International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.13, No.03, pp 132-141, 2020

Prevalence of Glioblastoma-Not Otherwise Specified (NOS) Based on the Clinical and Histopathology Findings in Main Tertiary Referral Hospital in Bandung, Indonesia

Hendrikus Masang Ban Bolly[1,2,3]*, Ahmad Faried[1,4], Danny Halim[1], Yulius Hermanto[4], Firman Priguna Tjahjono[1], Muhammad Zafrullah Arifin[1]

[1]Department of Neurosurgery, Faculty of Medicine, Universitas Padjadjaran – Dr. Hasan Sadikin Hospital, (FK UNPAD – RSHS), Bandung, West Java, Indonesia;
[2]Doctoral Program in Medicine, Faculty of Medicine, Universitas Padjadjaran, bandung, West Java, Indonesia
[3]Faculty of Medicine, Cenderawasih University, Jayapura, Papua, Indonesia;
[4]Oncology and Stem Cell Working Group, FK UNPAD – RSHS, Bandung, Indonesia

Abstract : Introduction: Glioblastoma is the deadliest malignant brain tumors in adults. The main challenges in treating glioblastoma are its resistance to the chemo-radiotherapy, poor outcome and low survival rate. The World Health Organization (WHO) 2016 classification identifies two types of glioblastoma by its mutational status of isocitrate dehydrogenase (IDH); since our national insurance experiences budget-limitation, we could not freely apply it in our institutions. We aims to find the prevalence and outcome of glioblastoma-not otherwise specified (NOS) based on its clinical manifestations and histopathology findings. **Methods:** We performed retrograde-analysis based on clinical and histology findings on 48 glioblastoma-NOS patients from 2012-2017. We analyzed its characteristic, primary complains, lesions location, macroscopic findings, therapy and the final outcomes. **Results:** Glioblastoma-NOS is the most common type of gliomas occurs in adults ages 49.29±12.13 years (range 17-72 years). The tumor predominantly involves the frontal lobe (25%) with chronic progressive headache as the chief complaint (90%); 93.8% of the patients underwent tumor removal and received chemo-radiotherapy after surgery based on the histopathology findings. The median survival is 18 months and the prevalence of glioblastoma-NOS in our tertiary referral hospital is 4.72%. **Conclusion:** Hopefully, our study will improve the understanding of the regional differences in glioblastoma-NOS prevalence and pave the way for identifying the regional risk factors that would allow us to improve the protocols on glioblastoma detection, prevention and management. Further studies, incorporating molecular techniques into a patient's tumor analysis for IDH1 mutant or wild type are required for the promise of personalized medicine.

Keywords : Glioblastoma-NOS; Clinical Manifestations; Histopathology Findings.

DOI= http://dx.doi.org/10.20902/IJPTR.2019.130301

Introduction

Glioblastoma as one of the most lethal glial brain tumor, has poor prognosis and low survival rate. Fifty percent of all intracranial brain tumor is glioblastoma and nearly 70 percent of primary malignant brain tumor cases relates to this type of tumor.[1,2] Other glial brain tumor are astrocytoma, oligodendroglioma, ependymoma and sub-ependymoma.[2] Since glioblastoma tipically manifest as highly aggressive and difficult to treat tumours without clinical forewarning, there has to be a method to overcome the challenge in preparing effective treatment and improve the survival rate. Genetic profile has become increasingly important because some genetic changes (e.g. isocitrate dehydrogenase-IDH mutation in diffuse gliomas) have been found to have important prognostic implications. Genetic profile for glioblastoma in respect of IDH-enzyme mutations differentiates the developmental of glioma as *de novo* (primary) or secondary resources. This mutation profile also differentiates the clinical history, median survival of each its therapy modality and epidemic profile of glioblastoma. Many genetic parameters included in the World Health Organization (WHO) 2016 classification can be assessed by immunohistochemistry, but it is acknowledged that some centre may not have the ability to carry out molecular analyses and that some results may not be conclusive.[3]

The glioblastoma-not otherwise specified (NOS), reserved for cases where complete IDH evaluation was not conducted, is defined as the high-grade glioma and denotes a diffuse glioma with predominantly astrocytic differentiation and anaplasia. It has microscopic characteristic similar with nuclear atypia and in most cases possesses the cellular pleomorphism, mitotic activity and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis that is consistent with a WHO grade IV glioblastoma, whereby the of IDH mutation status remains inconclusive or unavailable.[4] In our centre, since the medical insurance system has not kept up with the pace of technical development and the limited national insurance budget, we could not freely apply immunohistochemistry examination; this leads us try to analyse the clinical characteristic of our patients with results of histopathology examination of glioblastoma-NOS. After the analysis, a comparison of primary- or secondary-glioblastoma status based on the WHO 2016 classification is created. The study aims to find the prevalence and outcome of the patients with glioblastoma-NOS based on its clinical manifestations and histopathology findings (WHO grading criteria).

Methods

This is a descriptive study utilizing retrospective data of our centre medical records and histopathology registers for all glial tumor patients recorded between 2012 and 2017 in Dr. Hasan Sadikin Hospital (RSHS) Bandung, West Java, Indonesia. The hospital is a 900 bed, state-funded tertiary referal hospital who serves an approximately 50 million people in the vicinity. We designate the identify of all intra-cranial tumors of glioblastoma (WHO grade IV) patients and categorize the clinical profile of the site of the tumors based on the chief complaint, radiology examination, demographic data, the *therapeutic modalities* after surgery. We also trace the prognostic and survival status of the patients after hospitalization.

Results

The characteristics found in the results of population-based study were presented in Table 1; that shows the number of glial tumor and glioblastoma-NOS patients in RSHS over *a* six-year *period* from 2012-2017. We identify 1016 patients with central nervous system (CNS) tumor, consisting of both brain and spine tumor during the period; Of the 239 evaluated glial tumor cases classified as WHO grade I, II, III and 48 are identified as glioblastoma-NOS (WHO grade IV) from all gliomas. Glial tumor area distribution are shown in Table 1 and Figure 1.

Table 1. Characteristics of glial tumor and glioblastoma-NOS patients in Neuro-Oncology, Bandung centre

Characteristic	All Glial Tumor Total N = 239; N (%)	Glioblastoma-NOS Total N = 48; N (%)
Sex		
Male	128 (53.4%)	26 (54.2%)
Female	111 (46.4%)	22 (45.8%)
Age, mean; ± SD (range)	40.6±18.48 (14-40)	49.29±12.13 (17-72)
Location of the tumor		
Parietal	48 (20.8%)	5 (10.4%)
Parietal-Temporal	22 (9.21%)	8 (16.65%)
Parietal-Occipital	13 (5.44%)	8 (16.65%)
Frontal	38 (15.90%)	12 (25.0%)
Fronto-Parietal-Temporal	24 (10.04%)	6 (12.5%)
Fronto-Parietal	23 (9.6%)	9 (18.8%)
Temporal	2 (0.84%)	0
Occipital	2 (0.84%)	0
Cerebellum	3 (1.26%)	0
Brain Stem	27 (11.30%)	0
Optic Nerve	9 (3.77%)	0
Thalamus and Basal Ganglia	24 (10.64%)	0
Corpus Callosum	2 (0.84%)	0
Intra-Ventricle	2 (0.84%)	0
Survival rate, mean± SD (range)	30.3±9.11 (CI 95%:28.2-35.4)	18.21±9.3(CI 95%:16.61-22.1)

The mean age for glial tumor is 40.6 ± 18.48 years old and it ranges from 14 to 40 years. Of the 239 cases, 128 cases are males (53.4%) and 111 are females (46.4%), resulting in similar disease prevalence in both genders. The mean age for glioblastoma-NOS is 49.29 ± 12.13 years old and it ranges from 17 to 72 years (Table 1); Of the 48 cases, 26 cases are males (54.2%) and 22 are females (45.8%), resulting in similar disease prevalence in both genders ratio is 1.1:1 (54.2:45.8%) and relevant glioblastoma-NOS case shown in Figure 2. Chief complaints are headache (89.5%), lessening consciousness (6.25%) and seizure (4.25%). Most patients complain on a progressive headache before performed the imaging examination and some of the patients underwent radiographic procedure after had seizure or decreased of consciousness.

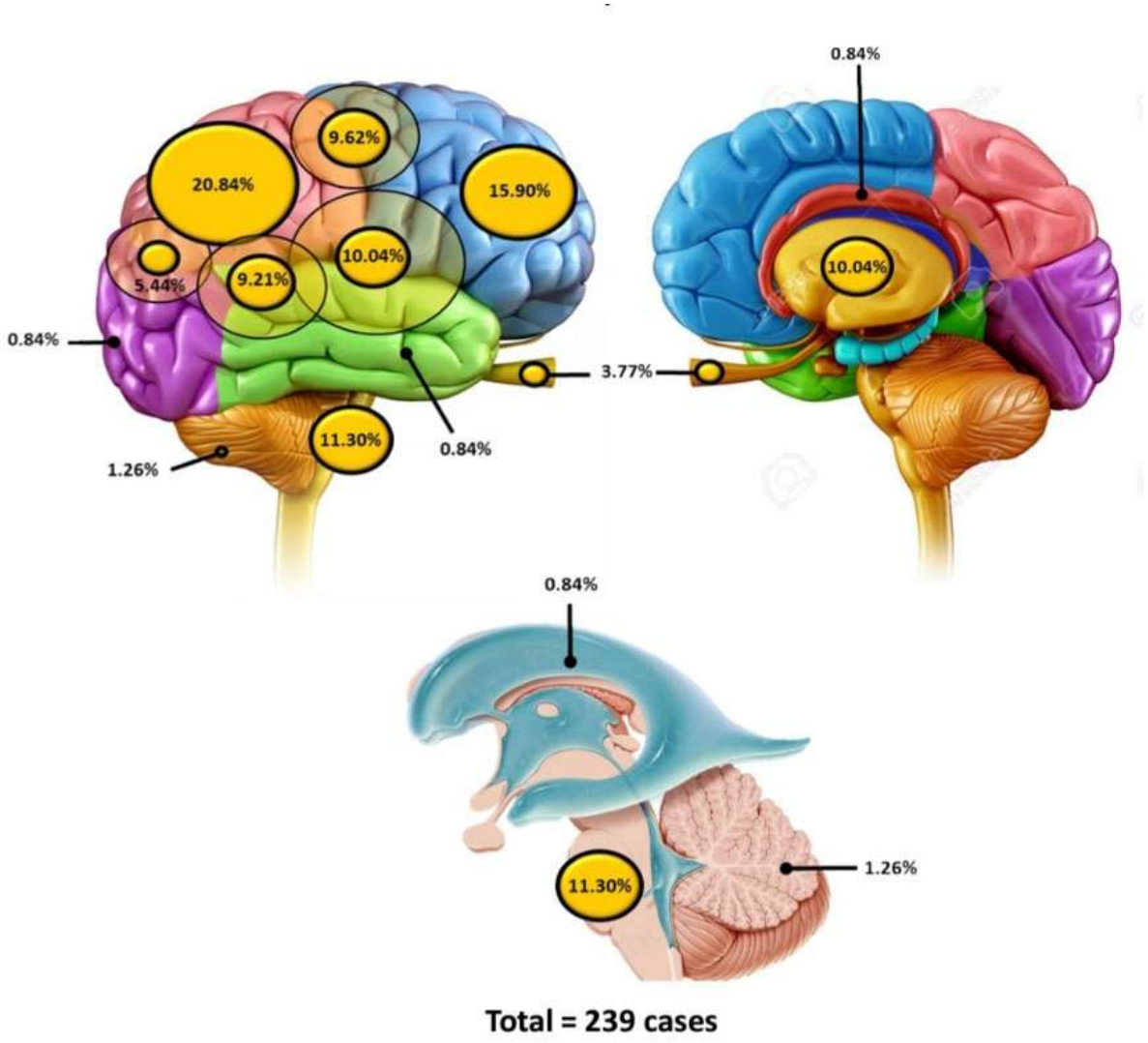

Figure 1. Glial tumors location distributions in our Neuro-Oncology, Bandung, Indonesia

Forty six patients undergo open craniotomy tumor removal and only two patients perform biopsy procedure. Brain imaging is conducted to all patients; the most common primary location involves the frontal lobe (56.3%; frontal, fronto-parietal, fronto-parieto-temporal), followed by the parietal lobe both parieto-temporal (16.65%), parieto-occipital (16.65%) and parietal lobe (10.4%). Forty six patients require post-operative ventilatory support; prolonged ventilator support is required in 8 (16.67%) patients. Pulmonary complication is noted as the dominant complications including pneumonia. The shortest mortality rate is observed in 3 months and the longest is in the period of 37 months of hospitalization following the operation and the initial chemo- and radio-therapy.

Table 2. Distributions of brain tumor cases in Dr. Hasan Sadikin Hospital (RSHS), Bandung, West Java, Indonesia

Tumor		Location	Years					
			2012 (n=177)	**2013 (n=169)**	**2014 (n=179)**	**2015 (n=177)**	**2016 (n=182)**	**2017 (n=132)**
Glioma	LGG		**9**	**9**	**8**	**8**	**7**	**4**
	HGG	Frontotemporoparietal	3	2	2	2	1	1
		Temporoparietal	3	4	3	5	3	4
		Parietal	4	9	10	12	9	6
		Frontal	6	7	6	2	1	5
		Others	6	2	5	5	8	6
		Total HGG	**22**	**24**	**26**	**26**	**22**	**22**
Meningioma		Sphenoid wing	24	10	11	9	12	13
		Convexity	31	21	22	19	20	7
		Sellar region	9	15	9	20	13	6
		Clinoidal	5	1	4	3	0	3
		Optic sheath	5	1	1	1	1	0
		Enplaque	19	4	3	0	3	6
		Petroclival	5	1	1	0	3	0
		Olfactory groove	2	4	4	1	5	2
		Petrous	3	2	2	2	2	0
		Parasagital	5	5	0	0	3	3
		Temporal base	5	4	6	4	8	4
		Sphenoorbita	2	27	23	21	26	16
		Total Meningioma	**115**	**95**	**86**	**80**	**96**	**60**
Others			31	41	59	63	57	46

Patient of glioblastoma will receive of 60 Gy and 2 Gy/fraction for 3D conformal radiotherapy in our place. The regiment for initial chemotherapy in our place consist of temozolomide 75 mg per body surface area for 42 days together with radiotherapy. The median survival rate of glial tumor is 53 months, glioblastoma-NOS is 18 months and the glioblastoma-NOS prevalence in our tertiary referal hospital is 4.72% (Table 2 and Figure 3). The comparison between WHO 2016 Classification and our study results is shown in Table 3.

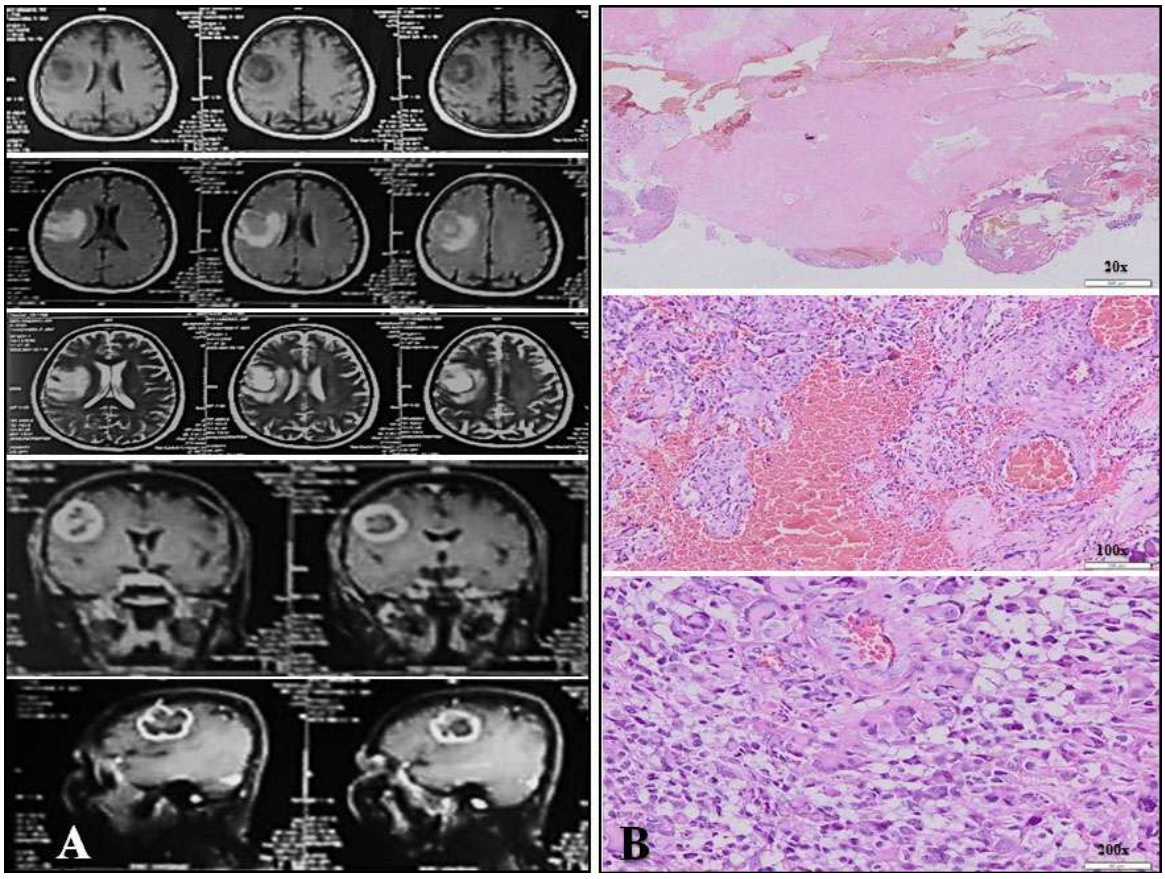

Figure 2. A). Magnetic resonance images of a patient of glioblastoma suspected (upper: T1WI axial pre contrast, T1WI axial post contrast, T2WI axial; middle: T1WI coronal post contrast; lower: T1WI sagital section post contrast. B). Photo-micrograph showing the histopathological characteristic of glioblastoma-NOS for area of necrosis (upper, HE, magnification 20x); Large hemorrhage and atypic cells (middle, 100x); Microvascular proliferation, giant cell with bizarre nuclear of giant cells, diffuse pattern and cellular pleomorphism (lower, 200x).

Discussion

Clinical criterion population-based study in Switzerland and histopathological evidence, mention that only 5% of all glioblastoma is secondary-glioblastoma. When IDH1 mutant is used as a molecular marker for secondary-glioblastoma, the rate reaches 9% of all glioblastoma by population and reaches 6-13% of hospital-based cases.[3] This type of glioblastoma can originate from diffuse astrocytoma malignancy (WHO grade II) and anaplastic astrocytoma (WHO grade III), also known as secondary-glioblastoma.[3] Based on WHO 2016 classification at the population level, secondary-glioblastoma develops at a median age of diagnosis of 44 years, whereas primary-glioblastoma has a median age of 62 years (Table 2). In our study, the median age of glioblastoma-NOS is 49 years, but Central Brain Tumor Registry of the United States (CBTRUS) 2000-2006 has shown much younger median age of diagnosis for glioma malignant-NOS at 38 years.[5] The findings of 4.72% of our glioblastoma cases in our national tertiary referral hospital is lower than in Malaysia which is 7.5%[6] and in Philippines, which is 7.8%.[7]

The ratio of men to women in IDH mutant is 0.96:1 while in primary-glioblastoma (IDH wild type, WT) is 1.63:1.[3] The average clinical history diagnosed as secondary-glioblastoma is 16.8 months, 2.67 times longer than primary-glioblastoma (6.3 months). Male to female ratio of primary-glioblastoma is 1.42:1, whereas of secondary-glioblastoma is 1.05:1. In comparison our result for glioblatoma-NOS is 1.1:1. In this case, the mean length of clinical history of glioblastoma with IDH1 mutation is 15.2 months, compared to glioblastoma with IDH-WT 3.9 months.[3] Glioblastoma can be subdivided into 3 distinct subtypes based on molecular expression; (1) epidermal growth factor receptors, (2) neuro-fibromatosis related protein 1 and (3) platelet-

derived growth factor receptor-α or IDH1 mutation each defined as a classic, mesenchymal and proneural subtype, respectively.[8]

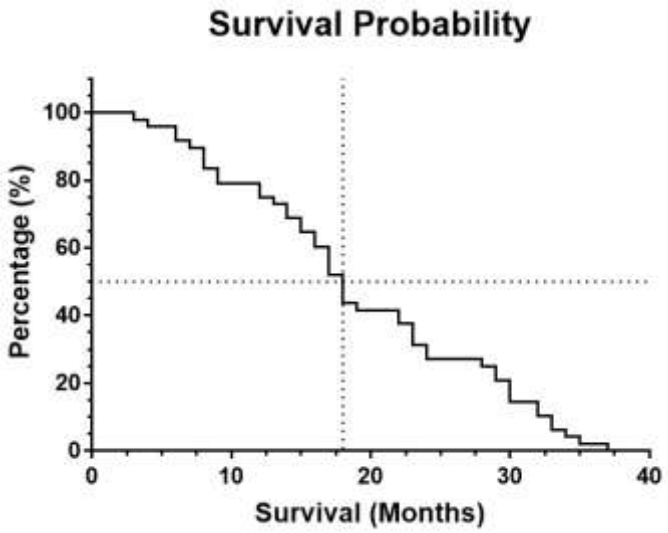

Figure 3. The median survival of glioblastoma-NOS in our tertiary referal hospital, Dr. Hasan Sadikin Hospital, is 18 months.

Glioblastoma molecular subclassification can be prognostic value with proneural type showing better prognosis which may, again be due to the fact that the IDH mutations occur with high frequency in proneural type. These distinctions are important because they may account for the differences seen in prognosis in tumors that are histologically similar. Proneural is commonly found in the frontal lobe, while classic and mesenchymal subtypes are commonly found in the temporal lobe.[4,9,10] Glioblastoma IDH mutant has a predominant location in the frontal lobe, specifically the area around the lateral ventricular rostral extension.[11] Clinical symptoms of glioblastoma IDH1 mutations are related to dominant location preferences in the frontal lobe, resulting in symptoms such as behavioral changes and dominant neurocognitive; although some symptoms of focal neurological deficits such as hemiparesis and aphasia can also be found. In contrast to glioblastoma IDH-wild type, because of the slow evolution of diffuse astrocytoma or anaplastic astrocytoma, tumor-related edema is not too extensive and shows a slower symptom development than patients with glioblastoma-wild type.[11]

Table 3. World Health Organization (WHO) Classification 2016 vs our study results in RSHS

	IDH-wildtype glioblastoma	**IDH-mutant glioblastoma**	**Glioblastoma-NOS RSHS**
Synonym	Primary glioblastoma	Secondary glioblastoma	unknown
Precursor lesions	Not identifiable, develops de novo	Diffuse astrocytoma, anaplastic astrocytoma	unknown
Proportions of glioblastoma	~90%	~10%	~20%
Median age at diagnosis	~62 years	~44 years	~49 years
Male to female ratio	1.42:1	1.05:1	1.1:1
Mean length of clinical history	3.9 months	15.2 months	unknown
Median overall survival rate	15 months	31 months	19.31±9.3 months
Tumor location	Supratentorial	Preferentially frontal	Dominantly frontal
Necrosis	Extensive	Limited	Minimal

Analysis of surgical and radiotherapy treatment for patients indicates that the mean survival rate of patients with glioblastoma IDH positive mutant is 27.1 months; 2.4 times longer than glioblastoma IDH-wild type patients (11.3 months).[3] This result is in line with WHO studies showing that glioblastoma IDH mutant patients treated with radiotherapy and or chemotherapy have a median survival rate of 31 months; 2 times longer than glioblastoma IDH-wild type.[3] Without any therapy, life expectancy of glioblastoma patients is 4 months, whereas aggressive therapies such as surgery, chemotherapy and radiotherapy, will increase the median survival rate up to 15 months.[12] Our patients receive temozolamide for six months and radiotherapy (about 5000 cGy) after the surgery. The result of the combination indicates higher survival rate rather than using single treatment.[13,14] However, we do not have IDH state examination, but our patients have survival rate for about 18.31±9.3 months after combining the therapies. Our result shows longer survival rate than IDH1 wild type but shorter than IDH1 mutant profile. This may occur due to several factors, (1) our centre applies only one chemotherapy agent for six months (temozolamide) with irregular follow-up. Our national insurance does not cover other types of chemotherapy, such as Bevacicumab (as anti-angiogenic agents/anti-VEGF monoclonal antibody), Erlotinib and Gefitinib (antibodies targeting EGFR), or tyrosine kinase inhibitor. We also lack effective supportive treatments for patient, consisting of the management of cerebral edema, seizures, certain conditions related to the functional disturbances of gastrointestinal tract, osteoporosis, cognitive impairment and mood disorders[14]; (2) short duration of radiotherapy procedure since aside from glioblastoma patients, significant number of patients covered by the national insurance also need to obtain that treatment; (3) loss of follow-up on the side effect of chemo-radiotherapy due to patients' low socioeconomic status; and (4) unproven drug resistance problem.

Surgical treatment will not overcome glioblastoma that has highly invasive nature. The molecular and cellular characteristics of glioblastoma made it more resistant to radiotherapy and chemotherapy.[12] This study indeed has limitations, including the retrospective nature of the study and the regionalism of the data used. To the best of the author's knowledge, this study is the first study conducted by Indonesian researchers to analyse prevalence of glioblastoma-NOS based on the clinical and histopathology findings.

Conclusions

In our case, incorporating molecular techniques into a patient's tumor analysis for IDH1 mutant or wild type is required for the promise of personalized medicine. Hopefully, our study will improve the understanding of regional differences in glioblastoma-NOS prevalence and pave the road for identification of the regional risk factors that should lead us to improved protocols on glioblastoma detection, prevention and management. Continued study on applying IDH1 by immunochemistry staining examination will be helpful to provide better information about glioblastoma in our centre as well as to treat glial tumor cases in the future.

Funding

The Grants-in-Aid the Ministry of Research, Technology and Higher Education of the Republic of Indonesia 13/E/KPT/2018 and 06/E/KPT/2019 INSINAS (Faried A).

Conflict of Interest

All the authors declares that he has no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Faculty of Medicine, Universitas Padjadjaran research committee with the Approval No. 249/UN6.KEP/EC/2019; with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

References

1. Gokturk D, Hasim K, Sda C, Dervis MY. The Effect of Ascorbic Acid Over the Etoposide- and Temozolemide-Mediated Cytotoxicity in Glioblastoma Cell Culture: A Molecular Study. *Turk Neurosurg*. 2018:28(1);13-18.
2. Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. *Neuro-Oncology* 2010;12:104-113.
3. Ohgaki H, Kleihues P, von Deimling A, Louis DN, Reifenberger G, Yan H, et al. Glioblastoma IDH-mutant In WHO Classification of Tumours of the Central Nervous System Edited By David N Louis et al. France, International Agency for Research on Cancer. 2016, 52-56.
4. Ellingson BM, Lai A, Harris RJ, Selfridge JM, Yong WH, Das K, et al. Probabilistic radiographic atlas of glioblastoma phenotypes. *AJNR Am J Neuroradiol*. 2013;34(3): 533-40.
5. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2006. Source: Central Brain Tumor Registry of the United States, Hinsdale, IL. 2010. Website: www.cbtrus.org.
6. Dzali NB, Zahary MN, Abu Bakar NH, Jaafar H, Taib WRW. Distribution pattern of brain tumour in a tertiary hospital in East Coast Malaysia. *Malaysian Journal of Public Health Medicine* 2017,2:41-48.
7. Roxas RC, Pedro KM, Rivera JP and Batara JMF. Current treatment status of adult brain tumors in the Philippine general hospital. *J Neurol Neurorehabil Res*. 2017, 2(1):7-13.
8. Verhaak RG1, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* 2010;17(1):98-110.
9. Lai A, Kharbanda S, Pope WB, Tran A, Solis OE, Peale F, et al. Evidence for sequenced molecular evolution of IDH1 mutant glioblastoma from a distinct cell of origin. *J Clin Oncol*. 2011;29(34):4482-90.

10. Li R, Li H, Yan W, Yang P, Bao Z, Zhang C, Jiang T, You Y. Genetic and clinical characteristics of primary and secondary glioblastoma is associated with differential molecular subtype distribution. *Oncotarget* 2015;6(9):7318-24.
11. Hayat MA (ed.), Tumors of the Central Nervous System, Volume 1, Springer Science plus Business Media B.V. 2011. Page 3-8.
12. Louis D, Suva ML, Burger PG, Perry A, Kleihues P, Aldape KD, et al. Glioblastoma IDH-wild type in WHO Classification of Tumours of the Central Nervous System Edited By David N Louis et al. France, International Agency for Research on Cancer. 2016, 28-45.
13. Hanif F, Kanza M, Kahkashan P, Saima MM, and Shabana US. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. *Asian Pac J Cancer Prev*. 2017:18(1);3-9.
14. Urbanska K, Justyna S, Maciej S and Pawel S. Glioblastoma multiforme-an overview. *Contemp Oncol (Pozn)* 2014;18(5):307-312.

*****