.com

Clinical and radiological presentation of gliomas

Clinical presentation of gliomas varies according to topographic location and grade of tumours. Seizures and headache are most frequent presenting symptoms in majority cases; seizures being more common among younger age group. Cognitive disorders, on the other hand, are common presenting symptoms, especially in the elderly age group. Other symptoms are visual field defects, gait imbalance, aphasia and sensory deficits.[2,7]

Treatment choices and prognosis of gliomas are affected by the anatomic and topographic location of these tumours besides different subtypes. The frontal lobe is the most common location, followed by temporal, parietal and occipital lobes. Right or left side predominance poses no significant variance.[8]

In the present era, magnetic resonance imaging (MRI) (T1-weighted, T2-weighted and gadolinium-enhanced sequences) has become the mainstay of clinical tumour imaging and has largely replaced contrast enhanced computed tomography (CT), as it provides high-resolution multiplane structural information. Most brain lesions present as space-occupying lesions. Non-enhancing lesions mostly represent as non-neoplastic, benign or low-grade lesions. Contrast enhancement, peri-tumoural oedema, ill-defined borders, mass effect, necrosis and haemorrhage favour high-grade lesion.[9,10] Radiological findings combined with isocitrate dehydrogenase-1 (IDH1) mutation status can predict the prognosis of glial tumours. IDH-mutant tumours usually have better prognosis.

However, prognosis of these IDH-mutant tumours worsens with multifocal contrast enhancement and peri-tumoural oedema at radiology.[11]

Pathogenesis

Pathogenesis of gliomas is a multistep process and has various contributing risk factors. History of exposure to ionizing radiations, familial risk factors and other conditions associated with brain tumours can also contribute to the risk. Also, there is reported evidence of inverse relationship of gliomas with allergic conditions and atopy with glioma patients having low serum immunoglobulin-E (IgE) levels.[2,12] Various acquired genetic alterations (ATRXm, TERTm, EGFRamp, TP53m, IDH1/2m, 1p19q-codel) have been found to be associated with different histological subtypes and grades of gliomas and also carry grave prognostic significance. Hereditary predisposition, such as in tumour syndromes (e.g. patients with neurofibromatosis type I, Turcot syndrome, Li-Fraumeni syndrome, tuberous sclerosis, Lynch syndrome), though rare, are important contributing factors in the pathogenesis of gliomas. Apart from tumour syndromes, evidence of familial clustering of gliomas is also present, with first-degree relatives at higher risk of tumour development.[13]

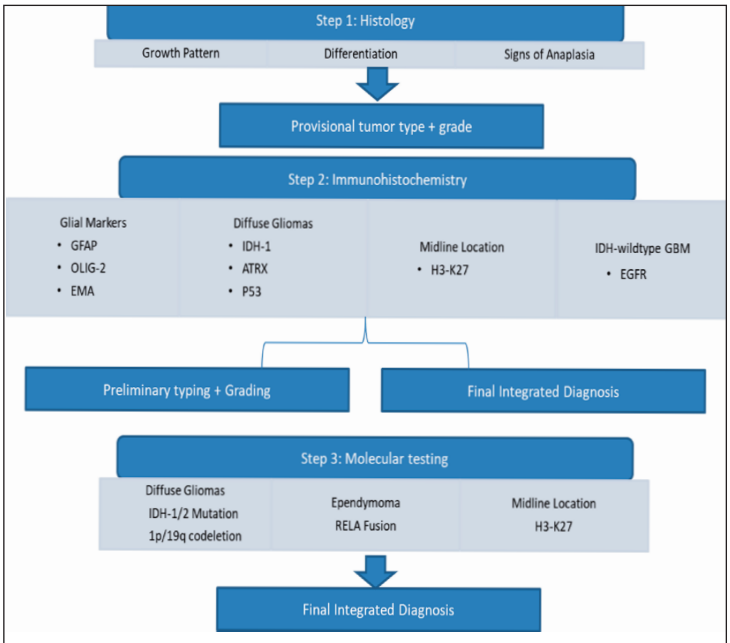


Figure-1: Pathway for integrated glioma diagnosis according to World Health Organisation (WHO) 2016 classification. Histology followed by immunohistochemistry and eventually molecular tests are required to reach final diagnosis. Glial fibrillary acidic protein (GFAP), Epithelial membrane antigen (EMA), Codon 27 lysine-to-methionine mutation in H3 histones (H3-K27), Epidermal growth factor receptor (EGFR), V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A (RELA).

Major changes in World Health Organisation (WHO) 2016 classification of gliomas

In the modern era, the diagnostic algorithm of gliomas follows the updated World Health Organisation (WHO) 2016 classification and incorporates histological typing and grading of tumours using the four-tiered WHO grades I–IV along with the ancillary immunohistochemistry (IHC) studies and molecular characterisation. This facilitates the clinicians in predicting the biological behaviour, prognosis and outcome of the tumours. Most importantly, it has indicated the major diagnostic role of IDH1 or IDH2 in the diagnosis of gliomas, subtyping these tumours into 3 major categories according to IDH mutation: IDH mutant, IDH wild type (WT) and not otherwise specified (NOS) category, a diagnosis that is reserved for those tumours where IDH status is not known or cannot be performed. Glioblastoma multiforme (GBM) is divided into primary GBM that most frequently arises de novo and is IDH WT, and secondary GBM that most frequently has a precursor lesion and is IDH mutant.[14,15]

Thus, the updated classification is a major step forward, leading to a more accurate diagnosis of gliomas that has undoubtedly aided targeted therapeutic management of the patients.[16] The customary norm of using neuropathological diagnoses primarily based on the microscopic features has now become redundant by the molecularly-oriented diagnoses.[17] A three-tiered integrated diagnostic algorithm for integrated diagnosis of gliomas is a standard practice worldwide (Figure 1).

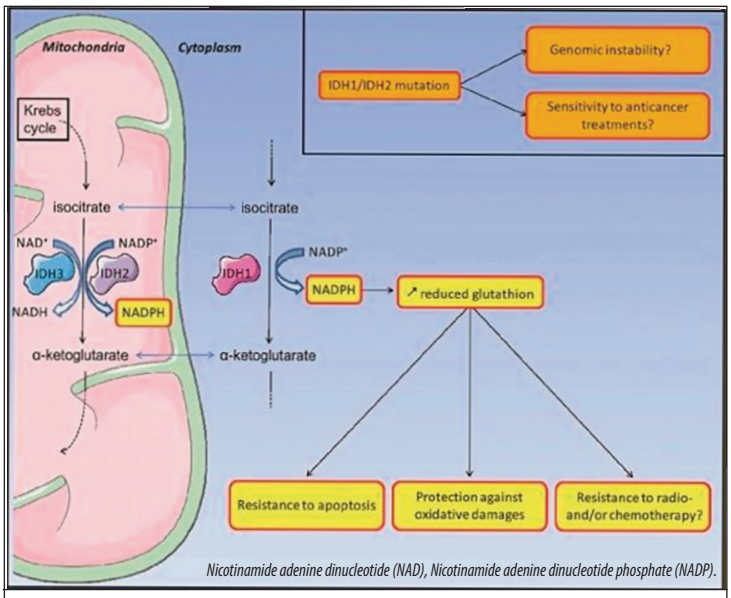


Figure-2: Role of Isocitrate Dehydrogenase (IDH) in genomic instability.[21]

IDH mutation and gliomas

IDH mutation is an initial step in the development of gliomas.[18] Its role in brain tumours was first reported in 2008 when mutations in IDH1 and IDH2 were identified in a vast majority of gliomas and secondary glioblastomas. The major significance of IDH1 is recognised in the pathway of lipid synthesis and the cellular glucose sensing. IDH also contributes to the control of both the mitochondrial oxidation and reduction reactions.[19,20] IDHs catalyse the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG) with the production of NADH/NADPH. Therefore, they are crucial enzymes in the Krebs cycle (Figure 2).[21]

Of all the reported mutations in gliomas, 90% affect the IDH1 gene which has further different types of mutations. Location of IDH1 gene on chromosome 2q33.3 makes its molecular mapping precise. More than 90% of cases constitute the p.R132H substitution, followed by p.R132C and p.R132G as particular point mutations.[22]

Methods

The narrative review comprised search for articles on

Table-1: Comparison of different studies conducted in over 10 years.

Author	Place of Study	Year of Publication	Duration of Study	Study Design	Sample Size	Age	Predominant Gender	Conclusion
Gravendeel et al.[28]	Netherland	2010	1989-2009	Cohort Study	496	____	_____	IDH mutation status aid in glioma sub-classification. Better survival rates found in mutated tumours.
Jha et al.[24]	India	2011	____	Cross sectional descriptive	100	10-67yrs.	_____	Highest frequency of IDH mutation found in DA and OG tumours and Younger age at presentation and better survival.
Mukasa et al.[25]	Tokyo(Japan)	2012	_____	Cross sectional descriptive descriptive.	250	12-80 yrs.	Male	IDH mutation has more prognostic significance for GIII gliomas as compared to LGG and has better PFS and OS rates as compared to IDH wildtype tumours.
Zhang et al.[27]	China	2014	2006-12	_____	203 (anaplastic gliomas)	Median age=42yr	Male	IDH1 mutation was found in 53% of anaplastic glioma patients and is a marker of good prognosis.
Pessoa et al.[26]	Northern Brazil	2015	_____	Cross sectional descriptive	34	1-74 yrs.	Male	IDH1 mutation is found both in low and high grade gliomas and is an early step in tumourigenesis.
Nadia Senhaj et al.[23]	Morocco	2016	2010-14	Retrospective study	117	3-90 yr	Male	Concordant results with prior studies and strong association of IDH mutation with glioma grade.
Rabia Javed et al.[6]	Pakistan (SKMCH-RC)	2020	2015-17	Cross sectional descriptive	214	18-80 years. Mean age= 39±21.3 years	Male	Glioblastomas are the most glial tumour type in our population and oligodendrogliomas are least common.

PFS: Progression-free survival, OS: Overall survival, DA: Diffuse astrocytoma, OG: Oligodendroglial, LGG: Low-grade glioma.

Table-2: Frequency of isocitrate dehydrogenase (IDH) mutation in different glial tumours.

Author	**DA** n(%)	**AA** n(%)	**1oGBM** n(%)	**2oGBM** n(%)	**O** n(%)	**AO** n(%)	**OA** n(%)	**AOA** n(%)
Gravendeel et al.,2010[28]	54/73 (74)	19/32 (59.3)	34/175 (19.4)		34/43 (79)	64/106 (60)	79% (22/28)	19/39 (49)
Jha et al.,2011[24]	15/18 (83.3)	7/8 (87.5)	6/47 (12.8)	4/6 (66.7)	3/7 (42.9)	8/9 (88.9)	4/7 (57)	3/4 (75)
Mukasa et al.,2012[25]	18/29 (59)	8/29 (28)	6/109 (6)	6/13 (46)	19/25 (76)	10/15 (67)	4/7 (57)	4/5 (80)
Zhang et al.,2014[27]	_____	(42)	_____	_____	_____	(75)	_____	(49)
Pessoa et al.,2015[26]	1/3 (33.3)	2/3 (66)	_____	_____	1/2 (50)	_____	_____	2/3 (66)
Nadia Senhaji et al.,2016[23]	5/8 (62)	4/6 (66.7)	8/62 (12.9)	_____	3/7 (43)	18/23 (78.3)	1/3 (33.3)	1/3 (33.3)
Rabia Javed et al.,2020[6]	28/34 (82.4)	6/34 (17.6)	14/81 (17.3)	_____	2/32 (6.3)	_____	_____	_____

DA: Diffuse astrocytoma, AA: Anaplastic astrocytoma, 1oGBM: Primary glioblastoma multiforme, 2oGBM: Secondary glioblastoma multiforme, O: Oligodendroglioma, AO: Anaplastic oligodendroglioma, OA: Oligoastrocytoma, AOA: Anaplastic oligoastrocytoma.

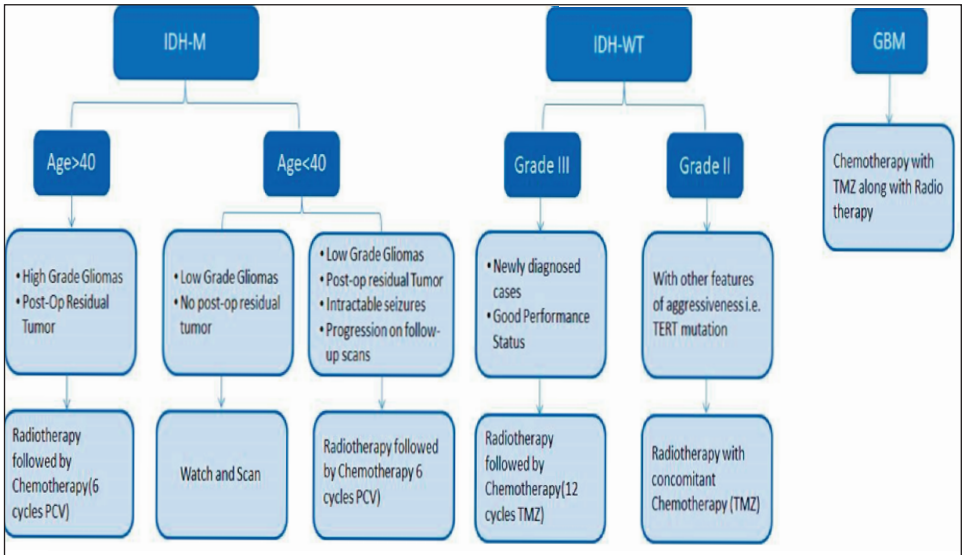
PubMed, MEDLINE, EMBASE, Cochrane Library databases as well as on the websites of Pakistani medical research journals, including the Journal of Pakistan Medical Association (JPMA), the Journal of the College of Physicians and Surgeons Pakistan (JCPSP), the Pakistan Journal of Medical Sciences (PJMS), the Pakistan Journal of Pathology, the Pakistan Armed Forces Medical Journal (PAFMJ) etc., published between January 2000 and August 2020. Key words used included 'Gliomas', 'Isocitrate Dehydrogenase 1', 'Mutation', 'Classification', 'Frequency', 'Prognosis' as well as variations thereof.

Inclusion and exclusion criteria: Surgical excisions of glial tumour conducted between the targeted period were considered. Irrespective of gender and age of the patients, glial tumours of all subtypes and grades, classified according to updated WHO classification,[14,15] were included. Population-based studies and studies referring only to clinical features were excluded. Incompletely classified tumours were also excluded.

Data Extraction: Different information was extracted from the shortlisted studies, such as first author's name, year of publication, geographical region in which the study was carried out, duration of study, sample size, gender and age of the studied sample, the prevalence rate of different glioma subtypes, study design and final conclusions made by the authors regarding diagnostic and prognostic significance of IDH mutation.

The prevalence and prognostic impact of IDH mutations in gliomas

IDH mutations are established to be considerably related with the histological grades of gliomas, with IDH1 mutation being more common than IDH2. These are more commonly found to be associated with grade II and III gliomas and secondary glioblastomas.[23] Various international studies have shown comparable results with the highest frequency of IDH1 mutation found in grade II and III astrocytomas and oligodendrogliomas followed by mixed oligoastrocytomas and secondary glioblastomas.[23-28] (Tables 1-2) Moreover, there is significantly strong evidence regarding prognostic impact of IDH mutation analysis in gliomas. A retrospective study on glioblastoma patients showed improved survival and a younger age at presentation in IDH mutant glioblastomas.[29] Similar results were shown by a meta-analysis[30] but these two studies focussed on glioblastomas only, lacking evidence for survival benefits in low-grade gliomas. On the other hand, a cross-sectional descriptive study conducted on Chinese population focussing only on anaplastic gliomas also favoured improved survival in IDH mutated tumours on follow-up.[27] However, a study on gliomas of all grades presenting in Indian population not only reported comparable frequencies of IDH mutation in diffuse gliomas when compared with reported literature from the West, but also critically reviewed the published evidence, concluding that IDH mutation was an independent prognostic marker with younger age at presentation and better clinical outcomes.[24] Therefore, in the light of strong convincing evidences provided by these studies, there are many ongoing trials that are focussed on devising a targeted therapeutic approach, like selective IDH inhibitors IDH-targeted vaccines, that may lead to better clinical outcomes above and beyond those offered by conventional strategies.[18] A study reported the frequency and characteristics of IDH mutations on 250 glioma cases of all subtypes and grades from Japanese population. There was inconsistent evidence regarding patients' survival in the data. An improved prognosis for grade III IDH mutant gliomas was observed compared to grade II, emphasising the role of molecular markers other than IDH1 mutation in prognostic determination for these tumours.[24] One retrospective study on 117 glioma cases[22] and another[25] on 34 glioma cases provided comparable frequencies of IDH mutation in different subtypes and grades of glioma, but no follow-up data or prognostic prediction was determined in these studies.[22,25] Unfortunately, despite a greater prevalence of these tumours in Pakistani population[5] data regarding spectrum of IDH mutation in gliomas is rare to find, and IDH mutation analysis is still not incorporated in routine glioma diagnosis as per the updated WHO criteria[14,15] even in leading neurosurgical centres and laboratories of Pakistan. This has led to an



Isocitrate dehydrogenase Mutant (IDH-M), Isocitrate dehydrogenase Wildtype (IDH-WT), Procarbazine, lomustine (CCNU) and Vincristine (PCV), Temozolomide (TMZ).

Figure-3: Management strategies for gliomas with the incorporation of molecular markers.

under- or over-diagnosis of these tumours with subsequent misdiagnosis and a potential halt in planning a targeted therapeutic approach for these patients by both surgeons and oncologists. Up till now, there is only a single published cross-sectional descriptive study from Pakistan and that too just recently, showing a mean age at presentation of 39±21.3 years (range: 18-80 years). Out of the total, 68.2% were GBM cases, followed by 82.7% IDH WT and 7.3% were IDH mutant. IDH mutation was most commonly found in grade II and III astrocytic tumours.[6] None of the study from Pakistan, however, has dealth with the prognosis or survival aspects of the patients in relation to IDH mutation analysis.

As such, there is convincing enough evidence concerning IDH mutant gliomas having a younger age at presentation compared to IDH WT tumours[31] and better progression-free survival (PFS) and overall survival (OS) rates compared to IDH WT tumours of same histological grades.[25] Moreover, primary glioblastomas are diagnosed at later ages in the form of full-blown tumours without any clinical, radiological and histological evidence of any low-grade precursor lesion and are of IDH WT, having a very dismal prognosis.[32]

On the basis of these findings, IDH1 mutation status testing is fairly pertinent and vital for diagnostic and prognostic respects. In fact, it has been combined in the standard diagnostic evaluation of diffuse gliomas worldwide. Furthermore, IDH1 testing is a potential stratification factor in the clinical trials for glioma patients and IDH1 inhibitors (AGI-5198) are being developed now and results may yield promising innovative therapeutic approaches.[33] Apart from diagnostic accuracy and prognosis stratification, this molecular sub-categorisation of gliomas has great impact on clinical management of patients and has helped in clinical decision-making for benefits of chemotherapy combined with radiation therapy[34] (Figure 3).

Assessment of IDH mutation status can be performed by methods on both IHC or deoxyribonucleic acid (DNA), with the former being more preferable as it is cost-effective, easy to perform and reliable. The results of both methods show highly concordant results.[35] In resource-constrained settings, like Pakistan, oncological research with incorporation of molecular techniques has progressed in a limited capacity over the past few years, particularly in terms of breast cancer and viral genotyping for female genital tract cancers and hepatic cancers. Availability of routine IHC diagnostic kits was the first step in classifying these tumours for prognostic impact that has led to successful addition of molecular classification of these tumours in the local population. A similar approach is needed for the diagnosis of gliomas. The standard treatment of gliomas is based on the maximum debulking surgery before radiotherapy (RT) or chemotherapy that may improve the response to post-operative adjuvant treatments where this trend has remained the same over the past many decades. Therefore, determining the IDH mutation along with other recommended molecular tests is a critical step to improve diagnostic and therapeutic outcomes for these patients. Presently, in Pakistan, treatment options for these patients are not based on surveillance data or recommended international guidelines. Therefore, studies addressing molecular subtyping and survival rates of patients with gliomas in the country are yet to be defined from the scratch. Further, lack of follow-up and failure of interdisciplinary approach have turned down the reference data available in Pakistan. Without any further delay, a comprehensive insight into the molecular diagnosis of gliomas is needed in order to improve the morbidity and mortality of these tumours.

Conclusion

Analysis of evidence abridges the frequency of IDH1 mutation in gliomas of different histological grades and

subtypes and emphasises its predictive significance in determining prognosis. Studies from all over the world report IDH1 mutation as a significant, independent factor for predicting longer OS and PFS in patients with gliomas. This information, though scarce in Pakistani data, opens new avenues for research on gliomas in the local population, emphasising the need for the incorporation of affordable and reliable techniques for IDH testing in routine glioma diagnosis by pathologists in countries even with resource-constrained laboratory settings. Comprehensive diagnosis of gliomas in line with international acceptable standards will not only help neurosurgeons and neuro-oncologists in treatment planning and prognostication of patients, but will also help improving OS of these patients in Pakistan.

Abbreviations

α-ketoglutarate (α-KG), D-2-hydroxyglutarate (D-2HG), Immunohistochemistry (IHC), World Health Organization (WHO), Alpha Thalassemia/Mental Retardation Syndrome X-Linked protein/gene mutation (ATRXm), Telomerase reverse transcriptase mutation (TERTm), Epidermal growth factor receptor amplification (EGFRamp), Tumor Protein (p53) mutation (TP53m), Complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) (1p/19q co-deletion), Nicotinamide adenine dinucleotide hydrogen (NADH), Nicotinamide adenine dinucleotide phosphate (NADPH).

Disclaimer: None.

Conflict of interest: None.

Source of Funding: None.

References

1. Observatory GC. Population fact sheet 2020. [Internet]. [cited 2020 NOV 20]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf.
2. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA. 2013;310:1842-50.
3. SKMCH-RC Statistics. Annual-Cancer-Registry-Report-2019. 2019 [cited 2020 SEP18]. Available from: https://shaukatkhanum.org.pk/wp-content/uploads/2020/08/Annual-Cancer-Registry-Report-2019.pdf.
4. Cohen AL, Holmen SL, Colman H. IDH1 and IDH2 mutations in gliomas. Curr Neurol Neurosci Rep. 2013;13:345.
5. Hashmi AA, Faridi N, Malik B, Edhi MM, Khurshid A, Khan M. Morphologic spectrum of glial tumors: an increased trend towards oligodendroglial tumors in Pakistan. Int Arch Med. 2014;7:33.
6. Javed R, Akhtar N, Hassan U, Azam M, Loya A, Hussain M, et al. IDH-1, ATRX AND 1P19Q CO-DELETION IN DIFFUSE GLIOMAS. Pak Armed Forces Med J. 2020;70:571-77.
7. Posti J, Bori M, Kauko T, Sankinen M, Nordberg J, Rahi M, et al. Presenting symptoms of glioma in adults. Acta Neurol Scand. 2015;131:88-93.
8. Oslobanu A, St I F. Anatomic locations in high grade glioma. Rom Neurosurg. 2015;29:271-7.
9. Upadhyay N, Waldman A. Conventional MRI evaluation of gliomas. The Brit J Radiol. 2011;84:S107-S11.
10. Weller M, Van Den Bent M, Tonn JC, Stupp R, Preusser M, Cohen-Jonathan-Moyal E, et al. Eur Assoc Neurooncol (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. The Lancet Oncol. 2017;18:e315-e29.
11. Wang K, Wang Y, Fan X, Wang J, Li G, Ma J, et al. Radiological features combined with IDH1 status for predicting the survival outcome of glioblastoma patients. Neuro-Oncol. 2015;18:589-97.
12. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a "state of the science" review. Neuro-Oncol. 2014;16:896-913.
13. Goodenberger ML, Jenkins RB. Genetics of adult glioma. Cancer Genet. 2012;205:613-21.
14. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-20.
15. Aldape K, Nejad R, Louis DN, Zadeh G. Integrating molecular markers into the World Health Organization classification of CNS tumors: a survey of the neuro-oncology community. Neuro-Oncol. 2016;19:336-44.
16. Wesseling P, Capper D. WHO 2016 classification of gliomas. NeuropatholAppl Neurobiol. 2018;44:139-50.
17. Komori T. The 2016 WHO classification of tumours of the central nervous system: the major points of revision. Neurol Med-Chir. 2017;57:301-11.
18. Chen R, Smith-Cohn M, Cohen AL, Colman H. Glioma subclassifications and their clinical significance. Neurother. 2017;14:284-97.
19. Mellai M, Caldera V, Annovazzi L, Schiffer D. The distribution and significance of IDH mutations in gliomas. Evolution of the Molecular Biology of Brain Tumors and the Therapeutic Implications: IntechOpen; 2013. p. 300-06.
20. Waitkus MS, Diplas BH, Yan H. Isocitrate dehydrogenase mutations in gliomas. Neuro Oncol. 2015;18:16-26.
21. Labussiere M, Sanson M, Idbaih A, Delattre JY. IDH1 gene mutations: a new paradigm in glioma prognosis and therapy? Oncol. 2010; 15:196-9.
22. Agnihotri S, Aldape KD, Zadeh G. Isocitrate dehydrogenase status and molecular subclasses of glioma and glioblastoma. Neurosurg focus. 2014; 37:E13.
23. Senhaji N, Louati S, Chbani L, Bardai SE, Mikou K, Maaroufi M, et al. Prevalence of IDH1/2 mutations in different subtypes of glioma in the north-east population of Morocco. Asian Pac J Cancer Prev. 2016; 17:2649-53.
24. Jha P, Suri V, Sharma V, Singh G, Sharma MC, Pathak P, et al. IDH1 mutations in gliomas: first series from a tertiary care centre in India with comprehensive review of literature. Exp Mol Pathol. 2011; 91:385-93.
25. Mukasa A, Takayanagi S, Saito K, Shibahara J, Tabei Y, Furuya K, et al. Significance of IDH mutations varies with tumor histology, grade, and genetics in Japanese glioma patients. Cancer Sci. 2012; 103:587-92.
26. Pessôa I, Sagica F, Anselmo N, Brito J, de Oliveira E. IDH1 and IDH2 mutations in different histologic subtypes and WHO grading gliomas in a sample from Northern Brazil. Genet Mol Res. 2015; 14:6533-42.
27. Zhang CB, Bao ZS, Wang HJ, Yan W, Liu YW, Li MY, et al. Correlation of IDH1/2 mutation with clinicopathologic factors and prognosis in anaplastic gliomas: a report of 203 patients from China. J Cancer Res Clin Oncol. 2014; 140:45-51.
28. Gravendeel LA, Kloosterhof NK, Bralten LB, van Marion R, Dubbink HJ, Dinjens W, et al. Segregation of non-p. R132H mutations in IDH1

in distinct molecular subtypes of glioma. Hum Mutat. 2010; 31:E1186-E99.
29. Bleeker FE, Atai NA, Lamba S, Jonker A, Rijkeboer D, Bosch KS, et al. The prognostic IDH1 R132 mutation is associated with reduced NADP+-dependent IDH activity in glioblastoma. Acta Neuropathol. 2010; 119:487-94.
30. Chen JR, Yao Y, Xu HZ, Qin ZY. Isocitrate dehydrogenase (IDH) 1/2 mutations as prognostic markers in patients with glioblastomas. Medicine. 2016; 95:e2583.
31. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. New Eng J Med. 2009; 360:765-73.
32. Dang L, Jin S, Su SM. IDH mutations in glioma and acute myeloid leukemia. Trends Mol Med. 2010; 16:387-97.
33. Rohle D, Muller PJ, Palaskas N, Turcan S, Grommes C, Campos C, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. Science. 2013; 340:626-30.
34. Molinari E, Curran OE, Grant R. Clinical importance of molecular markers of adult diffuse glioma. Prac Neurol. 2019; 19:412-6.
35. Zou Y, Bai HX, Wang Z, Yang L. Comparison of immunohistochemistry and DNA sequencing for the detection of IDH1 mutations in gliomas. Neuro Oncol. 2015; 17:477-8.