UNIVERSITY OF NAIROBI

EARLY NEUROCOGNITIVE OUTCOME POST RESECTION OF ADULT SUPRATENTORIAL GLIOMAS AT THE KENYATTA NATIONAL HOSPITAL

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STUDENT'S DECLARATION

I declare that this research is my original work and has not been presented before for any awards or degree.

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DEDICATION

I dedicate this work to all glioma patients and their caregivers. Thank you for opening a window into the world of your experience. You have taught me empathy, grace and endurance.

LIST OF ABBREVIATIONS AND ACRONYMNS

3MS: - Modified Mini- Mental State Examination.
ACE III: - Addenbrooke Cognitive Examination III
AANS: - American Association of Neurologic Surgeons.

ADL: - Activities of Daily Living

AED: - Antiepileptic Drugs

ALA: - Aminolevulinc Acid

APOE: - Apolipoprotein E

ATRX: - Alpha-thalassemia/mental retardation, X-linked

BRAF: - v-raf murine sarcoma viral oncogene homolog B1

CMV: - Cytomegalovirus

CNS: - Central Nervous System

DNA: - Deoxyribonucleic Acid

ECOG: - Eastern Cooperative Oncology Group

EGFR: - Epidermal Growth Factor Receptor

EOR: - Extent of Resection

FGFR1: Fibroblast Growth Factor Receptor 1

FISH: - Fluorescence in situ hybridization

GBM: - Glioblastoma Multiforme

GTR: - Gross Total Resection

HGG: - High Grade Glioma

HRQOL: - Health Related Quality of Life

ICG: - Indocyanine Green

IDH: Isocitrate Dehydrogenase

CIMPACT-NOW: Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO

ISM: - Intraoperative Stimulation Mapping

KNH: Kenyatta National Hospital

KPS: - Karnofsky Performance Scale (KPS)

LGG: Low Grade Glioma

LITT: - Laser interstitial thermal therapy

MDM4: - MDM4 Regulator of P53

MEP: - Motor Evoked Potential

MGMT: - O6-methylguanine-DNA methyltransferase

MMED: - Masters of Medicine

MMSE: - Mini-Mental Status Examination

MOCA: - Montreal Cognitive Assessment

NANO: - Neurologic Assessment in Neuro-Oncology (NANO)

NCF: - Neurocognitive Function

NIHSS: - The NIH Stroke Scale

NOS: - Not Otherwise Specified

OS: - Overall Survival

PCV: - Procarbazine

PFS: - Progression Free Survival

QOL: - Quality of Life

RCT: - Randomized Control Trial

RTNT: - Real-Time Neuropsychological Testing

RTW: - Return To Work

SLA:-Stereotactic Laser Ablation

SLF: - Superior Longitudinal Fasciculus

STR: - Subtotal Resection

TERT: - Telomerase reverse transcriptase

TTF: - Tumor Treating Fields

UON: - University of Nairobi

WHO:- World Health Organization

WM: - Working Memory

OPERATIONAL DEFINITIONS

1. Low grade Glioma: -Histologic grade 1 or 2 Glioma
2. High grade glioma: - Histologic grade 3 or 4 Glioma
3. Early cognitive outcome: Cognitive outcome within three months after resection of glioma.
4. Cognitive outcome: - Functional measure of outcome based on ACE III Cognitive assessment tool.
5. Categories for extent of resection in supratentorial gliomas WHO grade 2 or 3

   Supramaximal resection: - Beyond T2/FLAIR-hyperintense tumor borders.

   Complete resection: 100% Resection of T2/FLAIR-hyperintense tumor

   Near total resection: - > 90% resection of T2/FLAIR hyperintense tumor + <= 5cm3 residual t2/flair hyperintense tumor.

   Subtotal resection: - >= 40 % resection of T2/FLAIR hyperintense tumor + <= 25cm3 residual T2/FLAIR hyperintense tumor.

   Partial resection: - 1-39 % resection of T2/FLAIR Hyperintense tumor +/- >25 cm3 residual tumor of T2/FLAIR.

   Biopsy - No reduction of tumor volume and administered for tissue-based diagnosis.

6) Categories for resection in supratentorial GBM. [1]

   Supramaximal resection: - Beyond contrast-enhancing tumor borders.

   Complete resection: - 100% Resection of contrast-enhancing tumor.

   Near total resection: >95% resection of contrast enhancing tumor + < 1cm3 residual contrast -enhancing tumor.

   Subtotal resection: -80 % Resection of contrast enhancing tumor + < 5cm3 residual contrast enhancing tumor.

   Partial resection: - 1-79 % Resection of contrast enhancing tumor +/- >5 cm3 residual contrast enhancing tumor.

   Biopsy: - No reduction of tumor volume and administered for tissue-based diagnosis.

8.) Neurosurgical Unit: - Ward 4C, Neurosurgery Clinics, All consulting units within KNH.

9.) Supratentorial: - Glioma in the intracranial location above the tentorium cerebelli

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ABSTRACT

Introduction: Gliomas are among the commonest primary brain tumors in our setting. Despite significant advances in molecular diagnosis and elucidation of pathogenesis, the prognosis remains poor especially for High grade gliomas. Maximal safe resection is the first step in the multimodal management of gliomas. However, surgical resection is limited by the lack of a clearly defined brain-tumor interface which is due to tumoral infiltration beyond the radiologically defined boundaries. Traditionally, Overall Survival, progression free survival and Extent of resection are used to define oncologic outcome in gliomas. Oncologic outcome however, does not reflect the complete patient status and hence the need for functional outcome determination. Cognitive outcome which is a key functional outcome measure in gliomas is the subject of this study.

Study Design: Prospective Cohort Study.

Broad Objective: To determine the Early Neurocognitive outcome post resection of adult supratentorial gliomas at the KNH. (Kenyatta National Hospital)

Study area: Neurosurgery Unit at the KNH. (Kenyatta National Hospital)

Study Population: Adult patients with supratentorial gliomas presenting to KNH. (Kenyatta National Hospital)

Sample size: We examined twenty patients (20) with supratentorial gliomas who met the inclusion criteria.

Data collection: An interviewer based questionnaire incorporating the ACE III (Addenbrooke Cognitive Examination III) Cognitive Assessment tool was administered at three instances as follows:- Within two weeks Preoperatively (T0), at one week postoperatively (T1) and at four weeks postoperatively (T2).

Data Analysis: Statistical Package for Social Sciences version 23.0 software was used for analysis. The pre and post operative cognitive scores were then analyzed to determine the cognitive outcome and presented as frequencies and proportions for categorical data or as means with standard deviations for continuous data. The overall and domain specific early

cognitive scores were analyzed and presented as frequencies, proportions and means with standard deviation. The relationship between cognitive outcome and extent of resection as well as that of the histologic subtype was assessed with the use of Fisher's Exact test. Statistical significance was considered where the p-value was <0.05.

Results :- Ninety five percent (95 %) of patients had cognitive impairment at baseline. Mean age of presentation was 34.3 years for LGG (Low grade glioma) and 43.8 years for HGG (High Grade Glioma). 55% of patients had LGG while 45% had HGG. Overall, there was transient decline in cognition from T0-T1 and a gradual improvement beyond the baseline from T1-T2. This improvement was across all domains but was significant in the total ACE score *(P- value 0.025*), memory (P -*value 0.008*) and fluency (*P -value 0.001*). LGG showed the greatest improvement in cognition especially in the fluency domain (*P- value 0.030*). Sixty percent (60 %)of the tumors were subtotally resected while 40 % were grossly resected. The subtotally resected tumors showed significant cognitive change in the domains of Attention (P-*value 0.029*), fluency (P-*value 0.045*) and Visuospatial association (P-*value 0.017*). Grossly resected tumors had a significant cognitive change in memory (P- *value 0.046*) and fluency (P- *values 0.024*).

Conclusion: Surgery for supratentorial gliomas results in a transient decline in cognition one week postoperatively after which significant improvement in cognition beyond the baseline is noted one month post operatively. The transient decline is likely due to the effects of surgery on the tumor bed and the subcortical circuits while the improvement is likely due to enhanced plasticity and reduction in mass effect from the tumor. LGG have the most significant improvement in cognition especially in the domains of memory and fluency. Extent of resection and histologic subtype likely have no significant effect on the change in total ACE III cognitive scores at one month postoperatively.

INTRODUCTION AND BACKGROUND

Gliomas are a heterogeneous group of central nervous system tumors that arise from glial cells. Globally, they are the most common primary CNS tumors with an estimated incidence of 4.67-5.73 per 100,000 persons. [1,2]

The patient's age , gender, and histologic subtype of the glioma significantly affects the incidence of gliomas. These factors might explain the wide range of incidences reported by various authors.[1,2,3] For instance, the incidence rate for various histologic types of gliomas ranges from 0.59 -3.69 for glioblastoma, 0.56-0.18 for Pilocytic astrocytomas, 0.44-0.37 for Anaplastic astrocytomas and 0.10-0.27 for oligodendrogliomas. [3] The influence of age is also significant with Glioblastoma and Anaplastic astrocytoma reported to have a peak incidence in patients aged 75-84 years whereas oligodendrogliomas seem to be most common in younger patients aged 35- 44 years.[3] Generally, females are reported to have a higher incidence of gliomas. However, among patients with pilocytic astrocytoma the incidence is reported to be equal in both males and females.[3] Various authors report an upward trend in the incidence of glioblastomas over the last decade. For instance, in the UK the incidence is reported to have increased from 2.4 to 5.0 from 1995 to 2015.[3] This increase is largely attributed to increased exposure to ionizing radiation, an increased life expectancy and improved access to neuroimaging especially in the developed nations.[3] Nationally the true incidence may be difficult to ascertain due to the challenges in record keeping. However, retrospective studies conducted at the Kenyatta National Hospital do provide an insight into the incidence. In one such study by Muriithi et al gliomas were the second most common CNS tumors (26.3 %) after meningiomas (41.4.%). Glioblastomas were the most common histologic subtype constituting 55 % of all gliomas. The median age at diagnosis was slightly lower than the global average at 39.65 years.[4] Akalaum et al reported a higher proportion of gliomas considering all CNS tumors diagnosed at KNH. In their study, gliomas comprised 36-48% of all CNS tumors. The majority of gliomas were Pilocytic astrocytoma's at 25%. GBM constituted 17.8%.[5] These cross sectional studies by Muriithi and Akalaum et al do present a varied picture of gliomas but do underscore the fact that Gliomas are among the commonest CNS tumors in our setting perhaps only second to meningiomas.

Gliomas remain a challenging disease especially for neurosurgeons and neuro-oncologists. The prognosis remains guarded despite significant advances in elucidating the molecular pathways involved in gliomatogenesis. For instance, the 5-year survival rate after diagnosis with a malignant CNS tumor in the US was estimated to be 35.8% according to the CTBRUS report of 2013-2017. Of all the malignant tumors considered in this report, Glioblastoma patients had the lowest five-year survival rate at 6.8%. In addition to the guarded prognosis, the treatment of these tumors is associated with significant financial obligations that are borne by the caregivers and the patients. Glioblastoma is the commonest and the most aggressive of all glioma histologic subtypes. The most recent advancement in molecular pathogenesis of glioma considers Glioblastoma to be the culmination of a series of molecular changes from a low-grade glioma to a high-grade glioma. This process which is referred to as gliomatogenesis can occur primarily or secondarily. GBM is currently considered an incurable disease with a median age of 46.3 years at diagnosis. As mentioned previously, the prognosis of GBM is poor with an estimated median overall survival of 15 months and the lowest five-year survival rate of all glioma subtypes at 6.8%. The five-year survival rate of other glioma subtypes is significantly higher that of GBM and is estimated to be 51.6% for diffuse astrocytoma, 30.2% for anaplastic astrocytoma, 82.7% Oligodendrogliomas, 94.4% Pilocytic astrocytoma, 47.3% for Astrocytoma NOS and 60.2% for anaplastic oligodendroglioma.[6] Rodger et al in their land- mark study demonstrated that the use of the STUPP regimen improved survival for GBM patients from 12.6 months to 14.2 months. [7]

Low grade gliomas are more common in young adults with a median age at diagnosis of 35 years. The prognosis of these tumors is much better than that seen with GBM. They have an average survival of 7 years for astrocytoma and up to 15 years for those with oligodendrogliomas. Despite their seemingly better prognosis, LGG represent an earlier stage in gliomatogenesis and do eventually transform to HGG.

Most gliomas arise sporadically although about 5% have a familiar origin.[8] Familiar gliomas are associated with NF-1, Turcot and Li- Fraumeni syndrome. Exposure to ionizing radiation is now a defined risk factor for gliomas. Associations have been suggested between gliomas and allergy and mobile phone use. Some studies have demonstrated that allergy is

associated with a reduced incidence of oligodendroglioma and anaplastic astrocytomas. The link between mobile phone use and CNS tumors seems to have been partly answered by the INTERPHONE study. In this study no definite risk was demonstrated with mobile phone use. However, at higher levels of exposure there seems to have been an increased risk of gliomas. In addition, effects of long-term exposure to heavy mobile phone use were not elucidated in this study. The association between mobile phone use and gliomas thus remains partly answered and should perhaps be the basis of further research.[9, 10.]

Traditionally, outcome assessment following glioma surgery has been determined using various oncologic parameters such as extent of resection, progression free survival and overall survival. Recently, neurosurgeons have become more conscious of the quality of life of patients and thus expanded the outcome measures to also include functional outcome determinants such as Activities of daily living, Neurologic outcome, Seizure outcome, and Neurocognitive outcome. Neurocognitive outcome is best determined by comparing the preoperative cognitive status with the postoperative cognitive status. An early cognitive outcome is determined within three months postoperatively after which it is referred to as late neurocognitive outcome. Early cognitive outcome is the subject of this study.

LITERATURE REVIEW

A.) Pathology and Management of LGG

Oligodendroglioma, Diffuse astrocytoma and Oligoastrocytoma have classically been considered the histologic subtypes constituting LGG. Histologically they are all diffusely infiltrating tumors but with certain distinguishing morphologic characteristics. The histologic hall mark of oligodendrogliomas is a “fried egg” appearance which refers to cells that have a clear perinuclear halo and round uniform nucleus. An additional background of capillary branches gives the so-called chicken-wire appearance. Diffuse astrocytoma is characterized by numerous small well differentiated ovoid astrocytic cells in a fibrillary background. Oligoastrocytoma which is now an obsolete entity, was used to describe LGG with features of both oligodendroglioma and a diffuse astrocytoma.[11]

Following the 2016 WHO classification of CNS tumors, it has become increasingly clear that gliomas do have unique molecular signatures that significantly correlate with treatment response and hence prognosis. As a result of this paradigm shift, classification of LGG integrates specific molecular features into the histopathologic classification. The integrated molecular classification of LGG thus has three entities which are; Oligodendroglioma with IDH mutation and 1P/19q codeletion, Diffuse Astrocytoma with IDH mutation, and Diffuse astrocytoma without IDH mutation (IDH Wild Type). This shift towards an integrated molecular classification is however not universally applicable especially in resource limited settings. The WHO thus made provisions for diffuse LGG to be classified histologically, into either diffuse astrocytoma NOS or oligodendroglioma NOS. Figure 1 is a summary of the integrated molecular diagnosis of LGG. [11]

IDH mutation status is a major molecular signature that is considered in classifying gliomas. These mutations are classified as canonical or non-canonical. Canonical mutations refer to IDH -1 mutations in the R-132 protein. They are most common and are demonstrated in about 90% of IDH-mutant diffuse gliomas. Immunohistochemistry is an easily available technique of detecting this mutation using a specific antibody targeting the mutant protein. Non-canonical IDH mutations refer any other IDH mutations other than those at the R-132 protein. These are found in the minority of glioma cases and are estimated to represent about 5% of IDH . The detection of non-canonical IDH mutations is more demanding and requires IDH1

and IDH2 sequencing. Astrocytic tumors have been shown to mostly have IDH 1 mutations while most oligodendrogliomas have IDH 2 mutations.

1p 19 p codeletion is another important molecular signature considered in the classification of gliomas. The chromosomal deletion can be partial or involve the whole arm. Partial deletions are found in astrocytic tumors while whole arm deletions are specific to oligodendrogliomas. Compared to IDH mutation, detection of 1p 19q codeletion is much more complex and is done using either the FISH (Fluorescent in Situ Hybridization) or CGH method. FISH is the most commonly used method; however, it is not able to differentiate whole arm and partial deletions.[12]

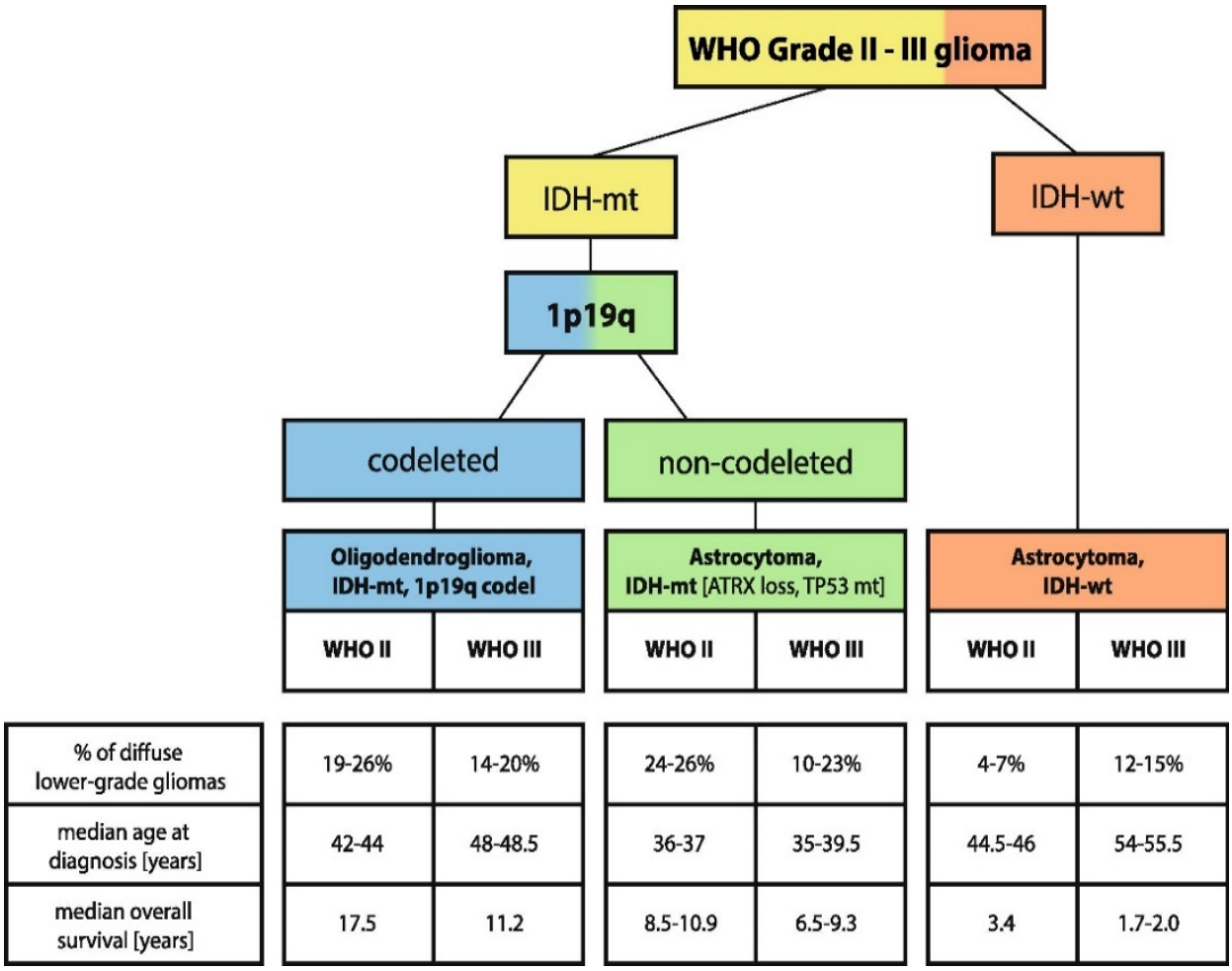
TP53 and ATRX mutations are another group of important molecular signatures in gliomas. They are mostly found in astrocytic tumors and their presence is considered to confidently exclude a 1p19q codeletion mutation. The molecular signature of Oligodendrogliomas is thus considered to have IDH mutation, 1p19q codeletion but not TP53 or ATRX mutation. On the other hand, the molecular signature used to define IDH mutant gliomas is the presence of IDH, ATRX and TP53 Mutation with no codeletion of 1p/19q. The determination of TP53 and ATRX mutation can thus be used to circumvent the use of 1p19q codeletion which is more demanding as earlier discussed.[12] This observation has informed the 2021 cIMPACT-NOW update 2. A definite diagnosis of diffuse astrocytoma IDH Mutant can thus be confidently made without further testing for 1p19q codeletion if the tumor has the following features; a definite astrocytic histology, IDH, ATRX and TP53 Mutation. [13]

The molecular features of IDH wild type diffuse gliomas elicited great interest after the 2016 classification as it was observed that this group of tumors had a varied response to treatment and their outcome mirrored that of high-grade gliomas despite their classification as Low-grade gliomas.[14] Some authors have thus subclassified IDH -Wild type diffuse astrocytomas into three subgroups based on their prognosis as:- *Early stage GBM*, *Diffuse Glioma (Not elsewhere classified)* and *diffuse astrocytoma wild type* . Early stage GBM has the worst prognosis while Diffuse astrocytoma subgroup has a more favorable prognosis.

The three subgroups have unique molecular signatures that represent the recent advancements in the molecular pathogenesis of gliomas and have partly informed the new 2021 classification. In this current classification specific consideration is given to IDH wild type

gliomas as detailed in the WHO cIMPACT-NOW update 3. This update recommends that IDH wild type glioma with amplification of EGR, TERT promoter mutation or a combined loss of chromosome 10 and loss of chromosome should be considered as an IDH-wild type low grade glioma with molecular features of glioblastoma.[15]

The 2021 classification has also brought into light the varied natural history of IDH mutant gliomas. Some of these gliomas have been shown to progress more rapidly in a manner that mirrors glioblastomas. It is this observation that has informed the cIMPACT-NOW update 5. It is thus currently agreed that IDH mutant gliomas with a homozygous mutation of CDKN2A/B or showing microvascular proliferation or necrosis are to be considered as IDH mutant gliomas grade 4.[16]



% of diffuse lower-grade gliomas	19-26%	14-20%	24-26%	10-23%	4-7%	12-15%
median age at diagnosis [years]	42-44	48-48.5	36-37	35-39.5	44.5-46	54-55.5
median overall survival [years]	17.5	11.2	8.5-10.9	6.5-9.3	3.4	1.7-2.0

FIGURE 1: INTEGRATED MOLECULAR DIAGNOSIS OF LGG [12]

In the diagnosis and subsequent follow-up of gliomas, MRI is considered the gold standard. The FLAIR sequence is particularly important in determining the tumor volume both pre and post operatively. In addition, the fact that gliomas have been shown to extend for up to 20 mm beyond the limits defined by the FLAIR sequence, make this sequence an important tool in defining the EOR. MRI is also the gold standard in follow-up of gliomas. It has been shown to be accurate in determining the glioma size and growth rate. The growth rate of LGG is estimated to be 4mm/year.[16,17] MRI volumetry has been shown to be useful both pre and postoperatively. In fact, EOR is most accurately defined as the difference between pre and postoperative tumor volume. Various methods have been devised to calculate the glioma volume. Once such method is based on 2D images of the CT scan or MRI and uses the abc/2 rule. The drawback of this method is its inability to accurately determine the volume of irregular shapes such as gliomas. It is thus not an accurate method. The recommended method is using axial MRI cuts derived from the FLAIR sequences. An addition of all the affected areas on the FLAIR sequence is then applied to a 3D computerized segmentation program that then works out the volume. Volumetry has been shown to be the most accurate measure of growth rate and also a useful surrogate for transformation.[16,17] Since MRI volumetry is not affected by the post-resection cavity it also useful in determining response to treatment in gliomas. MRI can also be useful in determining the IDH status of gliomas. The principle behind this utility of MRI is based on the fact that IDH mutant tumors have been shown to have intracellular accumulation of 2-hydroxyglutarate (2HG). Using MRS it is possible to noninvasively detect and quantify intratumoral 2HG. 2HG MRS has been shown to have an excellent predictive value in the determining the IDH status of gliomas with a specificity and sensitivity of 91% and 95% respectively.

The overall objective in the treatment of LGG is to prevent malignant transformation or at least increase the progression free survival of LGG. Surgery is the initial step in the treatment of LGG. While considering how much of tumor can be safely resected the overall goal is not a tumor free cavity but preservation of the quality of life while still achieving satisfactory resection. How much tumor is safely and maximally resectable is thus a complex decision that is tailormade to the patient's expectations and preoperative functional status. It thus important to utilize a personalized pre operative and intraoperative strategy that incorporates anatomical and functional planning. The quality of life is profoundly affected by damage of both cortical

and subcortical pathways during glioma resection. These pathways are part of the sensory, motor and association cortices whose integration defines higher functions such as attention, memory, visuospatial association and language. These pathways are thus important determinants of QOL. In order to achieve maximum safe resection and still preserve function in eloquent areas, various operative adjuncts have been used and they include; real-time neuropsychological testing (RTNT), Awake craniotomy, navigated transcranial magnetic stimulation (nTMS), Neuronavigation and image guided surgery, LITT, 5-ALA and intraoperative neuro-monitoring.[17,18,19]

Until recently, surgery for LGG was controversial with some surgeons adopting a wait and see strategy while others advocated for early surgical resection. Even among those who opted for early surgical resection the debate still continued with some opting for maximum safe resection and others for biopsy. This debate is now settled with multiple studies demonstrating a clear benefit of early maximum safe resection and associated improvement of both overall and progression free survival. The gain in survival is significant and is reported to be between 61.1 to 90 months. In this regard , the first step in the management of LGG including those that are asymptomatic and incidentally discovered is early maximum safe resection.[20] It is postulated that LGG discovered early are generally of a small size and thus the likelihood of achieving GTR are much higher. GTR has been shown to improve survival in LGG. Another postulated mechanism of improved survival after maximal safe resection in LGG is the interference with the natural history of LGG. Low grade gliomas have three phases in their natural history. The first phase is a period of quiescence, followed by a second phase of rapid growth and finally malignant transformation. The time period to transformation is varied and is reported to be between 4-29 months.[21] Maximum safe resection improves survival by prolonging time to malignant transformation. This has been clearly demonstrated in several studies. One such study by Smith et al. reported a median time to malignant transformation of 10.1 years and a median time to progression of 5.5 years in LGG patients who had more than 90 % extent of resection. The advantage conferred by maximum safe resection is thus directly proportional to the extent of resection.[22] This correlation has been redemonstrated in several studies. One such study reports a 5-year survival rate of 93% in patients with over 90 % EOR and a comparably less survival advantage of 70 % for an EOR between 70 and 90 % are

estimated. Xia etal in their metanalysis concur with several authors that increased OS in LGG is strongly associated with a greater extent of resection. [23] The landmark study by Brown et al adds to the finality on the debate of extent of resection in LGG. This study concludes that GTR compared to subtotal resection is correlated with a significant reduction in mortality and increased progression free survival.[24]

While it is generally agreed that maximum safe resection offers a survival advantage, it is still not determined how much EOR confers an effective survival advantage. This is the subject of several studies and no value has been agreed on. I will briefly review some of the studies. Shawn et al reported that a preoperative tumor volume of less than 55 cm3 and a post op residual volume of less than 1.9cm3 had the longest OS.[25] Roelz et al in a randomized controlled trial reported a clear advantage of resection versus biopsy. Of the resection group this study reported a survival advantage with a residual tumor volume of less than 15cm3.[26] Kavouridis et al. demonstrated that in IDH- Mutant and IDH-wild type gliomas volumetric differences of 1cm3 in the residual tumor volume significantly impacted survival. This same study demonstrated that a survival advantage in oligodendroglioma is achieved with a residual tumor of not more than 8 cm3.[27] Kazuya et al reported a clear advantage of greater extent of resection with cut off of 85.3% . This advantage was however limited to IDH mutant gliomas and not the IDH wild type gliomas. [28] It thus remains to be determined how much extent of resection confers survival advantage. However, the studies reviewed so far illustrate that perhaps different cut off values apply depending on the histologic and molecular subtype of glioma. What this implies is that a defined diagnosis will determine how much of tumor should be resected. The future will perhaps place a greater emphasis on intraoperative definitive diagnosis as a guide for the minimum value of EOR. A novel concept of supratotal resection has been the subject of research over the past decade. It refers to resection tumor beyond the FLAIR margins as defined on MRI scans. Duffau et al followed 16 patients with LGG who had supratotal resection and concluded that indeed supratotal resection does have an impact on delaying malignant transformation. The impact of supratotal resection on survival and functional outcome however remains to be determined. More studies are thus needed to conclusively address this question.[29]

In addition to improved survival, maximum safe resection of LGG also offers the advantage of better seizure control. Postoperatively after glioma surgery it is estimated that only about 3

% of patients develop seizures. Most of these patients will have short term seizures related to the surgery and only about 9.5% will proceed to develop late onset seizures and this is usually 2-6 years after surgery. Most of these late onset seizures are mostly due to tumor progression. It thus clear that surgery for LGG does indeed lead to better seizure control and that the recurrence of seizures could actually be an early sign of tumor progression. In an effort to preserve eloquent cortex during surgical resection of LGG, some surgeons have advocated for an approach that includes an initial conservative resection followed by a reoperation several years later. The principle behind this approach is the concept of brain plasticity. This implies that brain functions previously within the vicinity of the tumor are remapped onto adjacent cortex or on a completely different area of the brain sometimes even on the contralateral hemisphere. This remapping is postulated to be induced by the process of tumor resection, tumor progression and the neurorehabilitative processes such as physiotherapy.[30]

The benefits of radiotherapy in LGG remain debatable. In an attempt to resolve this controversy, LGG patients post-surgical resection are classified into either low risk or high-risk groups. Factors considered in these stratification include age >55 years, histologic subtype of glioma, tumor diameter, tumor crossing the midline, presence of neurologic deficits preoperatively, the IDH status, 1p19q codeletion status.[31] Based on these factors the probability of progression is determined and patients are classified as low or high risk. The greatest benefits of adjuvant radiotherapy and chemotherapy have been demonstrated in the high-risk group. The benefits of early radiotherapy on OS and PFS have however been marginal.[32] Brown et al further confirm this in their study where no reduction in mortality was associated with early radiotherapy. Their study however showed that adjuvant chemotherapy in LGG was associated with reduction in mortality and better 5-year survival. The benefits of chemotherapy were however more pronounced in the IDH mutant gliomas than the IDH wild type gliomas. [25]

With regard to adjuvant radiotherapy, one pertinent question has been whether to initiate radiotherapy soon after surgery or wait for disease progression. The EORTC22845 trial reported a lower incidence of seizures and marginally better median progression free survival but no difference in overall median survival with use of early radiotherapy.[33] The RTOG 9802 trial showed similar results as the EORTC 22845 trial.[34] Based on these two landmark trials the

optimal dose to be used in radiation of LGG is considered to be between 45 and 54 Gy in 1.82 Gy fractions. Higher doses have not been found to be beneficial.[35]

Use of chemotherapy still remain debatable. The RTOG 9802 Trial, concluded that concomitant PCV and radiotherapy was associated with significant improvement in overall survival and PFS. The greatest benefits were however reported in patients with IDH mutant gliomas or 1p19q codeletion. Baumert et al in a RCT on the use of TMZ versus Radiotherapy in high-risk LGG patients found no difference in the PFS between the two groups. Results on median and overall survival are still unavailable. [35] The use of Temozolomide in Grade II LGG is the subject of phase 3 RTOG study, it's use is thus at the clinician's discretion.[36,37]

The median survival for LGG is 5.6-13.3 years. Survival is dependent on several factors which include the extent of resection and molecular features, including isocitrate dehydrogenase (IDH) 1 and 2 mutations, and 1p19q codeletion. Poor prognostic factors include; sub-total resection, astrocytic histology, Age >55 years, impaired cognitive status and tumor location in a non-frontal area. Favorable prognostic factors include, small tumor volume, epilepsy, and greater EOR. [11,38] A good cognitive status defined as an MMSE>26 is currently considered to portend a better prognosis.[38,39.] Presence of 1p19q co-deletion, MGMT methylation and IDH Mutation are considered favorable molecular factors.

Seizures are among the commonest clinical manifestations in LGG. IDH mutation status and superficial cortical location are considered significant risk factors for seizures.[39] The best control of LGG associated seizures is obtained with maximum safe surgical resection, radiotherapy and chemotherapy augment the role of surgery. Due to the slow radiologic resolution of tumors a seizure frequency can be used to monitor response to treatment. LGG associated seizures have a focal onset and as such antiepileptic drugs (AEDS) used in focal seizures such as zonisamide, levetiracetam and carbamazepine are used in the treatment of symptomatic patients. Due to its rapid titration, good tolerability and lack of drug interactions, Levetiracetam is the first drug of choice. If seizures are poorly controlled with levetiracetam then Valproic acid should be considered as an add on drug. A summary of adjuvant treatment in LGG and current supporting evidence is shown in the figure 2 .

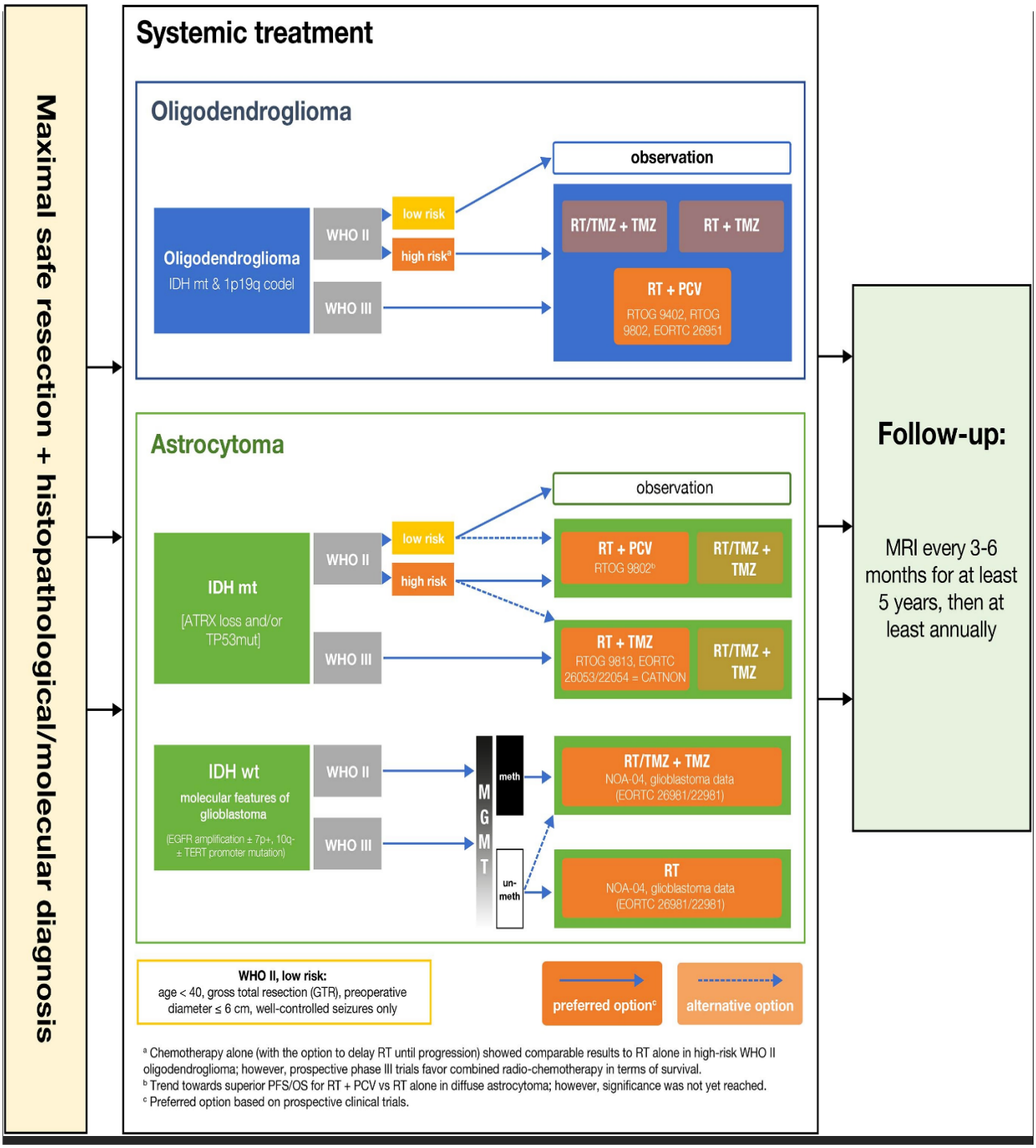


FIGURE 2:-SUMMARY OF ADJUVANT TREATMENT FOR LGG

Summary of the available evidence for adjuvant treatment strategies of WHO grade II-III glioma. [12]

B) Pathology and management of HGG.

Glioma pathology has undergone significant changes over the last decade which culminated in the introduction of an integrated molecular classification of CNS tumors in 2016. A recent 2021 c- IMPACT -NOW update has further revised the classification of high-grade gliomas. This changes although welcome pose a challenge since most of the studies on treatment of gliomas were done before these significant changes in classification. The traditional histologic classification still continues to be in use especially in resource constrained settings where the facilities for detailed molecular diagnosis are limited. Molecular classification however has significant advantages especially in prognostication of glioma patients to the various treatment options.

Multimodal therapy is the current standard in the treatment of HGG. [40, 41] Maximum safe resection represents the initial step in this treatment process. Multiple studies have demonstrated the benefits of maximum safe resection in HGG. Brown et al in a landmark study which was a meta-analysis of 37 studies concluded that GTR was associated with a reduction in mortality and overall improvement in survival.[42] Sanai et al , reported that EOR of over 78% in HGG portends a significant survival advantage in newly diagnosed GBM. Annete et al in a recent study concluded that supratotal resection of newly diagnosed GBM in young patients is associated with survival advantage. This survival advantage was also reported in elderly patients after GTR. [43] Taken together these studies underpin the fact that the EOR in HGG is a significant determinant of survival. The overall survival after GTR is estimated to improve to 64.9 -75.2 months in Grade III gliomas and 11.3- 18.5 months in Grade IV tumors. With regard to recurrent GBM the extent of resection, KPS score are key determinants of survival. Some authors report that minimum threshold of 80% for EOR is required to confer survival advantage in recurrent GBM. In IDH -Wild type gliomas a greater extent of resection is still a key determinant of outcome even in the presence of MGMT methylation.[44,45] The AANS in their 2021 updated guidelines for management of newly diagnosed GBM still advocate for maximum safe resection, less than GTR should be considered depending on the patient's functional status, comorbidities and proximity to eloquent cortex. This recommendation adds a new dimension of Onco- functional balance where less than GTR is acceptable in the setting of significant comorbidities.[46] Even for butterfly gliomas and in patients over 65 years, maximum safe

resection is still recommended. In order to maximize the extent of resection, AANS recommends the use of intraoperative MRI or 5-aminolevulinic acid (5-ALA).[46]

Rodger et al demonstrated that the addition of concomitant Temozolomide to adjuvant radiotherapy in the management of GBM results in a statistically improved median survival of 14.6 months compared to 12.1 months for those who had radiotherapy alone. This study further showed an improvement in the two-year survival rate in those who received concomitant Temozolomide versus radiotherapy alone. The STUPP regimen which is based on this landmark study by Rodger et al is thus the recommended standard of care for HGG after maximum safe resection. The optimal number of cycles for Adjuvant Temozolomide remains controversial. Some advocate for 6 cycles while others administer up to 12 cycles. Bin Huang et al in their study compared adjuvant therapy using standard 6 cycles and more than 6 cycles. Their study demonstrated significant differences in KPS and cognition and that were in favor of more than 6 cycles of adjuvant Temozolomide.[47] The detection of tumor borne CMV antigens in GBM sparked an interest in immunotherapy for HGG. However, immunotherapeutic successes against GBM have been limited, despite decades of effort.[48,49] Laser Interstitial Thermotherapy (LITT) is currently used in the management of recurrent GBM.[50]

C.) Outcome assessment in gliomas

Outcomes following glioma surgery are classified as either functional or oncologic. Measures of oncologic outcome include PFS, OS and time to malignant transformation. Residual tumor volume and EOR are other secondary markers of oncologic outcome. Oncologic outcome is predominantly oriented towards radiologic changes which may not fully represent the patient status. For instance, an apparent response after use of Bevacizumab may not be due to tumor response but rather a normalization of blood supply in the tumor.[51.] Functional outcome is a composite that includes; Activities of daily living, neurologic outcome, cognitive outcome, Seizure outcome, and HRQOL. Each of these components can be quantified using various tools.[52] Neurologic outcome is measured using the NANO and NIHSS scales.[53] Activities of daily Living (ADL) can be determined using several tools that include; the Modified Rankin Scale, KPS, ECOG/WHO Scale and the Barthel Index. Seizure outcome is assessed using the

Engel score. The EOT QLQ-C30 and QLQ- BN20 are used to assess the HRQOL. Figure 3 is a summary of the components of functional outcome assessment.

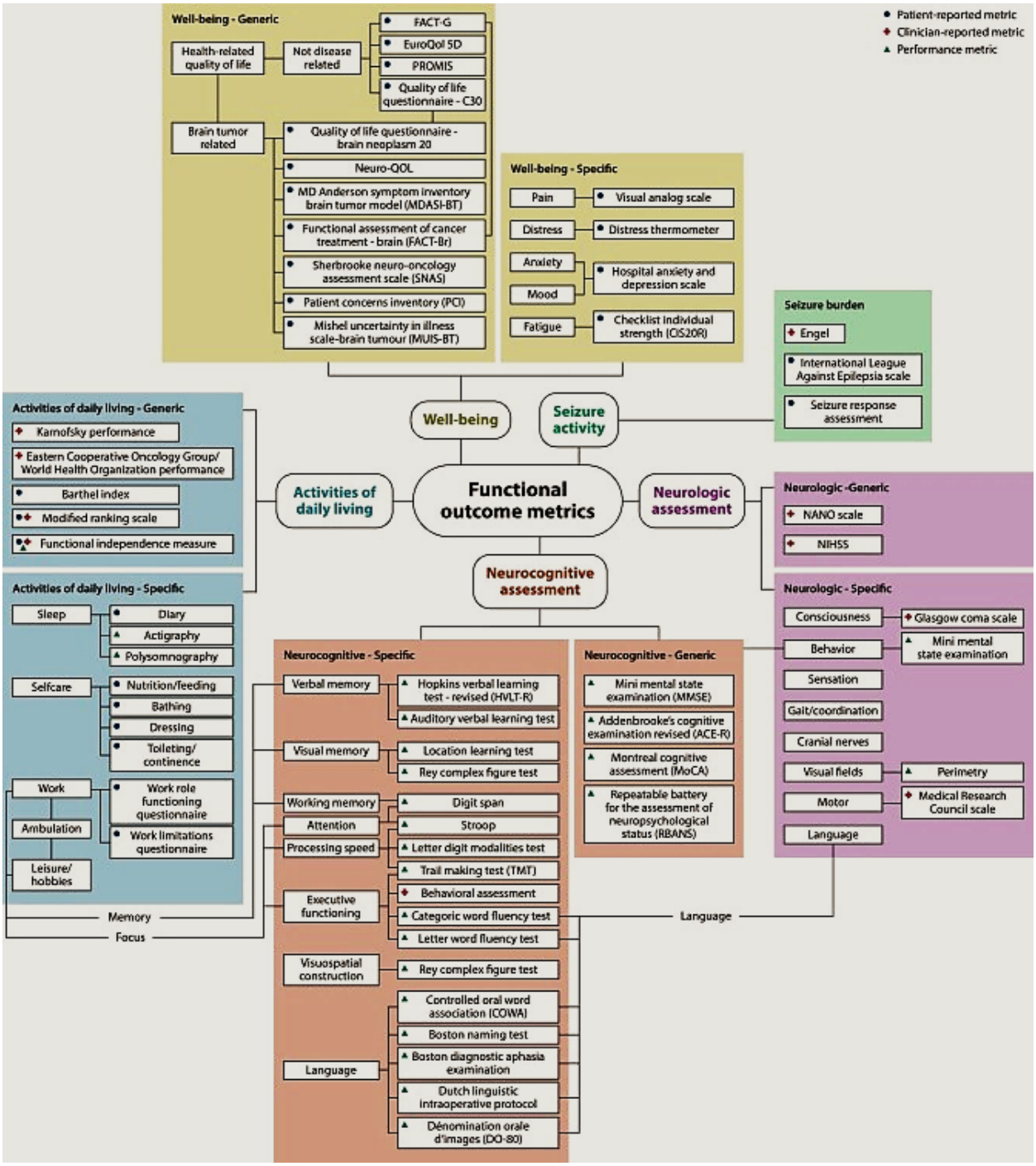


FIGURE 3: SUMMARY OF FUNCTIONAL OUTCOME MEAURES[52]

Neurocognitive outcome assesses several higher functions such as memory, fluency attention, executive function, visuospatial association, and language. The Clinical trial core test batteries are ideal for cognitive outcome assessment but are not very useful in every day clinical practice due to the lengthy time required to administer them and the need for specially trained personnel.[54,55] MMSE has also been used to asses cognitive outcome but has been found to very insensitive in less than severe cognitive impairment. The ACE-III, Montreal cognitive assessment tool are alternatives to the MMSE. Some authors have reported better sensitivity with the ACE-III but more studies are required to validate the tool in glioma patients.[56]

Traditional outcome does not represent a complete assessment of the patient's status.[57] It is this realization that has gradually shifted the management of gliomas towards an oncofunctional balance approach. Oncofunctional balance refers to the balance between surgical resection and functional outcome in glioma surgery. Based on this principle the operating surgeon develops a patient centered resection strategy that is guided by the patient's expectation and preoperative functional status. [58]

As a whole adult brain tumors are associated with cognitive symptoms that impact the QOL. In addition, treatment for gliomas is expensive and burdensome for the care givers and patients. [59] O'Keeffe et al report that High grade gliomas result in a poor quality of life of the caregivers with 29% experiencing financial difficulties and 60 % experiencing burnout. [60] Although it may be argued that LGG have a better Oncologic outcome that HGG, LGG are commonly associated with fatigue that more often warrants more therapeutic and scientific attention. [61] Not surprisingly GBM affects the professional life of the patients significantly. Studies report that only a minority of GBM patients are able to resume work after treatment and usually it's on apart time basis. The majority of patients become dependants.[62,63] However, studies have shown that use of awake surgery is associated with a high rate of return to work thus improving the functional outcome.[64,65] A majority of long term GBM survivors have been reported to have significant cognitive dysfunction that impacts their quality of life. [66] Maximum safe resection has been shown to prevent the decline in functional outcome in HGG patients and hence improve the quality of life and survival.[67]

D) Cognition and gliomas.

Cognitive dysfunction is defined as an impairment in any of the following domains; Intelligence, processing speed, learning and memory, visual spatial function, language, attention, motor function and emotion. [68]These cognitive domains are classified into "basic" functions and higher functions. Language, memory, attention, executive functions and social cognition constitute the so-called higher functions. Gnosis, Sensorimotor functions, visuospatial orientation, and praxis constitute the basic functions. Both higher and basic functions interact with each other and thus no cognitive function works in isolation. [69] Cognitive deficits in glioma patients are caused by direct pressure on the normal brain by the tumor, reactive edema and glial invasion by the tumors resulting functional disconnection of key pathways involved in cognition.[70] This underpins the fact that the complex interaction between the glioma and normal brain significantly impacts cognition. The recognition of cognitive impairment needs more than just a routine clinical evaluation since most of these patients lack insight into their degree of cognitive impairment. It is thus useful to use standard tools that are domain specific in cognitive assessment. Recently, studies on the human brain connectome, which is a brain map of cognitive pathways as opposed to traditional anatomical based connections, has given us a clearer understanding of the cognitive symptomatology in glioma patients. For instance, using this model researcher have been able to understand how a right frontal glioma affects cognitive function that is predominantly controlled by pathways in the left hemisphere. In other words, cognitive dysfunction does not necessarily reflect the disruption of pathways adjacent to the tumor but can affect connections even in the contralateral hemisphere. The human cognitive pathways are thus intricately connected beyond what we have traditionally understood anatomically.[71]

There are varied reports on the prevalence of cognitive impairment in gliomas. Some authors have pointed out that glioma patients have a cognitive impairment in at least one domain. Other studies have pointed out that LGG have a cognitive impairment of 27-83 %. Ellen et al reported a similar prevalence in LGG of 19-83%.[72] One other study reported an overall cognitive impairment of 51.9 % with domain specific impairment as follows; visuospatial abilities (19.2 %), processing speed (38.5 %), language (29.6 %) and memory (29.6 %) [73] The variation in the cognitive assessment tools is a major reason for the variance in the incidence and prevalence

rates. More research is needed to truly define the incidence and prevalence of cognitive dysfunction in gliomas. The figure below shows a summary of cognitive domains assessed in gliomas.

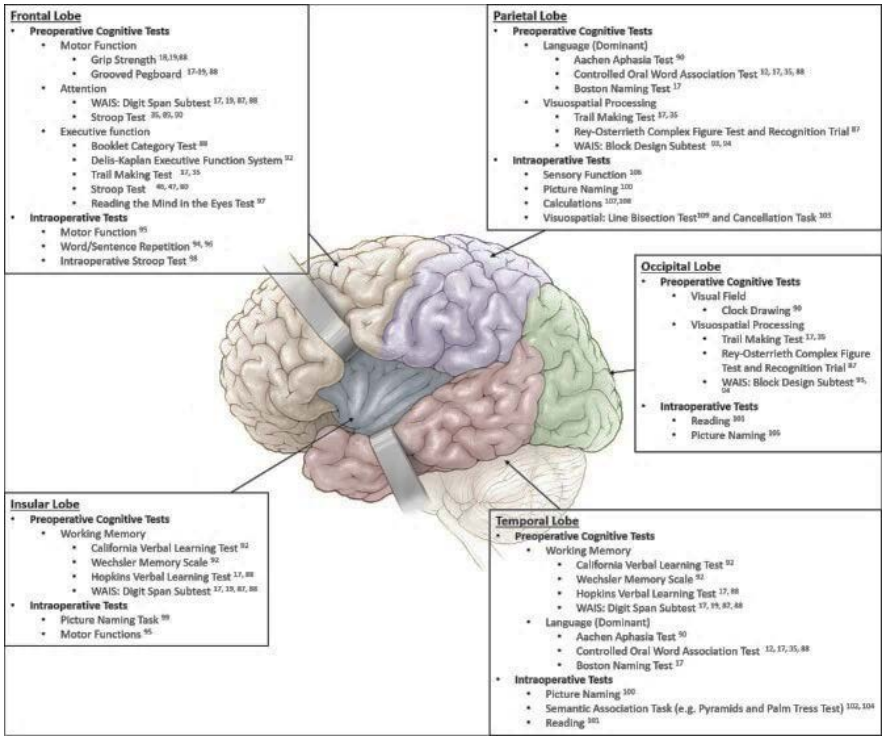


FIGURE 4: COGNITIVE DOMAINS IN GLIOMA

Cognitive domains and respective tests

Assessment of NCF in glioma patients requires formal neurocognitive testing. The utility of neurocognitive testing is in determining the effect of treatment on cognition. This means determining how different treatment regimens affect neurocognitive function .However, the use of formal neurocognitive testing and determination of cognitive outcomes in research is not widespread and hence the ability to determine long term cognitive outcome and the effect of the different treatment approaches on cognition is limited.[74] Cognitive decline is a more sensitive indicator of tumor progression than radiologic evidence. This was clearly shown by Paul et al who reported that even in glioma patients with no radiologic evidence of progression decline in the MMSE scores was significantly associated with rapid tumor progression and death. Cognitive decline in these patients is largely due to subtle tumor progression that begins way before the radiologic changes are evident.[75] The QOL is significantly affected by glioma surgery. For instance, RTW (return to work) one year after awake surgery for left sided gliomas is

significantly affected by preoperative tumor volume and memory status. Executive function, verbal fluency, and movement have been shown to be the most important determinants of QOL following awake surgery for LGG. Cognitive testing has a utility in predicting the prognosis of gliomas. Some studies have shown that impairment of executive function and processing speed 3 months after resection of glioblastoma are independent predictors of poor survival. Functional performance status thus allows for prognostication in glioblastoma patients.[76]

More than half of all glioma patients have cognitive dysfunction before treatment. The tumor and its effects on the brain thus significantly contribute to cognitive impairment. The variable occurrence of cognitive dysfunction in these patients is largely unexplained.[77] Factor associated with cognitive impairment in gliomas include IDH Status, use of antiepileptic, older age, tumor location, extent of peritumoral edema, tumor size, and the rate of the tumor growth.[78.] Subclinical tumor progression is a significant contributor to cognitive decline after glioma surgery. Benign intracranial lesions do not seem to be associated with cognitive decline after surgery. [79] Genetic factors do seem to have a role in determining cognitive function in glioma patients. One study found that polymorphism in DNA repair and telomerase genes predicts cognitive decline in glioma patients. APOE e -4 carriers with low grade gliomas have not shown any statistically significant cognitive impairment compared to non-carriers. [80] Lesion momentum is a significant cause and risk factor for neurocognitive decline. This implies that HGG which have a faster rate of growth will present with profound cognitive deficits compared with slow growing gliomas. Slower growing tumors have more reorganization of the glial neural networks hence less cognitive impairments. IDH Wild type gliomas which have a faster growth rate than the IDH mutant types have more cognitive dysfunction. Subcortical plasticity which is the phenomenon underlying lesion momentum plays a significant role in compensating for damage to cognitive pathways hence the lesser cognitive deficits seen in LGG patients.[81]

In the short term the use of radiotherapy has been associated with transient cognitive effects however in the long-term use of radiotherapy is associated with cognitive dysfunction and leukoencephalopathy.[82] The effect of radiotherapy on cognition is further supported by Surma et al whose study showed that more cognitive deficits are seen in LGG patients receiving early radiotherapy. Another school of thought proposes that the biggest contributor to cognitive decline is the tumor and that radiotherapy only compounds this decline and at higher doses.[83] In

support of this hypothesis , Klein et al in a study comparing the effect of radiotherapy and Temozolomide on memory in high risk LGG patients one year after treatment concluded that radiotherapy did not result in memory dysfunction. This was however a short term study and cannot be used to conclusively determine the effect of radiotherapy on memory.[84] In recognition of this shortcoming in their study Klein et al did a follow up study that showed that irrespective of the dose of radiation used all LGG patients who received radiotherapy had a decline in cognition 13 years after treatment. Patients who did not receive radiotherapy remained stable. Another study showed that use of radiotherapy in the treatment of LGG is associated with cognitive decline even at doses less than 2 Gy.[85] Interestingly , the use of proton therapy in LGG has been shown to result in preservation of cognition. However, tumor lateralization is still an important determinant of cognitive outcome as demonstrated by Schurman et al where left sided tumors showed more impairment at baseline but a greater improvement in verbal memory over time. [86] Medical treatment using donepezil, methylphenidate and modafinil has been shown to be ineffective in abating cognitive deterioration in patients receiving radiotherapy.[87] In consideration of all the arguments raised above, it appears the early cognitive decline is likely due to the tumor but in the long term use of Radiotherapy is definitely associated with cognitive decline even at low doses of radiation.

In consideration of the effect of chemotherapy on cognition in gliomas most studies have pointed to a role of chemotherapy induced neurotoxicity as a key contributor to cognitive decline. Various factors have been associated with increased neurotoxicity and hence cognitive decline and include; intra-arterial and intrathecal administration of chemotherapy, concomitant radiotherapy and chemotherapy, various drug delivery techniques that result in breaking the blood brain barrier and the presence of the Apo lipoprotein E4 allele. Interestingly some studies have shown that use of Concomitant Temozolomide especially in GBM does not seem to cause cognitive decline. This was also demonstrated by Zhu et al conclude that in newly diagnosed glioblastoma, there is no evidence that adjuvant treatment with TTF and Temozolomide affects HRQOL, Cognition and functional status in the long term. [88]

In considering the cognitive effects due to antiepileptic drugs it is important to consider the effect of traditional AEDs and those of newer AEDS separately. Traditional AEDS include Valproic acid, phenytoin and carbamazepine. Several studies have shown that these drugs are

associated with impairment of memory, attention and psychomotor speed. The cognitive decline due to these drugs may be potentiated by their drug interactions especially with chemotherapeutic agents that result in neurotoxicity. [89] Newer generation AEDs include levetiracetam, Topiramate and oxcarbazepine. Studies have shown that these drugs are generally associated with fewer cognitive effects than the classic AEDS. Of the newer agents Topiramate has been shown to result in the greatest cognitive decline. Interestingly, De Groot et al in a small cohort study showed that glioma patients on levetiracetam performed better on verbal memory than patients not on any antiepileptics.[90]

The effects of steroids on cognitive function are often underestimated. Steroids have been shown to result in behavioral disturbances, mood disorders, dementia and even impairment in memory. The effect of steroids is either functional or structural. Steroids have been shown to cause structural changes to certain areas of the brain such as the hippocampus and the prefrontal cortex through their neurotoxic effects. Some studies have reported a reversal of some of these changes with the discontinuation of steroids.

Besides surgery, tumor effects, radiotherapy, chemotherapy, steroids and AEDS the location of the glioma is also an important determinant of cognition. According to Yoshi et al, it is more plausible to preserve cognitive function in right sided gliomas than left sided gliomas.[91] Gliomas in the temporal lobe have been extensively studies and some authors have reported that cognitive decline is observed maximally in the subacute period. More studies are however required to fully explain this. Right temporal lobe gliomas typically have been shown to have less severe cognitive deficit than left sided glimas.[92]. Regarding IDH status and cognition, studies have shown patients with IDH- wild type gliomas have more pronounced cognitive decline that IDH mutant gliomas this is perhaps due to the reduced functional connection pathways in IDH wild type gliomas.[93]

D.) Glioma surgery and cognition

Few studies are available that compare pre- and post-operative cognitive status. As such it is difficult to truly determine the incidence of cognitive change that is directly attributable to surgery. Some authors have reported an improvement in cognition, others have reported a stable neurocognitive status. A decline in neurocognitive status has been reported too. Mioto et al studied the preoperative cognitive status of glioma patients and found that comparison to LGG,

HGG are associated with a higher incidence of cognitive impairment. The array of domains involved in HGG was also wider and include memory, executive function, fluency and processing speed. [94] Raysi et al reported an improvement in memory and processing speed but noted that the effect of surgery on cognition was also significantly affected by size of the lesion, perilesional edema and dominance.[95] Talacchi et al reported a mixed result with improvement of memory and decline in executive function. [96] In a follow-up study, Talacchi et al in a follow-up study further reported improvement was observed in the specific domains affected preoperatively but worsening in executive function occurred. They thus conclude that the net result outcome post operatively is a stable neurocognitive status. Reijneveld et al compared cognitive outcome in 24 LGG patients treated either surgically or conservatively and concluded that indeed surgery did result in cognitive decline. [97] Nakajima et al studied the cognitive outcome after use of awake surgery and concluded that the outcome showed a transient cognitive decline across all cognitive domains in the acute phase but a recovery of cognitive functions except for deep sensory perception and visuospatial association in three months. [98]Muto et al prospectively studied the quality-of-life following function-based resection of LGG found no postoperative cognitive worsening for patients without preoperative deficits. Notably, cognitive worsening was inversely related to the extent of resection in the following manner; partial resection (80%), subtotal resection (18%), total resection (16.7%). A greater EOR was thus strongly correlated with improved cognition. The authors thus conclude that function-based resection does result in preservation of cognitive function. Other authors have however found conflicting results and it will be useful to also assess the impact on high grade gliomas for a more complete assessment. [99] Non gliomatous tumors such as meningiomas do not seen to have profound cognitive deficits. One study reported that post -resection of frontal meningiomas resulted in only temporary cognitive decline that completely resolved in about three months. [100] Habets et al argue that most glioma patients already have cognitive deficits preoperatively and resection does not worsen cognition. [101] In a follow-up study focusing on HGG Habet et al reported that 79 % of these patients had a cognitive dysfunction in at least one domain. Post operatively at 5 weeks 49 % of the patients improved while 23 % declined cognitively. Ng JCH et al in a meta-analysis reported post-surgical improvement in memory, attention, language and learning but a decline in executive function. This review that focused on both LGG and HGG

and reviewed 11 studies involving 313 patients perhaps paints the true picture of the effect of surgery which is a mixed result that is domain specific.[102] Supratotal resection of HGG has a neurocognitive outcome that mirrors that of GTR which is transient decline in cognitive function and a recovery within three months. Memory and attention however seem to be affected chronically.[103]

The most comprehensive meta-analysis on the cognitive effects of surgery in gliomas is by Satoer et al who analyzed the 17 studies shown in Table 1. The conclusion from this study mirrored that by NJ et al. This study reported a universal decline in cognition in the immediate post-operative period and a gradual return to the baseline cognitive status in three months. Beyond three months the outcome was mixed with improvement and decline in various domains. Notably , Memory and attention showed a sustained decline in the long-term [104]

Author & year	Surgical intervention	Immediate postoperative	Follow-up testing	Tumor grade	*N*
Bello et al. 2007	Awake surgery	Yes	1 month and 3 months	LGG + HGG	88
Texico et al. 2007	Awake surgery	Yes	3 months	LGG	23
Yoshii et al. 2008	Awake surgery		Yes, but not	LGG[a] +	31
Chainay et al. 2009	Surgery	Yes	3, 7 days	LGG	7
Campanella et al. 2009	Surgery	Yes	No	LGG + HGG	20
Talacchi et al. 2011	(Sub)total surgery	Yes	No	LGG +	29
Papagno et al. 2011	Awake surgery	Yes	3 months	LGG +	44
Sarabi et al. 2011	Awake surgery	No	3 years	LGG	12
Wu et al. 2011	Awake surgery	No	Yes, but not	LGG +	33
Mattavelli et al. 2012	Awake surgery	Yes	No	LGG	22
Papagno et al. 2012	Awake surgery	Yes	3 months	LGG +	226[b]
Zhao et al. 2012	Awake surgery	Yes	3–6 months	LGG +	20
Santini et al. 2012	Awake surgery	Yes	3–6 months	LGG +	22
Satoer et al. 2012	Surgery	No	3–4 months	LGG +	28
Moritz-Gasser et al. (sub-study 2) 2012	Awake surgery	No	6–12 months	LGG	12
Moritz-Gasser et al. 2013	Awake surgery	Yes	6 months	LGG	8
Satoer et al. 2013	Awake surgery	No	3–4 months	LGG + HGG	27

TABLE 1: SUMMARY OF KEY STUDIES ON COGNITION IN GLIOMA

Also, meningiomas were included, but this group could be separated from glioma patients in our analysis

[b] At least one follow-up at 3 months was collected for 117 patients

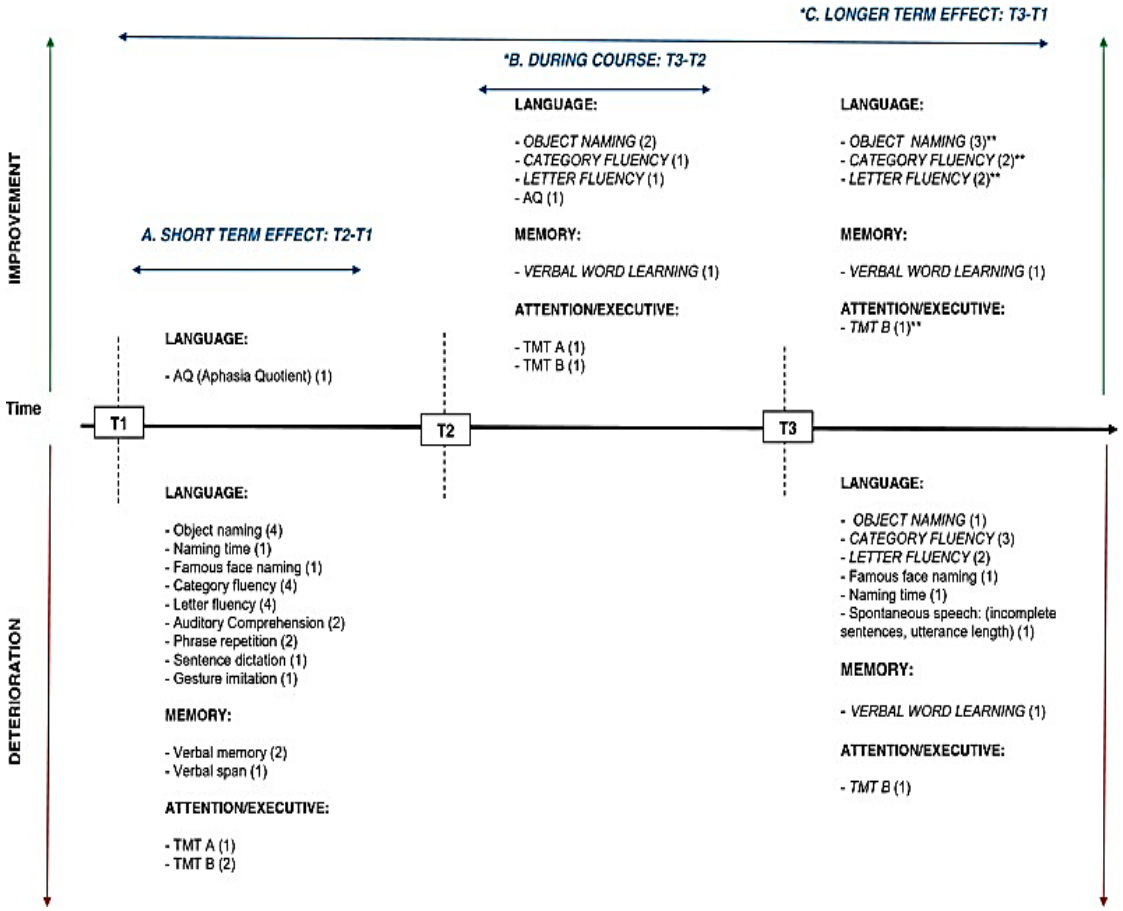


FIGURE 5: SUMMARY OF NEUROCOGNITIVE OUTCOME AFTER GLIOMA SURGERY

T1 before surgery, *T2* directly after surgery, *T3* follow-up after surgery. *Below the timeline*, a summary is provided of tasks which deteriorated between test moment in the different cognitive domains, whereas improvements are shown *above the timeline*. Comparisons between three different test moments are illustrated: *A* T2-T1, short-term effect of surgery; *B* T2-T1, during course; *C* T3-T1, longer-term effect of surgery.

Although maximum safe resection has been shown to improve survival, the quality of life has to be preserved. In this regard excision of tumor especially in eloquent cortex must be done with consideration of the brain tumor interface which is often not apparent in gliomas. Surgical adjuncts such as; Fluorescence guide surgery (using 5-ALA, Fluorescein or ICG), Neuronavigation, Intraoperative MRI, use of exoscope, intraoperative ultrasound, intraoperative mapping, intraoperative neuromonitoring, intraoperative histopathology and imaging probe devices and use of Raman Microscopy aid the surgeon in identifying this plane and thus achieve an oncofunctional balance.

One of the most useful adjuncts is intraoperative neuromonitoring during Awake surgery for gliomas. This technique has evolved and many neurosurgical centers are now able to use it in cases in which it was previously contraindicated.[105] It is well tolerated by the patients and has been shown to improve and preserve the quality of life in glioma patients.[106] The outcome however varies amongst authors and has been reported to be significantly affected by the patient's age and functional status preoperatively especially in HGG.[107] Most authors report a transient decline in cognitive function in the immediate postoperative period following awake craniotomy with improvement noted in the long term. [108] Awake craniotomy has also been shown to be associated with a high rate of return to work, however, this is significantly affected by preoperative tumor volume and memory status especially for left sided gliomas. A useful illustration on the utility of awake craniotomy is in the resection of right frontal gliomas. Studies have demonstrated that chronic spatial working memory deficits do occur in patients after resection of these gliomas. These deficits have been attributed to injury involving the dorsal front parietal subcortical pathways. The intraoperative neuromonitoring during awake craniotomy has been shown to preserve these pathways. [109] In their review of the cognitive effects of awake craniotomy some authors have noted that the most affected domain is processing speed although its effect is transient and seen during the early postoperative period.[110] A recent meta-analysis on the impact of intraoperative brain stimulation mapping on glioma concluded that it is results in greater EOR and lesser cognitive decline. The authors thus recommend use of ISM as a basic adjunct in glioma surgery.[111] Voxel based mapping may more accurately represent the eloquent cortex especially when mapping the language domain. This is based on the hypothesis that high grade gliomas do not cause diffuse deficits but selectively impact different subdomains of function in a particular voxel. The overall effect is better cognitive outcome especially for lesions involving the left hemisphere. [112]Based on investigations on brain connectomics and neoplastic potential, it was realized that eloquent areas are more accurately described as dynamic delocalized cortical subcortical circuits that are highly individualized. It is thus argued by some authors that real time cognitive monitoring using intraoperative electrical stimulation in glioma surgery increases the extent of glioma resection while sparing eloquent networks as opposed to image guided resection. In contrast to most studies that shows a trend towards preservation in cognition with ISM , D'Urso et al in their study on glioma surgery with intra-operative mapping report that 18% of the patients at 12 months a decline in function and only 10% of patients showed no deficits. This study, although from a single center, underscores

the importance of proper patient selection and further demonstrates that intra-operative mapping may be associated with cognitive deficits in some select cases. [113] The realization that ISM still does result in some deficits even though subtle and transient has resulted in a more recent innovation called Triple motor mapping. This involves direct cortical and Transcranial and MEP monitoring in addition to Bipolar and monopolar stimulation. This has been shown to better localize cortical and subcortical pathways and thus result in functional decline even in the early postoperative period. [114] The use of triple motor mapping has been well illustrated by Andrew et al in their case series of 59 operations. They were confidently able to identify the Corticospinal tract in 86.4% of cases and achieved an overall median EOR of 98% with less than 3% permanent motor deficits. [114] Another useful example of triple motor mapping is in the resection of frontal lobe gliomas involving the right hemisphere. Studies have shown that this lobe is involved in 'interference control'. The white matter fibers involved in this function are located adjacent to the inferior frontal gyrus and the striatum and are confidently identified using triple motor mapping.[115]

Intraoperative imaging is another useful adjunct that aids in maximum safe resection. Intraoperative MRI guided resection is associated with improved survival although it's an expensive modality.[116] Intra-operative ultrasound is an inexpensive yet very useful adjunct. Its use has been on the rise globally. Jakola et al in a study based on the EQ-5D questionnaire to assess the QOL on patients with intracranial gliomas it was concluded its use results in preservation of the QOL.[117]

E.) Cognitive assessment tools in gliomas.

Neurocognitive assessment is a noninvasive and useful addition to glioma patient care. [118] This assessment can be accomplished using formal neuropsychological test batteries or using brief cognitive screening tools. The Choice of which tools to use largely depends on the overall objective of cognitive testing. Neurocognitive testing has utility in clinical trials and in routine clinical practice. Clinical trials on cognitive function will typically require a vast array of domain specific information in both the dominant and non-dominant hemisphere. This level of detail is only possible through the core test batteries. One drawback of formal neuropsychological testing is the lengthy amount of time required to administer the tests. This has the potential to bias the results especially in glioma patients who regularly are fatigued. In addition, clinicians involved in daily patient care are generally not familiar with the tests. This test thus requires additional trained personnel to administer. In view of these reasons, formal core test batteries are best suited for research purposes. The cognitive

information required in daily patient care is oftenly brief, patient specific and required within a short time for purposes of clinical decision making. In view of this consideration, brief neurocognitive screening tools have their utility in routine patient care. These tests are less time consuming and are easily administered by most clinicians. The commonly used cognitive screening tools include, MMSE, MOCA and ACE. The major drawback of these tools is their inability to detect subtle changes in cognition. Their sensitivities however differ significantly and attempts have been made to increase their sensitivity. Some authors have reported sensitivities of screening tools that are strongly correlated with the formal core test batteries.

The MMMS is a modification of its predecessor, the MMSE. The MMMS has four additional components that assess long term memory, verbal fluency, recall and abstract thinking. This modification stretches the total MMMS score to 100 from the traditional 30 in the MMSE. Studies have put a cut off of 76-80 as the score below which cognitive impairment is described. The MMMS is reported to have a better discrimination of various grades of cognitive decline compared to its predecessor the MMSE[119, 120,121]. It is commonly used in studies on brain tumors and is reported to be a sensitive indicator of tumor progression. In addition this tool has prognostic significance in LGG. Studies have reported that a low baseline score is strongly correlated with a 5 years PFS of below 27%. In fact, a low MMSE score is currently considered a poor prognostic factor in LGG.

The MOCA is among the commonly used cognitive screening tools. It's reported to be more rigorous in the testing of higher functions as compared to the MMSE. However, in comparison to the core test batteries the sensitivity of this tool in detecting cognitive impairment is low. In fact, some authors discourage its use in brain tumor patients. The low sensitivity has also been cited as a big draw back to the use of the MMMS tool.[122,123]

Cog state is a computerized cognitive screening tool that is designed to be used by patients in the comfort of their homes. It's aimed at improving compliance. It's reported to be sensitive in detecting the recurrence of GBM when compared to the MMSE. Fields et al report that this tool has a 90% detection rate of cognitive decline compared to 37% in MMSE. This tool may be useful in outcome assessment in recurrent GBM. However it will require that the patients have some form of computer literacy [124, 125,126]

ACE and its subsequent versions, ACE-R and ACE III, is a useful tool used in brain tumors. It was designed to address the low sensitivity already noted in the MMMS tool.[127.] The update from the

original version were designed to address copyright issues with the MMSE and also increase its cross-cultural utility. The initial ACE tool had 26 components that were then grouped into 5 classes in the ACE-R version. These 5 classes are domain specific with a total score of 100. The five cognitive domains assed in the ACE-R are: visuospatial association, language, memory, fluency and attention. The ACE-R has a cutoff for each domain and takes about 20minutes to administer. It has a sensitivity of 84-94% for mild cognitive impairment which is better than that reported in MMSE. The ACE-III is the most recent version of the ACE tests; its revision was necessitated by copyright concerns raised by the developers of the MMSE. As a result, the ACE-R was modified to address these concerns. The ACE-III is the product of this redesign of the ACE-R. The ACE-III has been variously tested and compared with standard core test batteries used by neuropsychologists to assess various cognitive domains. It has been shown to significantly correlate with this core test battery even in the domain specific tests. In comparison with ACE-R, the ACE -III has been shown to have similar levels of sensitivity and specificity. The recommended cut off values for the ACE -III test is between 82-89. In view of the foregoing arguments , the ACE III tool will be used for this study due to its high sensitivity , specificity and significant correlation with core test batteries in key cognitive domains. [128,129,130.]

F.) Conceptual framework

Gliomas are either LGG or HGG. The first logical step in the multimodal management of these tumors is maximum safe resection. The overall goal of management is to achieve an oncofunctional balance. This means that we achieve maximum safe resection while maintaining an acceptable functional outcome for the patient. Cognitive assessment is a major determinant of the functional outcome. However, both functional and oncologic outcomes are interrelated as shown in Figure 6 below. In addition, several confounders such as use of AEDS, Use of steroids, Histologic subtype of tumor, Age, residual tumor volume also affect cognition both pre and postoperatively. A proper determination of post-surgical cognitive outcome will require that both pre- and post-operative cognitive status of the patient is determined. In addition, a consideration of all the identifiable confounders during statistical analysis of the findings is vital in the final determination of the research question.

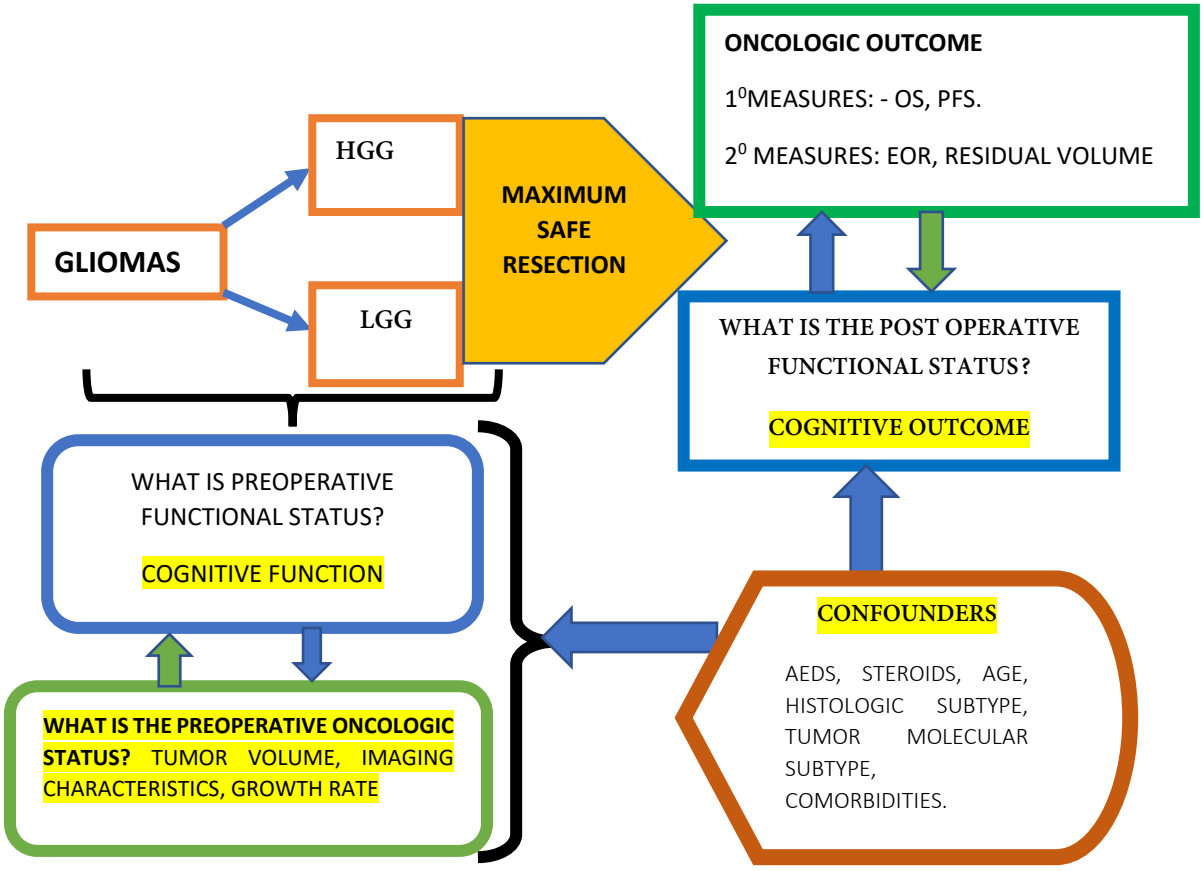


FIGURE 6: CONCEPTUAL MODEL

LIST OF VARIABLES

1) Demographics

Variable name	Type	Input values
Patient study ID	Numeric	Unique Number serialized from 001
Age	Numeric	Age must be more than 18 years
Educational level	Categorical	Must be at least 8th Grade
Sex	Categorical	Male or Female
Residence	Categorical	County of Residence

2.) Clinical Presentation

Variable Name	Type	Input Values
Illness Duration	Numeric	In weeks.
Clinical presentation	Categorical	Seizures, Paresis, Memory loss, Confusion, Headache, Aphasia, Other
Anticonvulsant Use	Categorical	Yes /No
Steroids use	Categorical	Yes/No
Comorbidities	Categorical	Diabetes, Hypertension, HIV, Prior Stroke, Others
Prior Head Injury	Categorical	Yes/No
Handedness	Categorical	Right/ Left

3.) Imaging Pre-Op

Variable name	Type	Entry values
Imaging type	Categorical	Head CT scan or MRI Brain
Side of lesion	Categorical	Right, left or Bilateral
Lesion Location	Categorical	Frontal, Parietal, Temporal, Occipital or Other.

Lesion Volume	Numerical	In mm cubic
Oedema	Categorical	Yes/No
Preop radiologic diagnosis	String	

4) Imaging Post Op

Variable name	**Type**	**Entry values**
Imaging type	Categorical	Head CT scan or MRI Brain
Residual tumor volume	Numeric	In cubic mm
Extent of resection	Categorical	Either Gross Total Resection or Subtotal Resection (Gross total resection means there is absence of any contrast enhancing tumor residual in the post operative CT scan, while subtotal means there is constrast enhancing residual tumor on the CT scan)

5) Histology

Variable name	**Type**	**Entry value**
Histology type	Categorical	Diffuse astrocytoma, Anaplastic glioma, GBM, Oligodendroglioma
WHO grade	Categorical	LGG or HGG
Immunohistochemistry	Categorical	IDH, ATRX, 1P19q codeletion, not done.

6) ACE III SCORES

Variable name	**Type**	**Entry value**
ACE III SCORE (T0)	Numeric	Summative score preoperatively
ACE III SCORE (T1)	Numeric	Summative score within one week postoperatively
ACE III SCORE (T2)	Numeric	Summative score obtained at 4 weeks postoperatively.

JUSTIFICATION OF THE STUDY

Traditional outcome assessment after glioma surgery has been largely oncologic focusing on EOR, OS and PFS. There is scant literature on the functional outcome specifically on cognitive outcome. In addition, available literature is based on non-standardized cognitive assessment tools and is thus not easily comparable or applicable to our setting. This research will fill this information gap especially in our local setting.

This is the first study in our setting assessing the pre and postoperative cognitive outcome in glioma patients. This study provides a baseline on which future researchers can build on. For instance, due to time constraints, this study has assessed early cognitive outcome at 3 months, future researchers could easily carry out a more complete study by following up the same cohort of patients beyond the three months used in this study.

The findings of this study are an indirect audit of our neurosurgical techniques in glioma surgery. We can easily answer the question of what our surgery does to the tumor but we are hardly able to scientifically answer the question of how surgery affects the patient's cognition and hence QOL. This study has begun to provide an answer to this question and will perhaps lead to the use of surgical adjuncts that help in maximizing safe resection while optimizing functional outcome.

This study will impact every day clinical practice by emphasizing pre- and post-operative cognitive assessment in all our glioma patients. This will have great benefits on the patients especially in prognostication and in the early detection of disease progression. In addition, this study adds to the available literature on the use of the ACE-III tool for cognitive assessment in glioma patients.

STUDY QUESTION/HYPOTHESIS

Does surgical resection of adult supratentorial gliomas cause early neurocognitive decline?

HYPOTHESIS

Surgical resection of adult supratentorial gliomas causes early neuro-cognitive decline.

OBJECTIVES

a) Broad objective.

1. To determine the early neuro-cognitive outcome post resection of adult supratentorial gliomas at the KNH.

b) Specific objectives.

1. To determine the overall and domain specific early cognitive outcomes post resection of adult supratentorial gliomas.
2. To evaluate the relationship between cognitive outcome and extent or resection.
3. To evaluate the relationship between cognitive outcome and the histologic subtype of gliomas.

METHODOLOGY

a) **Study design**: - This was a prospective cohort study.

b) **Study area**.: - The Neurosurgery unit at KNH (Ward 4c, Neurosurgery Outpatient Clinic and other consulting units within the hospital).

c) Study population.

- ✓ Adult patients with supratentorial gliomas.
- ✓ Inclusion criteria.
  - i. Age above 18 years
  - ii. Literate patient who can read and write and at least an eighth-grade education.
  - iii. Clinical and radiologic diagnosis of glioma.
  - iv. KPS score above => 70.
  - v. Indication for surgical intervention.
- ✓ Exclusion criteria.
  - i. Infratentorial lesions.
  - ii. A diagnosis other than glioma after histologic diagnosis.

d.) Sample size determination.

Sample size was calculated using the Fisher's formula;

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 75.0 % i.e., 0.75)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.75(1-0.75)}{0.05^2} = 288$$

Based on the average for the last two years, approximately 35 patients with gliomas are operated annually at Kenyatta National Hospital. 25% of these patients are in the pediatric age group and another 15% have Infratentorial gliomas. This gives an approximate number of 22 supratentorial glioma patients operated annually at KNH considering the study eligibility criteria. Adjusting the sample size for finite populations less than 10,000.

$$nf = \frac{n_0}{1 + \frac{n_0 - 1}{N}} = \frac{288}{1 + \frac{288 - 1}{22}} = 20$$

A Sample size of 20 patients was used for this study.

e.) Sampling and recruitment procedure

- ✓ Potential patients who meet the inclusion criteria described above were consecutively sampled from the Neurosurgical unit.
- ✓ Consent to be involved in the study was then sought from the patient after a clear explanation of the study.
- ✓ The patients or their caregivers then proceeded to fill and sign the consent form. This form is in Appendix 1.
- ✓ The patients were then assigned a unique identification number that was used for their record in the study.
- ✓ Patient demographic details were then recorded in the Data Collection tool in Appendix 2.

f.) Confounders for cognitive outcome are as follows.

i. Seizure history
ii. Anticonvulsant use
iii. Steroid use
iv. Prior history head injury

v. Comorbidities e.g., Diabetes, Hypertension, Prior stroke. etc.

All patients were on anticonvulsants, and 95 % were on steroids, only one patient had HIV and another hypertension. The analysis of the confounders was thus not done.

g.) Data collection procedures

- ✓ Data was collected using interviewer-based questionnaire (Data collection tool) incorporating the ACE III cognitive assessment tool. A few of the questions were varied to reflect the local context.
- ✓ All interviews were conducted by the principal investigator.
- ✓ Data was collected at three intervals for all patients. First interview was preoperatively (T0), within one week postoperatively (T1) and then at one month postoperatively (T2). There was provision of stretching the T2 up to 3 months postoperatively but all patients were examined at one month postoperatively.

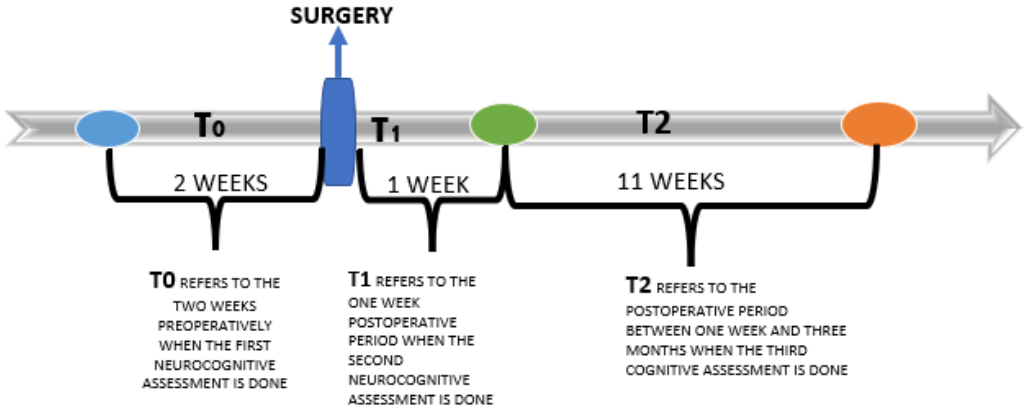


FIGURE 7: ILLUSTRATION OF T0,T1, T2 TIME PERIODS.

h)Materials.

- ✓ Printed questionnaire and consent forms.
- ✓ Stationery.
- ✓ Data analysis software.

i) Training and quality assurance procedures.

- ✓ The administration of the ACE III cognitive assessment tool was done by the principal investigator in accordance with the ACE III administration manual.

- ✓ The pre and postop images were reviewed by a radiologist to locate the lesion, determine tumor volume and extent of edema. However, it was not possible to determine the lesion volume in all our subjects due to the variability of the scanning location and MRI machines.
- ✓ A neuropathologist examined all the specimens post operatively

ETHICAL CONSIDERATIONS.

- ✓ This study posed no harm to the patients since the procedures were part of normal clinical routine for all neurosurgical patients.
- ✓ Indication for surgery for each patient was discussed with senior neurosurgeons in the unit, any patient deemed not fit for surgery was excluded from the study.
- ✓ Patients who opted out of the study were allowed to do so without any adverse effect to their expected course of treatment.
- ✓ All patients or their caregivers were promptly informed of the results of their cognitive assessment.
- ✓ Ethical approval to proceed with the study was sought from the KNH-UON Ethics and Research Committee. This study was granted approval as number P355/04/2022.
- ✓ Informed consent was sought from all participants. A Swahili translation of the informed consent form was availed to all participants not comfortable with the English version. See Appendix 1 for the English version and Appendix 2 for the Swahili version.

DATA ANALYSIS.

Data was captured using a structured questionnaire (Appendix 2 and 3), and checked for errors and completeness prior to entry into a Microsoft Excel Spreadsheet 2017. The data was later exported to the Statistical Package for Social Sciences version 23.0 for analysis. Demographic characteristics (age, education, sex and residence) as well as clinical data which include clinical presentation (illness duration, anticonvulsant use, steroids use, comorbidities, prior head injury, and handedness), imaging pre-op and post-op (imaging type, side of lesion,

lesion location, lesion volume, oedema, radiologic diagnosis, tumor volume, extent of resection), histology (type, grade and immunohistochemistry) and ACE scores were analyzed and presented as frequencies and proportions for categorical data or as means with standard deviations for continuous data. The overall and domain specific early cognitive outcomes post resection of adult supratentorial gliomas were analyzed and presented as frequencies, proportions as well as means with standard deviation. The relationship between cognitive outcome and extent of resection as well as that of the histologic subtype was assessed with the Fisher's Exact test. Statistical significance was considered where the p-value was <0.05.

STUDY RESULTS AND DISSEMINATION

The final version of this study shall be availed to both UON and KNH in soft and hard copies as per the laid-out guidelines. In addition, this paper will be presented at the EAANS annual conference and published in the EAJNS (East African Journal of Neurologic Sciences).

RESULTS.

20 patients were examined in this study and their cognitive outcomes determined at T0 (one week preoperatively), T1 (One week postoperatively) and at T2 (one month postoperatively). The results of the study are as presented below.

a) Age

	Mean Age (yrs.)	Median Age (yrs.)
Overall	38.6 (SD 16.0)	38.0 (IQR 21.5 -49.0)
LGG (Low Grade Glioma)	34.3 (SD 14.0)	34.0 (IQR 19.0 – 47.5)
HGG (High Grade Glioma)	43.8 (SD 17.5)	44.0 (IQR 37.0 -51.0)

TABLE 2: MEAN AGE OF PRESENTATION

Overall, the youngest patient was 18.0 years while the oldest was 75.0 years. For subset of LGG patients the youngest patient was 18.0 years while the oldest was 54.0 years while for HGG, the youngest patient was 18.0 years while the oldest was 75.0 years.

Age	Frequency, *n=20*	Percent
≤40	11	55.0
>40	9	45.0

TABLE 3: AGE OF PRESENTATION

b) Sex

65% of the participants were female**.**

Gender	Frequency, *n=20*	Percent
Male	13	65.0
Female	7	35.0

TABLE 4: SEX OF THE PARTICIPANTS

c) Clinical presentation

	Frequency, *n=20*	Percent
Illness duration (months)		
1 – 6	10	50.0
6 – 12	6	30.0
> 12	4	20.0
Presentation		**Percent of patients**, *n=20*
Seizures	16	80.0
Memory loss	4	20.0
Hemiparesis	4	20.0
Visual loss	3	15.0
Aphasia	3	15.0
Headache	1	5.0
Confusion	1	5.0

Anticonvulsant use		
Yes	20	100.0
Steroid use		
Yes	19	95.0
No	1	5.0
Comorbidities		
HIV	1	5.0
Hypertension	1	5.0
None	18	90.0
Handedness		
Right	20	100.0

TABLE 5: SUMMARY CLINICAL PRESENTATION

The mean duration of illness was 13.2 (SD 15.9) months, where the median duration was 6.5 (IQR 3.5 – 12.0) months. The minimum observed duration was 1.0 month while the maximum was 60.0 months. The mean duration of illness with LGG was 17.4 (SD 18.5) months, where the median duration was 11.0 (IQR 6.0 – 24.0) months. The minimum observed duration was 2.0 months while the maximum was 60.0 months. The mean duration of illness with HGG was 8.0 (SD 10.9) months, where the median duration was 4.0 (IQR 2.0 – 8.0) months. The minimum observed duration was 1.0 month while the maximum was 36.0 months.

All patients were on anticonvulsants and steroid use was in 19 out of the 20 patients. Seizures was the most common presentation.

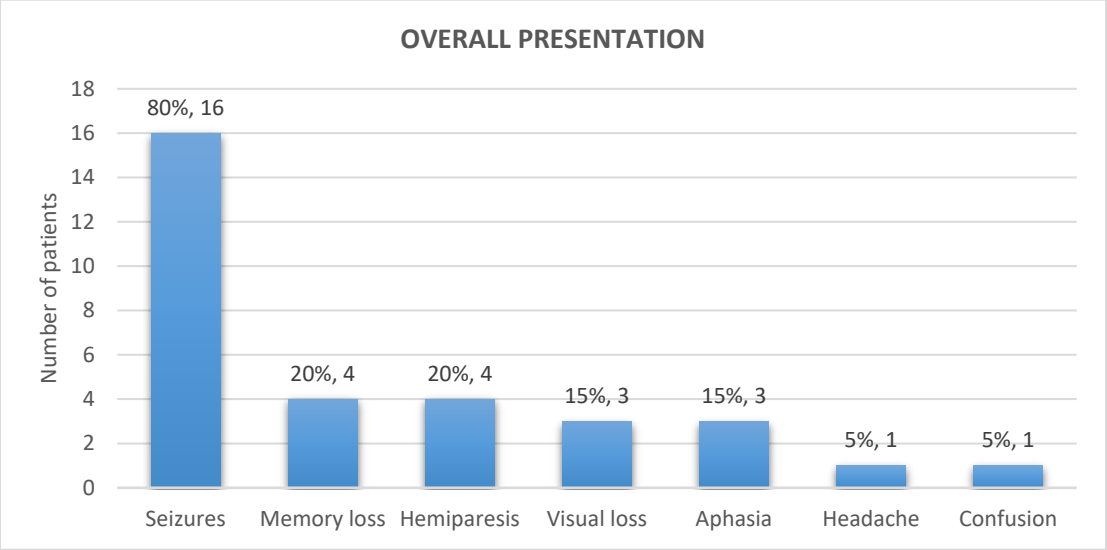


FIGURE 8: CHART SHOWING PRESENTING SYMPTOMS AND FREQUENCY

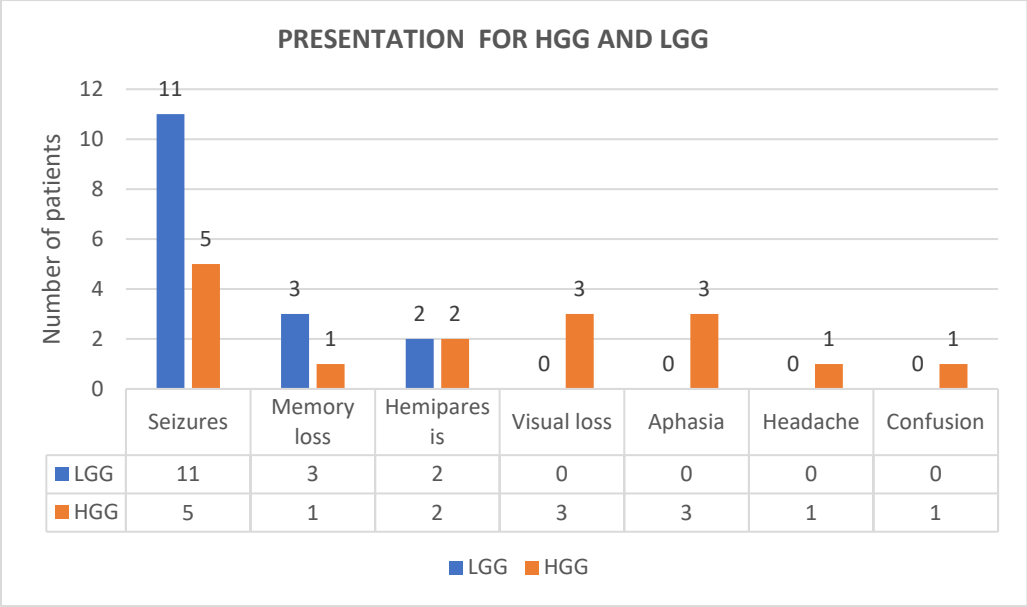


FIGURE 9: CHART SHOWING FREQUENCY OF PRESENTING SYMPTOMS FOR LGG AND HGG

Seizures was still the most common symptom in both LGG and HGG. Visual loss, aphasia, headache and confusion were only seen in HGG.

d) KPS Scores

Score	Frequency, *n=20*	Percent
70	7	35.0
80	5	25.0
90	3	15.0
100	5	25.0

KPS	LGG	HGG
70	1 (9.1)	6 (66.7)
80	4 (36.4)	1 (11.1)
90	2 (18.2)	1 (11.1)
100	4 (36.4)	1 (11.1)

TABLE 6: KPS SCORES

Most LGG had a KPS score of over 70 while most HGG had a KPS score of 70.

e) Preoperative imaging details.

	Frequency, *n=20*	Percent
Preoperative imaging modality		
MRI	20	100.0
Side of lesion		
Right	6	30.0
Left	13	65.0
Bilateral	1	5.0

Lesion location		
Bifrontal	1	5.0
Frontal	5	25.0
Frontal Parietal	4	20.0
Frontal Temporal	1	5.0
Parietal	1	5.0
Parietal Occipital	3	15.0
Temporal Parietal	3	15.0
Thalamic	2	10.0
Lesion volume		
Not calculated	20	100.0
Perilesional edema		
Yes	13	65.0
No	7	35.0
Pre-radiologic diagnosis		
LGG	8	40.0
HGG	12	60.0

TABLE 7: PREOPERATIVE IMAGING DETAILS

All the patients had a preoperative MRI but none had the lesion volume calculated. 65 % of the lesions were left sided and a majority of the lesions were in the frontal and frontoparietal region.

f) Histologic diagnosis.

Histological diagnosis	Frequency, n=20	Percent
LGG	11	55.0
HGG	9	45.0
WHO grade		
2	11	55.0
3	2	10.0
4	7	35.0
Immunohistochemistry		
Not done	19	95.0
IDH wild type	1	5.0

TABLE 8: HISTOLOGIC DIAGNOSIS

55% of the tumors were LGG. Immunohistochemistry was only done for one patient who had an IDH wildtype HGG. Of the 11 LGG patients one was an oligodendroglioma, and one was a ganglioglioma the other 9 were reported as Low-grade gliomas. Majority of HGG were WHO grade 4.

g) Postoperative imaging.

Postoperative scan modality		
CT scan	20	100.0
Residual tumor volume		
Not Calculated	20	100.0

Extent of resection		
Subtotal resection	12	60.0
Gross total resection	8	40.0
Intraoperative adjunct used		
Neuromonitoring	1	5.0
None	19	95.0

TABLE 9: POST OPERATIVE IMAGING DETAILS

All the patients had a CT scan for post operative imaging. None of the patients did an MRI. None of the patients had their post operative residual tumor volume calculated. Patients with no Contrast enhancing residual lesion were classified as having had Gross total resection. This was seen in 8 of the patients. 12 patients had grossly visible contrast enhancing residual tumor and were classified as having subtotal resection. Only one patient hand neuromonitoring used during surgery.

h) ACE III Cognitive Scores and overall outcome of cognition.

i. Baseline cognitive status at T0

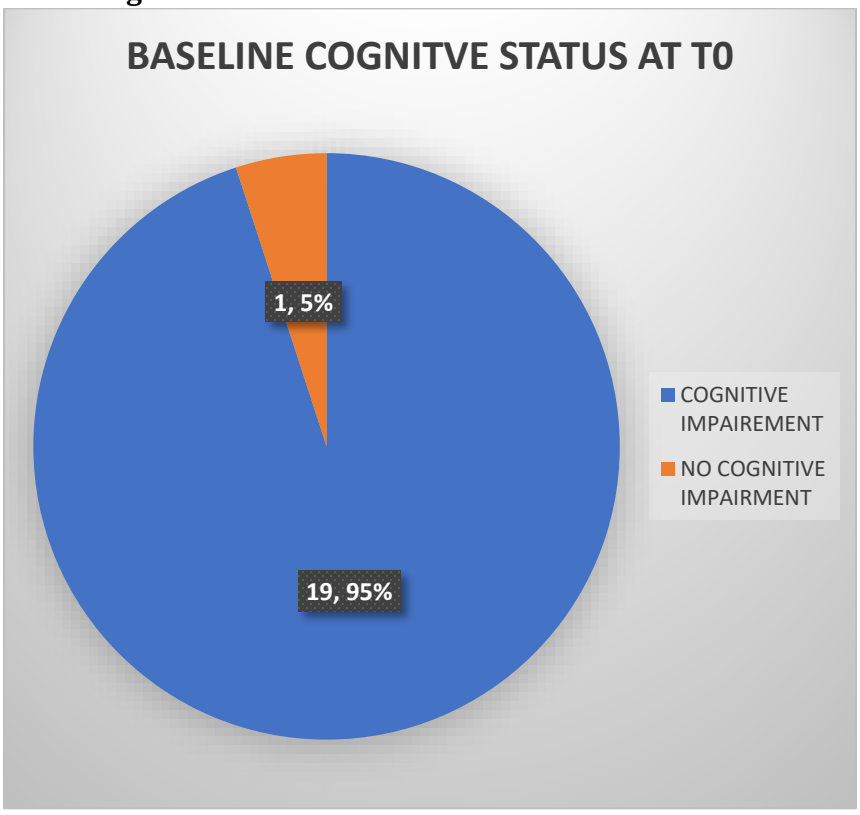


FIGURE 10: BASELINE COGNITIVE STATUS AT T0

Using a cut off of 88 for the total ACE III Score at T0 95 percent of the patients (19 out of the 20 patients) had cognitive impairment in at least one domain.

ii. Individual trends of total ACE III Scores at T0, T1 and T2 for all 20 patients.

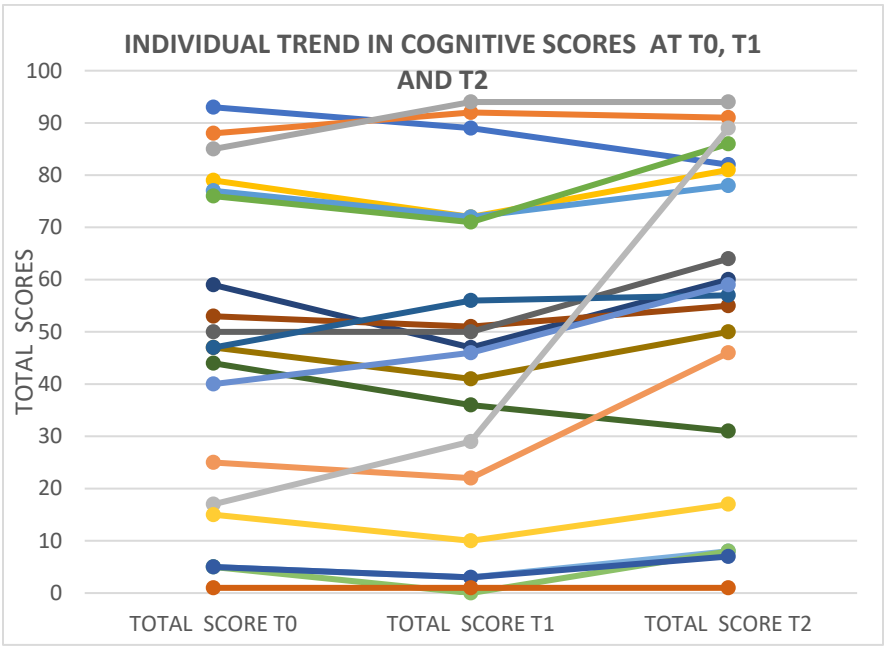


FIGURE 11: CHART SHOWING INDIVIDUAL TRENDS AT T0, T1 AND T2

Chart showing the individual trends in total cognitive scores from T0 to T1 and then to T2 for each of the 20 participants.

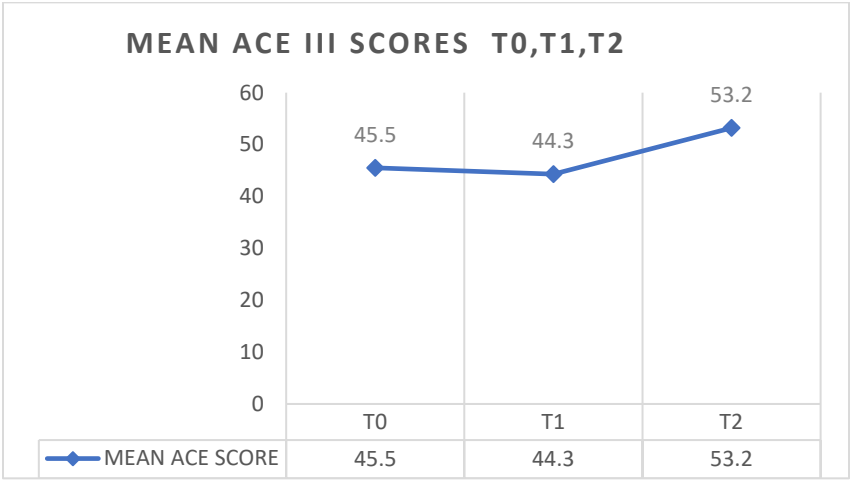


FIGURE 12: CHART SHOWING TRENDS OF THE MEAN SCORE AT T0, T1 AND T2

iii. Interval change in cognition from T0 to T1.

Shows the number of subjects who improved, deteriorated or remained unchanged. Shows the total score and domain specific scores.

	Decrease	No change	Improvement
Attention	9	9	2
Memory	10	8	2
Fluency	8	8	4
Language	5	10	5
Visuospatial	7	10	3
Total score	13	2	5

TABLE 10: OVERALL INTERVAL CHANGE T0- T1

13 patients were noted to have a decline in the total ACE III score from T0 to T1. 5 patients had an improvement and 2 remained unchanged.

iv. Interval change in cognition from T1 to T2.

	Decrease	No change	Improvement
Attention	1	9	10
Memory	1	4	15
Fluency	0	8	12
Language	3	7	10
Visuospatial	1	11	8
Total score	3	2	15

TABLE 11: INTERVAL CHANGE T1-T2

15 patients were noted to have an improvement in total ACE III scores. 3 patients had a decrease and 2 patients remained unchanged.

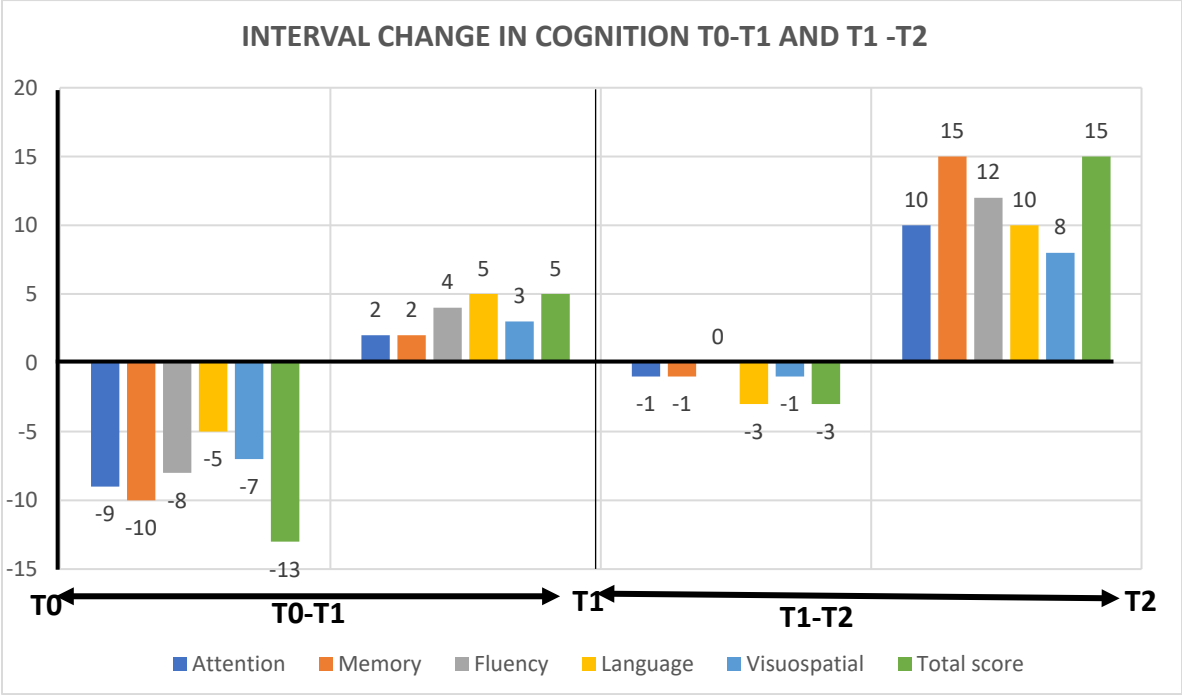


FIGURE 13: CHART SHOWING THE INTERVAL CHANGE T0-T1-T2

General decline in cognition noted in T0 -T1 interval while a general improvement was noted in the T1-T2 interval.

v. Interval change in cognition from T0 to T2.

	Decrease	No change	Improvement
Attention	3	12	5
Memory	3	5	12
Fluency	2	8	10
Language	2	7	11
Visuospatial	1	13	6
Total score	2	1	17

TABLE 12: INTERVAL CHANGE T0- T2

17 out of 20 patients were noted to improve in cognition between T0 and T2 interval. 2 Patients had a decline in cognition and 1 had no change in cognition.

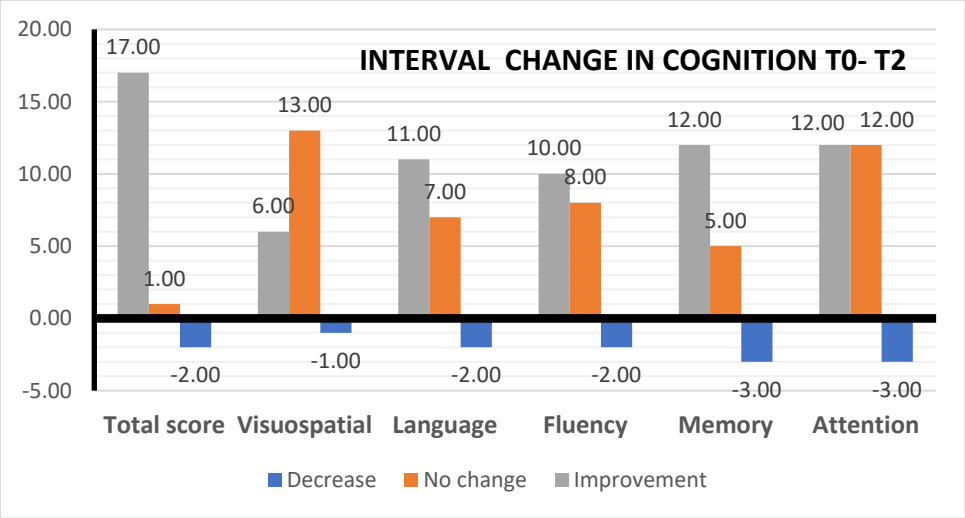


FIGURE 14: INTERVAL CHANGE T0-T2

From T0 to T2 there was an overall improvement in cognition. 13 patients had no change in the visuospatial domain.

v) Overall cognitive Outcome considering Total ACE III Scores.

	T0	T1	T2	p-value
Attention	12.1 ± 6.3	11.2 ± 6.3	12.9 ± 6.2	0.079
Memory	11.5 ± 8.4	10.5 ± 8.9	13.7 ± 8.8	**0.008**
Fluency	3.6 ± 3.6	3.4 ± 3.9	5.0 ± 3.8	**0.001**
Language	11.6 ± 9.7	12.0 ± 9.3	13.3 ± 9.6	0.093
Visuospatial	6.8 ± 6.1	6.6 ± 6.4	7.6 ± 6.5	0.085
Total score	45.6 ± 30.8	44.3 ± 31.2	53.2 ± 30.5	**0.025**

TABLE 13: OVERALL COGNITIVE OUTCOME CONSIDERING THE TOTAL MEAN SCORE AT T0, T1 AND T2

P values of <0.05 was noted in the total scores and the domains of memory and fluency.

i) Cognitive outcome of HGG versus LGG patients.

i. LGG (Low Grade Glioma)

	T0	T1	T2	p-value
Attention	13.6 ± 5.8	12.6 ± 5.2	15.0 ± 4.6	0.149
Memory	12.9 ± 7.4	11.1 ± 7.6	14.6 ± 6.2	0.076
Fluency	4.9 ± 3.5	4.4 ± 3.9	6.4 ± 3.4	**0.030**
Language	16.3 ± 8.2	16.6 ± 7.1	18.5 ± 7.4	0.222

Visuospatial	10.6 ± 5.1	10.5 ± 5.2	11.9 ± 4.8	0.157
Total score	58.3 ± 27.9	56.3 ± 26.8	66.4 ± 23.8	0.109

TABLE 14: COGNITIVE OUTCOME FOR LGG CONSIDERING THE MEAN SCORES AT T0. T1 AND T2

P value for fluency domain was <0.05 thus significant.

ii. HGG (High Grade Glioma)

	T0	T1	T2	p-value
Attention	10.3 ± 6.8	9.3 ± 7.3	10.3 ± 7.1	0.417
Memory	9.8 ± 9.7	9.8 ± 10.8	12.4 ± 11.5	0.104
Fluency	2.0 ± 3.1	2.1 ± 3.8	3.2 ± 3.9	0.098
Language	5.9 ± 8.6	6.4 ± 9.0	7.0 ± 8.3	0.178
Visuospatial	2.0 ± 3.3	1.9 ± 4.1	2.3 ± 3.7	0.487
Total score	30.0 ± 28.0	29.6 ± 31.1	35.3 ± 30.1	0.105

TABLE 15: COGNITIVE OUTCOME FOR HGG CONSIDERING THE MEAN SCORES AT T0, T1 AND T2

Neither the total score nor the domain specific scores had a P- Value of < 0.05 in HGG.

iii. Trend in Mean ACE III Total Scores for both LGG and HGG.

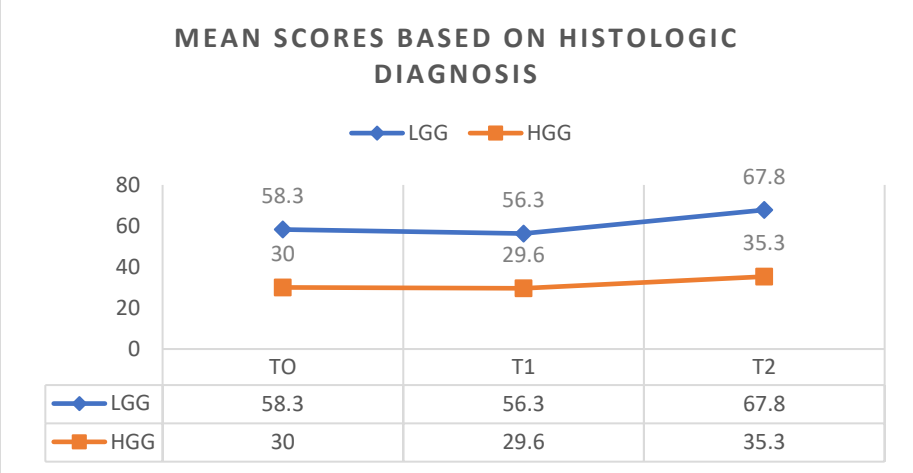


FIGURE 15: CHART SHOWING TREND OF THE MEAN TOTAL SCORES FOR BOTH LGG AND HGG

The mean trends in total cognitive scores for both LGG and HGG. The mean score for HGG is lower and only show a slight increase from T1 to T2. The curve for HGG is nearly flat. LGG show a significant increase from T1 to T2.

iv.) Association between Interval Change in cognition for HGG versus LGG T0-T1, T1-T2, T0-T2.

- **T0- T1: -** Neither the Domains nor the total score had a p value < 0.05

	Histologic diagnosis, *n (%)*		
Attention	**LGG**	**HGG**	**p-value**
Decrease	5 (45.5)	4 (44.4)	1.000
No change	5 (45.5)	4 (44.4)	
Improvement	1 (9.1)	1 (11.1)	
Memory			
Decrease	7 (63.6)	3 (33.3)	0.552
No change	3 (27.3)	5 (55.6)	
Improvement	1 (9.1)	1 (11.1)	
Fluency			
Decrease	5 (45.5)	3 (33.3)	0.603
No change	5 (45.5)	3 (33.3)	
Improvement	1 (9.1)	3 (33.3)	
Language			
Decrease	4 (36.4)	1 (11.1)	0.600
No change	5 (45.5)	5 (55.6)	
Improvement	2 (18.2)	3 (33.3)	
Visuospatial			
Decrease	4 (36.4)	3 (33.3)	1.000
No change	5 (45.5)	5 (55.6)	
Improvement	2 (18.2)	1 (11.1)	
Total score			
Decrease	8 (72.7)	5 (55.6)	0.796
No change	1 (9.1)	1 (11.1)	
Improvement	2 (18.2)	3 (33.3)	

TABLE 16: INTERVAL CHANGE COMPARING LGG AND HGG AT T0-T1

- T1- T2: Neither the domains nor the total score had a P Value <0.05

	Histologic diagnosis, *n (%)*		
Attention	**LGG**	**HGG**	**p-value**
Decrease	0 (0.0)	1 (11.1)	0.811
No change	5 (45.5)	4 (44.4)	
Improvement	6 (54.5)	4 (44.4)	
Memory			
Decrease	0 (0.0)	1 (11.1)	0.166
No change	1 (9.1)	3 (33.3)	
Improvement	10 (90.9)	5 (55.6)	
Fluency			
No change	3 (27.3)	5 (55.6)	0.362
Improvement	8 (72.2)	4 (44.4)	

Language			
Decrease	2 (18.2)	1 (11.1)	0.279
No change	2 (18.2)	5 (55.6)	
Improvement	7 (63.6)	3 (33.3)	
Visuospatial			
Decrease	0 (0.0)	1 (11.1)	0.252
No change	5 (45.5)	6 (66.7)	
Improvement	6 (54.5)	2 (22.2)	
Total score			
Decrease	1 (9.1)	2 (22.2)	0.770
No change	1 (9.1)	1 (11.1)	
Improvement	9 (81.8)	6 (66.7)	

TABLE 17: INTERVAL CHANGE COMPARING LGG AND HGG AT T1-T2

- T0 -T2: Neither the domains nor the total score had a P Value < 0.05

	Histologic diagnosis, *n (%)*		
Attention	**LGG**	**HGG**	**p-value**
Decrease	1 (9.1)	2 (22.2)	0.552
No change	8 (72.7)	4 (44.4)	
Improvement	2 (18.2)	3 (33.3)	
Memory			
Decrease	1 (9.1)	2 (22.2)	0.835
No change	3 (27.3)	2 (22.2)	
Improvement	7 (63.6)	5 (55.6)	
Fluency			
Decrease	0 (0.0)	2 (22.2)	0.142
No change	6 (54.5)	2 (22.2)	
Improvement	5 (45.5)	5 (55.6)	
Language			
Decrease	2 (18.2)	0 (0.0)	0.554
No change	3 (27.3)	4 (44.4)	
Improvement	6 (54.5)	5 (55.6)	
Visuospatial			
Decrease	0 (0.0)	1 (11.1)	0.796
No change	8 (72.7)	5 (55.6)	
Improvement	3 (27.3)	3 (33.3)	
Total score			
Decrease	1 (9.1)	1 (11.1)	0.711
No change	0 (0.0)	1 (11.1)	
Improvement	10 (90.9)	7 (77.8)	

TABLE 18: INTERVAL CHANGE COMPARING LGG AND HGG FROM T0- T2

j) Cognitive outcome and extent of resection.

i. Subtotal resection.

	T0	T1	T2	p-value
Attention	10.2 ± 6.6	8.6 ± 6.1	10.0 ± 6.5	**0.029**
Memory	8.3 ± 8.4	6.9 ± 7.9	9.6 ± 8.2	0.147
Fluency	2.6 ± 3.0	2.3 ± 3.3	3.3 ± 3.5	**0.045**
Language	8.1 ± 9.4	8.2 ± 9.4	8.9 ± 9.1	0.177
Visuospatial	5.4 ± 6.5	4.9 ± 6.6	5.7 ± 6.6	**0.017**
Total score	34.5 ± 30.3	31.9 ± 30.3	37.4 ± 29.2	0.089

TABLE 19: COGNITIVE OUTCOME FOR SUBTOTALLY RESECTED TUMORS CONSIDERING THE MEAN SCORE AT T0, T1 AND T2

Significant P- values noted for Attention, fluency and visuospatial domains. The Total score has no significant P value.

ii. Gross total resection.

	T0	T1	T2	p-value
Attention	15.0 ± 5.0	15.0 ± 4.6	17.3 ± 0.9	0.263
Memory	16.4 ± 6.1	15.9 ± 7.9	19.8 ± 5.7	**0.046**
Fluency	5.1 ± 3.9	5.0 ± 4.3	7.5 ± 3.0	**0.024**
Language	16.9 ± 8.0	17.8 ± 5.8	19.9 ± 6.0	0.253
Visuospatial	8.8 ± 5.4	9.1 ± 5.4	10.5 ± 5.5	0.255
Total score	62.1 ± 24.8	62.8 ± 23.3	76.9 ± 15.0	0.110

TABLE 20: COGNITIVE OUTCOME FOR GROSSLY RESECETED TUMORS CONSIDERING MEAN SCORES AT T0, T1 AND T2

Significant P values noted for domains of memory and fluency. The total score has no significant P value.

iii. **Trend in the Mean scores based on extent of resection.**

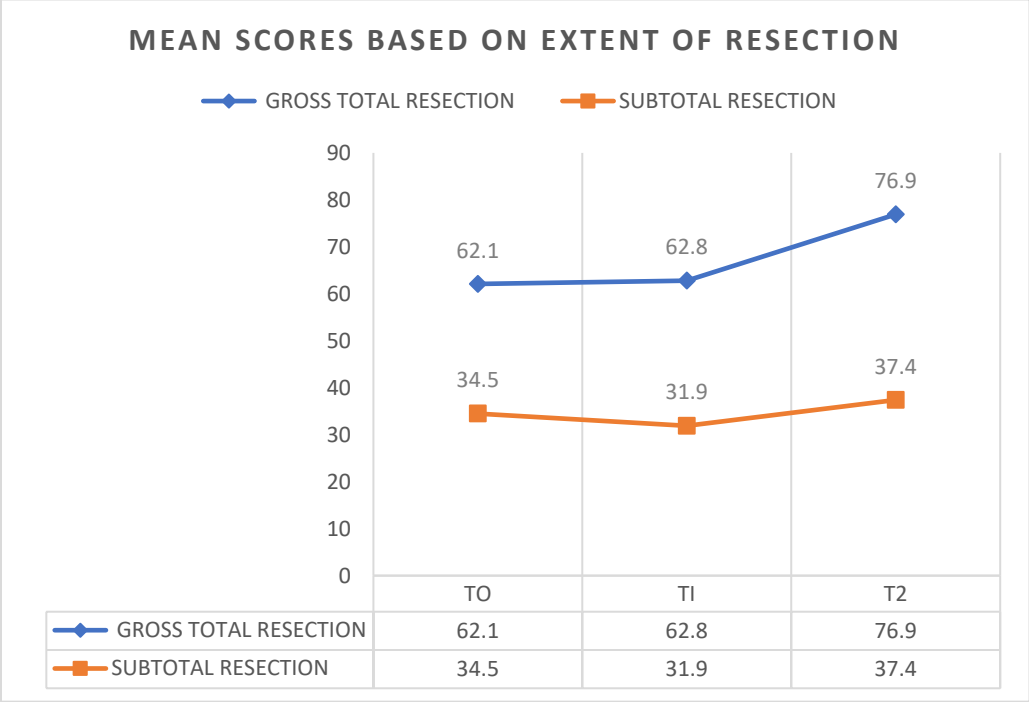


FIGURE 16: CHART SHOWING TH TRENDS IN THE MEAN FOR TOTAL SCORES FOR SUBTOTAL AND GROSS RESECTION

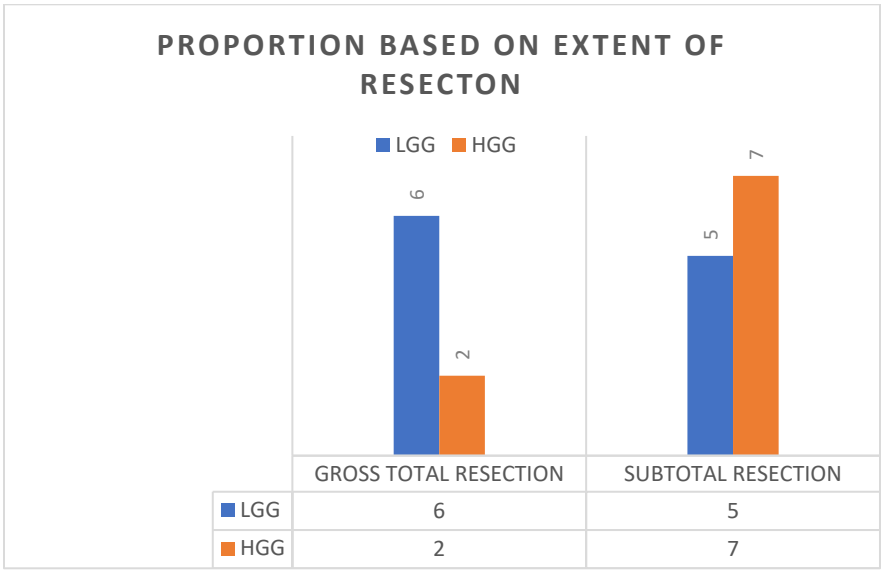


FIGURE 17: CHART SHOWING HISTOLOGIC SUB- TYPE OF TUMORS FOR BOTH SUBTOTAL AND GROSS RESECTION

iv. Association between extent of resection and interval change in cognition T0-T1, T1-T2, and T0-T2.

- **T0 -T1:** Neither the domains nor the total score shows a significant P- Value.

	Extent of resection, *n (%)*		
Attention	**Subtotal**	**Gross**	**p-value**
Decrease	7 (58.3)	2 (25.0)	0.170
No change	5 (41.7)	4 (50.0)	
Improvement	0 (0.0)	2 (25.0)	
Memory			
Decrease	5 (41.7)	5 (62.5)	0.563
No change	6 (50.0)	2 (25.0)	
Improvement	1 (8.3)	1 (12.5)	
Fluency			
Decrease	5 (41.7)	3 (37.5)	0.415
No change	6 (50.0)	2 (25.0)	
Improvement	1 (8.3)	3 (37.5)	
Language			
Decrease	3 (25.0)	2 (25.0)	0.633
No change	7 (58.3)	3 (37.5)	
Improvement	2 (16.7)	3 (37.5)	
Visuospatial			
Decrease	5 (41.7)	2 (25.0)	0.093
No change	7 (58.3)	3 (37.5)	
Improvement	0 (0.0)	3 (37.5)	
Total score			
Decrease	9 (75.0)	4 (50.0)	0.132
No change	2 (16.7)	0 (0.0)	
Improvement	1 (8.3)	4 (50.0)	

TABLE 21: INTERVAL CHANGE T0 -T1 COMAPRING SUBTOTAL AND GROSS TOTAL RESECTION

- **T1 – T2:** Neither the domains nor the total score shows a significant P- Value.

	Extent of resection, *n (%)*		
Attention	**Subtotal**	**Gross**	**p-value**
Decrease	1 (8.3)	0 (0.0)	1.000
No change	5 (41.7)	4 (50.0)	
Improvement	6 (50.0)	4 (50.0)	
Memory			
Decrease	1 (8.3)	0 (0.0)	1.000
No change	2 (16.7)	2 (25.0)	
Improvement	9 (75.0)	6 (75.0)	
Fluency			
No change	6 (50.0)	2 (25.0)	0.373
Improvement	6 (50.0)	6 (75.0)	

Language			
Decrease	2 (16.7)	1 (12.5)	1.000
No change	4 (33.3)	3 (37.5)	
Improvement	6 (50.0)	4 (50.0)	
Visuospatial			
Decrease	0 (0.0)	1 (12.5)	0.611
No change	7 (58.3)	4 (50.0)	
Improvement	5 (41.7)	3 (37.5)	
Total score			
Decrease	2 (16.7)	1 (12.5)	1.000
No change	1 (8.3)	1 (12.5)	
Improvement	9 (75.0)	6 (75.0)	

TABLE 22: INTERVAL CHANGE T1 -T2 COMPARING SUBTOTAL AND GROSS TOTAL RESECTION

- **T0 -T2:** Neither the domains nor the total score shows a significant P- Value.

	Extent of resection, *n (%)*		
Attention	**Subtotal**	**Gross**	**p-value**
Decrease	2 (16.7)	1 (12.5)	1.000
No change	7 (58.3)	5 (62.5)	
Improvement	3 (25.0)	2 (25.0)	
Memory			
Decrease	3 (25.0)	0 (0.0)	0.103
No change	1 (8.3)	4 (50.0)	
Improvement	8 (66.7)	4 (50.0)	
Fluency			
Decrease	2 (16.7)	0 (0.0)	0.232
No change	6 (50.0)	2 (25.0)	
Improvement	4 (33.3)	6 (75.0)	
Language			
Decrease	1 (8.3)	1 (12.5)	0.219
No change	6 (50.0)	1 (12.5)	
Improvement	5 (41.7)	6 (75.0)	
Visuospatial			
Decrease	1 (8.3)	0 (0.0)	1.000
No change	8 (66.7)	5 (62.5)	
Improvement	3 (25.0)	3 (37.5)	
Total score			
Decrease	2 (16.7)	0 (0.0)	0.495
No change	1 (8.3)	0 (0.0)	
Improvement	9 (75.0)	8 (100.0)	

TABLE 23: INTERVAL CHANGE T0 -T2 COMPARING SUBTOTAL TO GROSS TOTAL RESECTION

K. Cognitive outcome and use of steroids and anticonvulsants.

This analysis could not be done since both variables i.e., steroid use and anticonvulsant use are both constants. All patients were using both, with the exception of just 1 patient who did not use steroids.

DISCUSSION

This study was designed to determine the early neurocognitive outcome postresection of adult supratentorial gliomas at the KNH. Specifically, the researchers determined the overall and domain specific cognitive outcomes while employing the ACE-III cognitive assessment tool. Additionally, the study aims to evaluate the relationship between cognitive outcome and extent of resection and histologic subtype of gliomas.

The age of our patients largely correlates with the global trends in gliomas, however its noteworthy that the HGG patients in our study had an earlier age of presentation at a mean age of 43.8 years. This perhaps reflects the trend in our local setting as reported by Muriithi et al who found a mean age of presentation of 39.65 years for HGG. [3, 4, 12] Its thus telling that HGG present at an earlier age in our setting.

The clinical presentation was not unexpected but largely reflects the cohort of patients selected for this study. Most of our patients had the lesions on the left frontal parietal region and were all right-handed hence the finding of seizures, memory loss, aphasia and hemiparesis in majority of the patients. Not surprisingly the patients with HGG had KPS scores at 70, LGG had a higher KPS score. This reflects the strict inclusion criteria that naturally would result in more LGG patients being selected.

All our patients had MRI imaging done which is a reflection of its increased availability in our country over the past decade. However, its utility in the management of gliomas is still not fully appreciated as evidenced by the fact that none of the patients had the lesion volume calculated. This omission negatively affects the actual determination of extent of resection since a comparison between the pre and post op MRI lesion volumes is useful in determining how much of the tumor is excised.[40] The discrepancy between preoradiologic diagnosis and actual histologic diagnosis was noted. This was perhaps due to the presence of perilesional edema in a majority of lesions which were deemed to be HGG. This underpins the fact that not all lesions with perilesional edema are actually HGG. This should be the subject of further study in our setting.[16, 17]

Histologic diagnosis showed that majority of our patients had LGG. This was however not surprising since most of the patients chosen especially when the inclusivity criteria were applied were likely to be LGG patients. Most HGG who presented to us during the period of study had a KPS score of less than 70 and were thus excluded. The fact that this study had more LGG patients should thus

not be used to reflect the actual epidemiologic status of Gliomas at the KNH. In fact, prior studies have shown that HGG are the majority at 55 %.[4] However, we can infer that most glioma patients with a KPS of above seventy likely have LGG. The extent of glioma diagnosis in our setting is still not up to date considering the current global trends. Whereas the classification and diagnosis of Gliomas is now integrated incorporating molecular and histologic components, this is still not widely embraced in our setting.[12] Diagnosis for nearly all our patients did not progress beyond histology. Only one patient with an IDH wildtype HGG had immunohistochemistry. We postulate that this is due to the added expenses of the tests on the care-givers, majority of whom are needy and already overburdened. In addition, the immunohistochemistry and other useful molecular test are not part of the National Hospital Insurance Fund of whom all our patients are beneficiaries. The adoption of immunohistochemistry in our setting will need a paradigm shift in our health policy and especially health care funding for brain tumor patients. Some authors have suggested that limiting IDH testing to patient less than 55 years old as recommended in the 2016 WHO update will significantly reduce this financial burden. This a significant proposition in our setting.[131,132]

All our patients had post operative imaging done within one week of surgery. However, the imaging modality was uniformly a constrast based Head CT scan. None of the scans had a calculation of the residual tumor volume. As already stated, this practice had a huge implication on this study since the actual residual tumor volumes couldn't be determined.[40] Nevertheless, we classified extent of resection as either gross total or subtotal based on the absence or presence of contrast enhancing residual tumor respectively. Sixty percent of our patients had subtotal resection; majority of these tumors were HGG. Forty percent of our patients had gross total resection and a majority of these tumors were LGG. Notably only one patient had neuromonitoring used during resection. Several reasons may explain this finding on extent of resection. First, the unavailability of adjuncts makes the identification of the brain tumor interface difficult and the operating surgeons are thus unaware that there is still residual tumor at the time surgery is deemed complete.[19] Secondly, it may also reflect the surgeons caution and awareness that further neurologic and cognitive decline is almost inevitable with aggressive resection. This is especially true for patients who had HGG for whom the overall functional outcome of the patient seems to have been the goal even at the expense of gross total resection. [16,17.]

Ninety five percent (95 %) of our patients had cognitive impairment at baseline. This is likely due to the tumor effect on the subcortical circuits. The prevalence of cognitive impairment in gliomas ranges from 18- 90 % as reported by various authors. The lack of standardized cognitive assessment tools and heterogeneity of the studies may explain this variance.[73,77, 72,101.] In considering the trend in the mean cognitive scores at T0, T1 and T2, a general decline is noted from T0-T1 then an improvement is noted from T1-T2. The interval from T0- T1 showed an overall decline in cognition in 13 out of the 20 patients. This was uniformly seen for both LGG and HGG. This trend was also reported by Satoer etal in his metanalysis of 17 studies. [104] Other smaller studies have reported varied findings. [94- 103] We infer that this likely represents a transient decline in cognition due to the effects of surgery on the tumor bed. The domains of attention and memory were the most affected reflecting the effects of surgery and perhaps tumor location. The interval changes in cognition from T1- T2 revealed a reversal in decline as seen in the T0-T1 interval with 15 out of the 20 patients recording cognitive improvement beyond the baseline. The greatest improvement was in the domain of attention, fluency and memory. Not surprising and in-keeping with prior studies, the improvement was most marked in the domains most affected in the T0-T1 interval. [97,95] Further considerations of the T0-T2 overall change in cognition reveals that 85% of the patients recorded an improvement in cognition universally across all domains. This study thus shows that the general trend in cognition was a transient decline at one week postoperatively most likely due to the effects of surgery on the tumor bed, this was followed by a gradual improvement in cognition beyond the baseline across all cognitive domains over the next one month. The metanalysis by Satoer etal revealed an almost similar trend, however this study showed a significant improvement at the T1-T2 interval beyond the baseline. Additionally, and in converse to the Satoer metanalysis improvement was noted not just in the domains greatly affected at the T0-T1 interval but universally across all domains. Further analysis of the means scores at T0, T1 and T2 and their statistical significance reveals that indeed the interval change in the total scores was statistically significant with a P-Value of <0.025. This reflects the overall improvement in cognition as discussed above. Additionally, this improvement in cognition seems to have been largely due to improvement in the domains of memory and fluency which had P- values of 0.008 and 0.001 respectively. We can thus infer that within one month postoperatively our patients had a significant improvement in overall cognition with significant improvement noted in the memory and fluency domains. This change is likely due to several factors which include the decrease in the tumor volume

and hence the mass effect. Additionally, the fact that most of our patients had LGG could also explain the improvement. LGG represent a reduced lesion momentum and thus afford more time for plasticity and compensation of cognitive impairment. [78]These patients are naturally expected to score better cognitively and perhaps also have better improvement post surgically. The fact that most of the patients had subtotal resection of the tumors could also explain this finding. However, this is not uniformly demonstrated by prior studies. Mioto et al for instance, showed that a greater the extent of functional resection in LGG resulted in better cognitive outcome. [93]

Interestingly, the change in cognition was statistically significant only in the LGG especially in the fluency domain. The HGG which were the minority did not show any statistically significant change in cognition. This finding could largely be explained by the fact that LGG were the majority in the study albeit by a small margin. Additionally, the HGG trend when considering the mean of the total scores showed a nearly flat line. This shows that indeed the majority of HGG showed no change and if there was improvement it was probably to a small magnitude that was not statistically significant. Satoer etal report that most patients with HGG have significant impairment in cognition at baseline and this likely remains unchanged or declines postoperatively. Other studies have shown that even with supratotal resection of HGG the improvement in cognition is negligible and most patients still have profound impairment in the long term. [66,133]. This finding that HGG had no statistically significant improvement in cognition is thus surprising. Additionally, the decline in cognition could be an early indicator of progression. Indeed, two of the HGG unfortunately passed away within 8 weeks of surgery. These patients represent the small proportion of patients that had a decline in the one-month follow-up. It is likely that this decline did occur due to progression. [124] Another plausible reason for this finding in HGG could be because majority of this tumors were sub- totally resected. This corelates with the finding by Mioto etal discussed above.[93] We further considered the interval change in T0-T1, T1-T2, and T0-T2 and compared the change in HGG and LGG. None of the interval changes had a P value of <0.05. This finding is consistent with the metanalysis by Satoer etal and other studies that did not find a significant difference based on tumor characteristics. [104,134.] Notwithstanding the findings of these prior studies, the statistical insignificance is also likely due to the limited sample size and short follow up period. Further studies with bigger sample sizes and longer follow-up periods are required to conclusively answer this question.

In considering the differences in cognitive outcome for sub-totally versus the grossly resected tumors we considered the means scores at T0, T1 and T2 for each category. Notably, no statistically significant difference was seen in the total scores. However, for the subtotally resected tumors, majority of which were HGG, a significant change in attention, fluency, and visuospatial association was noted. The fact that these tumors were majorly HGG and whose initial presentation included visual loss and aphasia may explain this finding. Grossly resected tumors, majority of whom were LGG, showed a statistically significant change in memory, fluency. This closely reflects the overall change in cognition which as discussed above was majorly due to the improvement seen in the same domains in LGG. We sought to describe the interval change in T0-T1, T1-T2, and T0-T2 and compared the change in Subtotally and Grossly resected gliomas. None of the interval changes had a P- Value <0.05. This finding has been replicated by several studies but it could also be due to the limited sample size and the short follow-up period as noted above. [104, 134]

CONCLUSIONS.

1. Determination of cognitive outcome in supratentorial gliomas is a practical and useful outcome measure in the surgical management of gliomas.
2. Using the ACE III cognitive assessment tool, supratentorial gliomas show a transient decline in cognition one week postoperatively and gradual improvement across all cognitive domains at one month postoperatively.
3. Overall memory and fluency had the most significant improvement in cognition.
4. The initial transient decline in cognition is likely due to the effects of surgery on the tumor bed, while the gradual improvement is likely due to release of mass effect by the tumor, enhanced neuroplasticity, and the subtotal resection of tumors in our setting.
5. The improvement in cognition is most marked in LGG as compared to HGG.
6. At one month follow-up there was no statistically significant difference in the interval change in cognition at T0-T1, T1-T2 and T0-T2 intervals for both LGG and HGG. Although this is reflected in several studies it also is likely due to small sample size and short follow-up period.
7. At one month follow-up there was no statiscally significant difference in the interval change in cognition at T0-T1, T1-T2 and T0-T2 intervals for both Subtotally and Grossly resected tumors. Although this is reflected in several studies it also is likely due to a small sample size and short follow- up period.
8. Intraoperative adjuncts are not routinely used for glioma surgery in our setting. Their incorporation into routine surgical care will perhaps result in an even better cognitive outcome beyond what has been shown in this study.

LIMITATIONS OF THE STUDY.

1. The small sample size and the short follow- up period is a limitation. Longer follow-up periods coupled with an even bigger sample will provide more insight into the association between extent of resection, Histologic subtype and cognitive outcome.
2. Lack of immunohistochemical and molecular diagnosis in 19 out of the 20 patients.
3. Lack of preoperative MRI lesion volume calculation and post op MRI with accompanying residual volume calculation.

RECOMMENDATIONS.

1. Incorporate routine cognitive testing for Glioma patients both preoperatively and postoperatively.

2. Consider using ACE-III tool for routine clinical cognitive testing as suggested in 1 above.

3. Lobby for the inclusion of immunohistochemistry in the insurance package for brain tumor management for NHIF and other providers.

4. Develop guidelines that standardize the pre and post operative MRI imaging of glioma patients in our setting and align them with internationally recognized standards.

5. Consider redesigning a cognitive tool that is practically useful for glioma patients with KPS <70 who were excluded from this study.

6. Incorporate the regular use of adjuncts for maximum safe resection of gliomas.

APPENDICES

APPENDIX 1: CONSENT FORM ENGLISH

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:
EARLY NEUROCOGNITIVE OUTCOME POST RESECTION OF SUPRATENTORIAL GLIOMAS AT THE KENYATTA NATIONAL HOSPITAL

PRINCIPLE INVESTIGATOR

DR JEFFERSON WANYOIKE MWANGI

NEUROSURGERY RESIDENT, UNIVERSITY OF NAIROBI

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Introduction

Dr Jefferson Wanyoike is a senior Neurosurgery Resident at the UON. He is conducting research for his Masters of Medicine thesis. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the research. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form. Your decision to participate is entirely voluntary. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES ……. NO …….

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Protocol No. _____

WHAT IS THIS STUDY ABOUT?

This Research will assess the **functional outcome after surgery on gliomas,** which is on one of the commonest brain tumors. There will be approximately 35 participants in this study. These participants will be adults with a glioma and who meet our inclusion criteria. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in the study. The following will happen.

1. We will take you to a doctor's consultation room and one of our researchers will assign you a unique identification number that we shall use to track your record. The researcher will then ask you about your illness. He/she will then study your file and scans and record the findings on the data collection form. After which a brief Neurologic examination and an ACE-III cognitive test shall be done. This test is noninvasive. The Cognitive test and Neurologic examination can still be done later if you choose to but before the surgery. If you are eligible for surgery, Dr Jefferson shall organize to have your surgery within two weeks. If you're not eligible for surgery, then we shall proceed with other forms of treatment as we would normally do.
2. One week before the surgery, Dr Jefferson shall call you and give you instructions for admission as is the case with all our other elective patients. You will be required to come with all your medical records.
3. After the surgery within 72 hours. A Post-Operative Scan shall be done and another ACE-III cognitive assessment done. We will then continue treating you in the ward till discharge.
4. Within 3 months after discharge but not earlier than one month we shall review you again, and conduct the third Cognitive assessment and discuss the histology findings with you and advice you on the next course of action. We shall also provide you with a summary of your cognitive outcome. Any questions you have shall be answered.
5. You shall then be reviewed routinely in the Neurosurgery clinic after the third review.
6. Each interview shall last about 30 minutes.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview.

No additional surgical risk beyond what would be experienced outside of the study shall be introduced. If before surgery it is deemed that surgery is contraindicated, we shall act in your best interest and cancel the surgery. No new surgical technique shall be introduced beyond that which is routinely done for all our glioma patients. However, in the event that we have a surgical adjunct that the surgical team deems to be beneficial to you we shall inform you accordingly.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You will benefit by receiving free Cognitive testing. Should your test reveal need for further care we shall refer you appropriately. Also, the information you provide will help us better understand how our

surgery impacts patients with gliomas. This information is a contribution to science and helps improve patient outcomes.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Being in this study will not cost you anything beyond what you would have spent were you not part of the study. You will need to pay for your consultation, Lab works, drugs, imaging studies and histology besides the surgical fee.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

We shall endeavor to ensure that you do not spend anything beyond what you would have spent were you not a part of the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	Yes	No
I agree to have (define specimen) preserved for later study:	Yes	No
I agree to provide contact information for follow-up:	Yes	No

Participant printed name: …….

Participant signature / Thumb stamp …….Date …….

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher 's Name……. **Date**: ……...

Signature…….

For more information contact DR JEFFERSON WANYOIKE on 0721605980 or email @ jwjeffjunior86@gmail.com from 8:00am to 5:00 PM Monday to Friday

Witness

Name…… Signature /Thumb stamp: ……

Contact information…….. Date: .....

APPENDIX 2: CONSENT FORM SWAHILI VERSION.

RC/FORM/IC01

FOMU YA TAARIFA NA RIDHAA YA MSHIRIKI

MADA YA UTAFITI

MATOKEO YA AWALI YA UTAMBUZI BAADA YA UPSUAJI WA UVIMBE WA GLIOMAS KATIKA HOSPITALI YA RUFAA YA KENYATTA

MTAFITI MKUU
DR JEFFERSON WANYOIKE MWANGI

MKAZI WA UPASUAJI WA UBONGO KATIKA CHUO KIKUU CHA NAIROBI

MAWASILIANO: 0721605980

BARUA PEPE: jwjeffjunor86@gmail.com

UTANGULIZI

Daktari Jefferson Wanyoike in Mkazi mkuu wa Upasuaji wa Ubongo katika UON. Madhumuni ya fomu hii ya idhini ni kukupa taarifa utakayohitaji ili kukusaidia kuamua kama kuwa mshiriki au la katika utafiti. Jisikie huru kuuliza maswali yoyote kuhusu madhumuni ya utafiti, nini kitatokea ukishiriki katika utafiti, hatari na manufaa yanayoweza kutokea, haki zako kama mtu wa kujitolea, na jambo lingine lolote kuhusu utafiti au fomu hii ambalo haliko wazi. Wakati tumejibu maswali yako yote kwa kuridhika kwako, unaweza kuamua kuwa katika utafiti au la.Utaratibu huu unaitwa 'kibali cha taarifa'. Ukishaelewa na kukubali kuwa katika utafiti, nitakuomba utie sahihi jina lako kwenye fomu hii. Uamuzi wako wa kushiriki ni wa hiari kabisa. Unaweza kujiondoa kwenye utafiti wakati wowote bila kutoa sababu ya kujiondoa kwako. Kukataa kushiriki katika utafiti hakutaathiri huduma unazostahiki katika kituo hiki cha afya au vituo vingine. Tutakupa nakala ya fomu hii kwa rekodi zako.

Naweza kuendelea? NDIYO …….HAPANA …….

Utafiti huu umeidhinishwa na Itifaki ya Kamati ya Maadili na Utafiti ya Hospitali ya Kitaifa ya Kenyatta-Chuo Kikuu cha Nairobi No……..

UTAFITI HUU UNAHUSU NINI?

Utafiti huu utatathmini **matokeo ya utambuzi baada ya upasuaji kwenye uvimbe wa ubongo uitwao Glioma .** Uvimbe huu ni moja ya uvimbe wa kawaida wa ubongo. Kutakuwa na takriban washiriki 20 katika utafiti huu. Washiriki hawa watakuwa watu wazima walio na Glioma na wanaofikia vigezo vyetu vya kujumuishwa. Tunaomba idhini yako ili kuzingatia kushiriki katika utafiti huu.

NINI KITAENDELEA UKIAMUA KUWA KATIKA UTAFITI HUU?

Ikiwa unakubali kushiriki katika utafiti. Yafuatayo yatatokea.

1. **T**utakupeleka kwenye chumba cha mashauriano na mmoja wa watafiti wetu atakupa nambari ya kipekee ya utambulisho ambayo tutatumia kufuatilia rekodi yako. Kisha mtafiti atakuuliza kuhusu , makazi yako, ugonjwa wako, dawa zozote unazotumia na degedege. Kisha atasoma faili yako na kuchanganua na kurekodi matokeo kwenye fomu ya kukusanya data. Baada ya hapo uchunguzi mfupi wa Neurolojia na mtihani wa utambuzi wa ACE- III utafanywa. Uchunguzi wa Utambuzi na Uchunguzi wa Neurolojia bado unaweza kufanywa baadaye ikiwa utachagua lakini kabla ya upasuaji. Ikiwa unastahiki upasuaji, Daktari Jefferson atapanga kukufanyia upasuaji ndani ya wiki mbili. Iwapo hustahiki upasuaji basi tutaendelea na aina nyingine za matibabu.
2. Wiki moja kabla ya upasuaji, Daktari Jefferson atakupigia simu na kukupa maagizo ya kulazwa kama ilivyo desturi kwa wagonjwa wote wengine wanaokunja kwa upasuaji wa ubongo. Utahitajika kuja na rekodi zako zote za matibabu.
3. Baada ya upasuaji ndani ya wiki moja. Uchunguzi wa Baada ya upasuaji utafanywa na tathmini nyingine ya utambuzi ya ACE-III itafanywa. Tutakufuata hadi utakapotoka.
4. Ndani ya miezi 3 baada ya kuruhusiwa kutoka hospitalini tutakuona tena, na kufanya tathmini ya tatu ya Utambuzi na kujadili matokeo ya histolojia na wewe na kukushauri kuhusu hatua inayofuata. Pia tutakupa muhtasari wa matokeo yako ya utambuzi. Maswali yoyote uliyo nayo yatajibiwa.
5. Kisha utakaguliwa mara kwa mara katika kliniki ya Neurosurgery baada ya ukaguzi wa tatu.
6. Kila mahojiano yatadumu kama dakika 30.

JE, KUNA HATARI, MADHARA YOYOTE YANAYOHUSISHWA NA UTAFITI HUU?

Utafiti wa kimatibabu una uwezo wa kuanzisha hatari za kisaikolojia, kijamii, kihisia na kimwili. Jitihada zimewekwa kila wakati ili kupunguza hatari. Hatari moja inayoweza kutokea ya kuwa katika utafiti ni kupoteza faragha. Tutaweka kila kitu unachotuambia kama siri iwezekanavyo. Tutatumia nambari ya msimbo kukutambua katika hifadhidata ya kompyuta iliyolindwa na nenosiri na tutaweka rekodi zetu zote za karatasi kwenye kabati ya faili iliyofungwa. Hata hivyo, hakuna mfumo wa kulinda usiri wako unaoweza kuwa salama kabisa, kwa hivyo bado kuna uwezekano kwamba mtu anaweza kujua ulikuwa kwenye utafiti huu na kupata taarifa kukuhusu.

Pia, kujibu maswali katika mahojiano kunaweza kuwa na wasiwasi kwako. Ikiwa kuna maswali yoyote ambayo hutaki kujibu, unaweza kuyaruka. Una haki ya kukataa mahojiano au maswali yoyote yaliyoulizwa wakati wa mahojiano.

Hakuna hatari ya ziada ya upasuaji zaidi ya ile ambayo ingepatikana nje ya utafiti . Iwapo kabla ya upasuaji itaamuliwa kuwa upasuaji hauhitajiki, tutatenda kwa manufaa yako na kughairi upasuaji. Hakuna mbinu mpya ya upasuaji itakayoanzishwa zaidi ya ile ambayo hufanywa mara kwa mara kwa wagonjwa wetu wote wa glioma. Hata hivyo, katika tukio ambalo tuna kiambatanisho cha upasuaji ambacho timu ya upasuaji itaona kuwa ya manufaa kwako tutakujulisha ipasavyo.

JE, KUNA FAIDA YOYOTE KUWA KATIKA UTAFITI HUU?

Utafaidika kwa kupokea majaribio ya Utambuzi bila malipo. Iwapo utahitaji utunzaji zaidi, tutakuelekeza ipasavyo. Pia, maelezo utakayotoa yatatusaidia kuelewa vyema jinsi upasuaji wetu unavyoathiri wagonjwa wenye Glioma. Habari hii ni mchango kwa sayansi na husaidia kuboresha matokeo ya mgonjwa.

JE, KUWA KATIKA UTAFITI HUU KUTAGHARIMU CHOCHOTE?

Kuwa katika utafiti huu hakutakugharimu chochote zaidi ya kile ambacho ungetumia kama hukuwa sehemu ya utafiti. Utahitaji kulipia ushauri wako, kazi za Maabara, dawa, masomo ya picha na histolojia kando na ada ya upasuaji.

JE, UTAREJESHWA KWA PESA ZOZOTE ULIZOTUMIA SEHEMU YA UTAFITI HUU?

Tutajitahidi kuhakikisha kuwa hutumii chochote zaidi ya kile ambacho ungetumia kama hukushiriki katika utafiti.

VIPI IKIWA UNA MASWALI BAADAYE?

Ikiwa una maswali zaidi au wasiwasi kuhusu kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe mfupi wa maandishi kwa wafanyikazi wa utafiti kupitia nambari iliyotolewa chini ya ukurasa huu.

Kwa maelezo zaidi kuhusu haki zako kama mshiriki wa utafiti unaweza kuwasiliana na Katibu/Mwenyekiti, Hospitali ya Kitaifa ya Kenyatta-Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi Nambari 2726300 Ext. 44102 barua pepe uonknh_erc@uonbi.ac.ke.

Wafanyikazi wa utafiti watakurudishia malipo yako kwa nambari hizi ikiwa simu ni ya mawasiliano yanayohusiana na masomo.

UCHAGUZI WAKO MWINGINE NI GANI?

Uamuzi wako wa kushiriki katika utafiti ni wa hiari. Uko huru kukataa kushiriki katika utafiti na unaweza kujiondoa kwenye utafiti wakati wowote bila dhuluma au hasara ya manufaa yoyote.

KNH-UoN/ERC/FORM/IC0

FOMU YA RIDHAA (TAARIFA YA RIDHAA)

Kauli ya Mshiriki

Nimesoma fomu hii ya idhini au nimesomewa maelezo. Nimepata nafasi ya kujadili utafiti huu na mshauri wa utafiti. Nimejibiwa maswali yangu kwa lugha ninayoielewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu katika utafiti huu ni wa hiari na kwamba ninaweza kuchagua kujiondoa wakati wowote. Ninakubali kwa uhuru kushiriki katika utafiti huu.

Ninaelewa kuwa juhudi zote zitafanywa ili kuweka taarifa kuhusu utambulisho wangu wa kibinafsi kuwa siri.

Kwa kutia saini fomu hii ya idhini, sijaacha haki zozote za kisheria nilizo nazo kama mshiriki katika utafiti wa utafiti.

Ninakubali kushiriki katika utafiti huu: **Ndiyo**……☐….Hapana ☐

Ninakubali sampuli kuhifadhiwa kwa ajili ya utafiti wa baadaye: Ndiyo ☐ Hapana..☐

Ninakubali kutoa maelezo ya mawasiliano kwa ufuatiliaji: Ndiyo ☐ Hapana ☐

Jina lililochapishwa la mshiriki:……

Sahihi ya mshiriki / Muhuri wa kidole gumba…… …Tarehe……

Kauli ya mtafiti

Mimi, niliyetia sahihi chini, nimeeleza kikamilifu maelezo muhimu ya utafiti huu kwa mshiriki aliyetajwa hapo juu na ninaamini kuwa mshiriki ameelewa na ametoa ridhaa yake kwa hiari na kwa uhuru.

Jina la Mtafiti:……..Sahihi……..…Tarehe……..

Jukumu katika utafiti:……

Kwa maelezo zaidi wasiliana na DR JEFFERSON WANYOIKE kwa 0721605980 au barua pepe jwjeffjunior86@gmail.com kutoka 8:00 AM asubuhi hadi 5:00 PM Jumatatu hadi Ijumaa.

Shahidi

Jina……..Sahihi / Muhuri wa kidole gumba:……

Maelezo ya mawasiliano……Tarehe……

APPENDIX 3: DATA COLLECTION TOOL

A. PATIENT DEMOGRAPHICS

STUDY ID:

DOB

SEX:

RESIDENCE:

EDUCATIONAL LEVEL:

B. DETAILS OF PRESENTING ILLNESS

1. **ILLNESS DURATION:**
2. **SYMPTOMS AND SIGNS: -**
   1.
   2.
   3.
   4.
   5.
   6.
   7.
3. **ANTICONVULSANT USE: - YES** **NO.**
4. **IF YES TO 3 ABOVE SPECIFY THE ANTICONVULSANT DRUG CURRENTLY USING**
5. **IF YES TO 3 SPECIFY DURATION OF ANTICONVULSANT USE: -**
6. **STEROID USE: - YES** **NO**
7. **IF YES TO 6 ABOVE WHAT IS THE DURATION OF STEROID USE**
8. **ANY COMORBIDITIES (DIABETES, HYPERTENSION, ASTHMA, HIV, STROKE, OTHERS)**

1.

2.

3.

4.

5.

9. **HANDEDNESS: RIGHT** ☐ **LEFT** ☐

10. **PRIOR HEAD INJURY: YES** ☐ **NO** ☐

11. **KPS SCORE:** ☐

C. PREOPERATIVE IMAGING DETAILS

1. IMAGING MODALITY HEAD CT SCAN ☐ **MRI BRAIN** ☐

2. SIDE OF THE LESION: RIGHT ☐ **LEFT** ☐

3. LESION VOLUME: ☐

4. LESION LOCATION: - ☐

5. IS THERE PERILESIONAL OEDEMA: - YES ☐ **NO** ☐

6. PREOPERATIVE RADIOLOGIC DIAGNOSIS: ☐

D. HISTOLOGY DETAILS

1. **HISTOLOGIC DIAGNOSIS: -** ☐
2. **WHO GRADE: -** ☐
3. **IMMUNOHISTOCHEMISTRY: -** ☐

E. POSTOPERATIVE IMAGING DETAILS

1. IMAGING MODALITY: HEAD CT SCAN ☐ **MRI BRAIN** ☐

2. RESIDUAL TUMOR VOLUME:

4. EXTENT OF RESECTION:

4. INTRAOPERATIVE ADJUNCT USED:

(Indicate NONE if no adjunct used)

APPENDIX 4: ACE III COGNITIVE ASSESSENT TOOL

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

STUDY ID:.....

Date of testing:___/___/____
Tester's name:_____
Age at leaving full-time education:_____
Occupation: _____
Handedness: _____

ATTENTION

➢ Ask: What is the ➢ Ask: Which	Day _____ No./Floor	Date _____ Street/ Hospital	Month _____ Town	Year _____ County	Season _____ Country	**Attention** [Score 0-5] ☐ **Attention** [Score 0-5] ☐

ATTENTION

➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later".
➢ Score *only* the first trial (repeat 3 times if necessary).
➢ Register number of trials: _____

Attention [Score 0-3] ☐

ATTENTION

➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop."
➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4).
➢ Stop after five subtractions (93, 86, 79, 72, 65): ____ ___ ___ - ____

Attention [Score 0-5] ☐

MEMORY

➢ Ask: 'Which 3 words did I ask you to repeat and remember?' _____ _____

Memory [Score 0-3] ☐

FLUENCY

➢ **Letters**
Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".

Fluency [Score 0 – 7] ☐

				≥ 18	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				0-1	0
				total	correct

➢ **Animals**
Say: "Now can you name as many animals as possible. It can begin with any letter."

Fluency [Score 0 – 7] ☐

				≥ 22	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

M E M O R Y

Memory
[Score 0 – 7]

- Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

	1st Trial	***2nd Trial***	*3rd Trial*
JOHN KUKI P.O BOX 331- 0028 RUARAKA NAIROBI			

M E M O R Y

Memory
[Score 0 – 4]

- Name of the current President of Kenya.....
- Name of the Kenyan president who served for 24 years.. .....
- Name of the current USA president..... .....
- Name of the USA president whose father was Kenyan..... .....

L A N G U A G E

Language
[Score 0-3]

- Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "**Pick up the pencil and then the paper**." If incorrect, score 0 and do not continue further.
- If the subject is correct on the practice trial, continue with the following three commands below.
  - Ask the subject to "**Place the paper on top of the pencil**"
  - Ask the subject to "**Pick up the pencil but not the paper**"
  - Ask the subject to "**Pass me the pencil after touching the paper**" Note: Place the pencil and paper in front of the subject before each command.

L A N G U A G E

Language
[Score 0-2]

- Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations. Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

L A N G U A G E

Language
[Score 0-2]

- Ask the subject to repeat: **'caterpillar'; 'eccentricity; 'unintelligible'; 'statistician'**

Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.

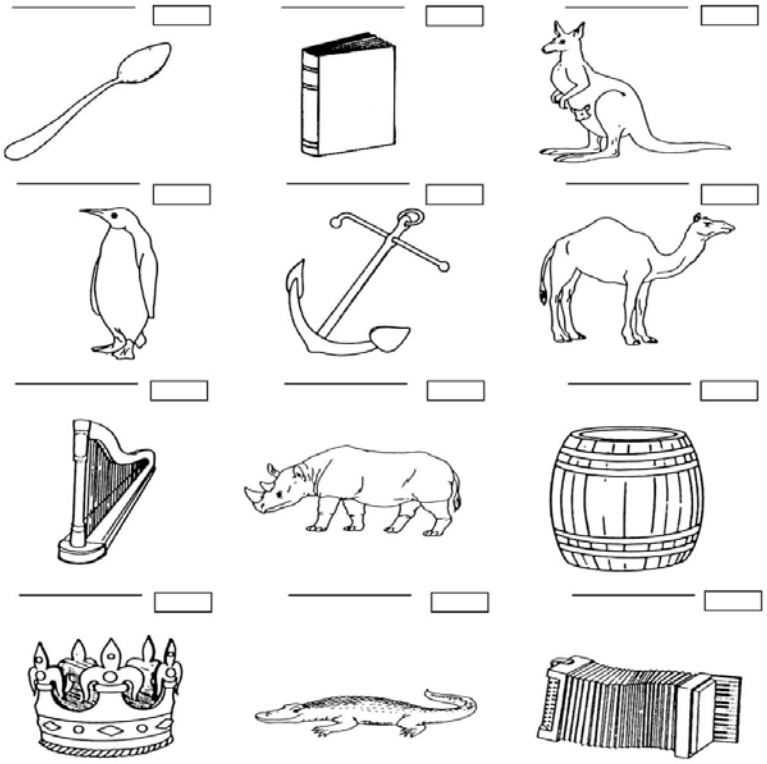
L A N G U A G E

➢ Ask the subject to repeat: **'All that glitters is not gold'**	**Language** [Score 0-1] ☐
➢ Ask the subject to repeat: **'A stitch in time saves nine'**	**Language** [Score 0-1] ☐

L A N G U A G E

Language [Score 0-12] ☐

➢ Ask the subject to name the following pictures:



L A N G U A G E

Language [Score 0-4] ☐

➢ Using the pictures above, ask the subject to:
- Point to the one which is associated with the monarchy
  .....
- Point to the one which is a marsupial
  .....
- Point to the one which is found in the Antarctic
  .....
- Point to the one which has a nautical connection
  .....

L A N G U A G E

➢ Ask the subject to read the following words: (Score 1 only if all correct)

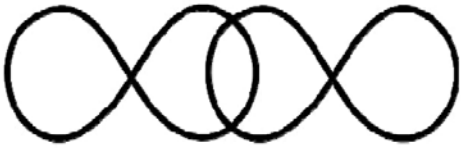
Language
[Score 0-1]
☐

sew
pint
soot
dough
height

V I S U O S P A T I A L A B I L I T I E S

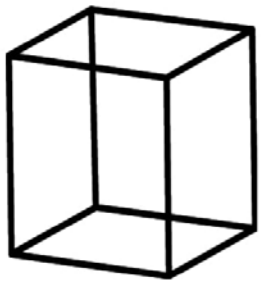
➢ Infinity Diagram: Ask the subject to copy this diagram

Visuospatial
[Score 0-1]
☐



➢ Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).

Visuospatial
[Score 0-2]
☐



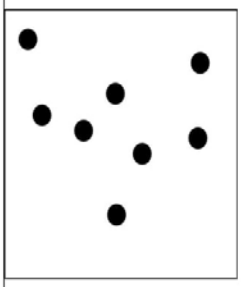
➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).

Visuospatial
[Score 0-5]
☐

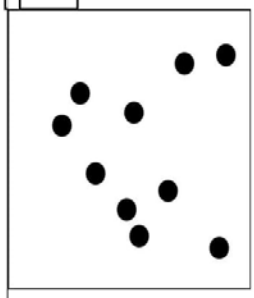
VISUOSPATIAL ABILITIES

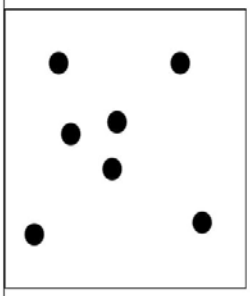
- Ask the subject to count the dots without pointing to them

Visuospatial
[Score 0-4]
☐

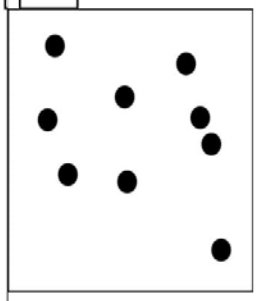


☐





☐



VISUOSPATIAL ABILITIES

- Ask the subject to identify the letters

Visuospatial
[Score 0-4]

MEMORY

- Ask “Now tell me what you remember about that name and address we were repeating at the beginning”

JOHN KUKI PO BOX 331- 0028 RUARAKA NAIROBI	....	**Memory** [Score 0-7]

MEMORY

- This test should be done if the subject failed to recall one or more items above. It all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right-hand side; and then test not recalled items by telling the subject “Ok, I’ll give you some hints: was the name X, Y or Z?” and so on. Each recognized item scores one point, which is added to the point gained by recalling.

Memory
[Score 0-5]

JOHN KUKI		JOHN KUKI		JOHN KUKI		recalled	
PO BOX		PO BOX		PO BOX		recalled	
331-0028		331-0028		331-0028		recalled	
RUARAKA		RUARAKA		RUARAKA		recalled	
NAIROBI		NAIROBI		NAIROBI		recalled	

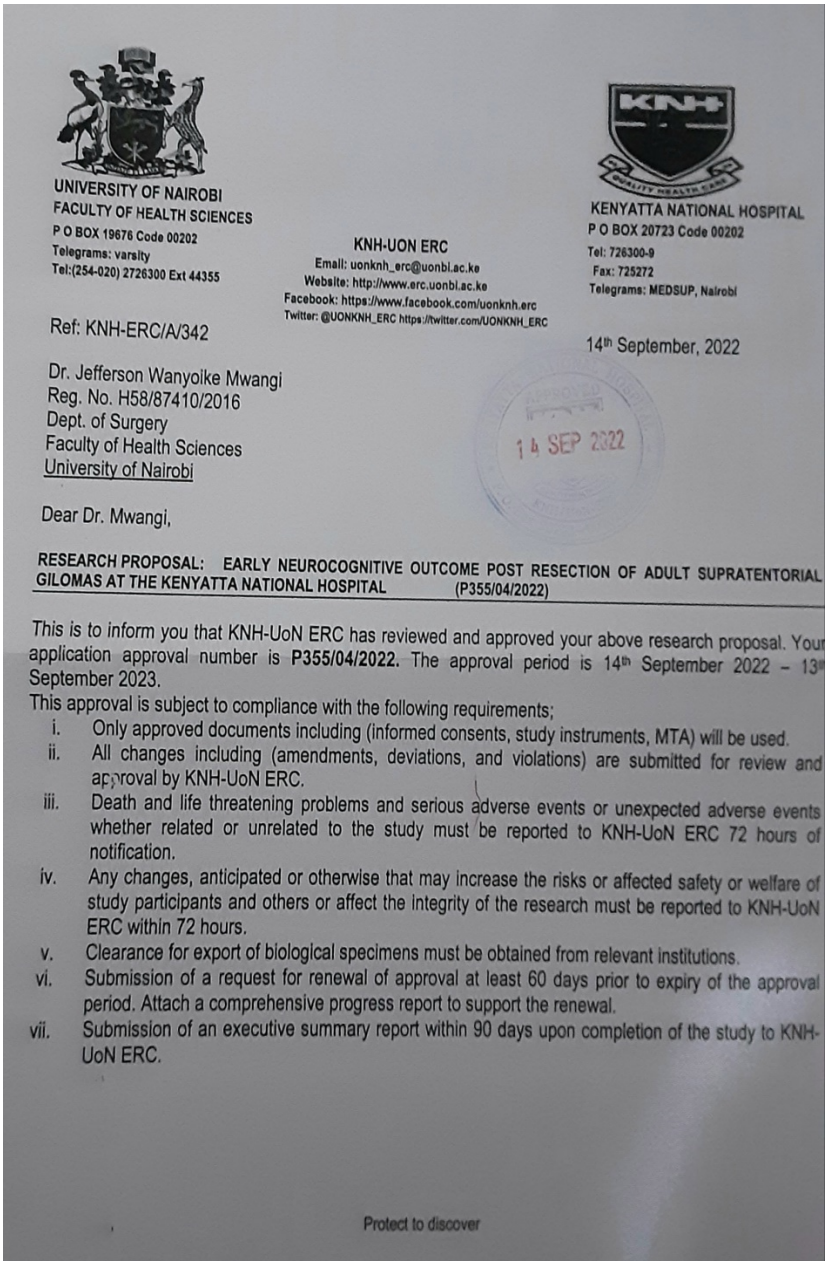
SCORES

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/ 26
Visuospatial	/16

APPENDIX 5: KPS SCORE

Score, %	State of Health
100	Healthy, no symptoms or signs of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment

APPENDIX 6 : KNH-UON ERC APROVAL



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14th September, 2022

14 SEP 2022

Dr. Jefferson Wanyoike Mwangi
Reg. No. H58/87410/2016
Dept. of Surgery
Faculty of Health Sciences
University of Nairobi

Dear Dr. Mwangi,

RESEARCH PROPOSAL: EARLY NEUROCOGNITIVE OUTCOME POST RESECTION OF ADULT SUPRATENTORIAL GILOMAS AT THE KENYATTA NATIONAL HOSPITAL (P355/04/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P355/04/2022.** The approval period is 14th September 2022 – 13th September 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Protect to discover

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