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Review Article

Dilemma in low-grade glioma surgery: Review of litreture and when to operate

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ABSTRACT

Diffuse low-grade gliomas (LGG) are tumours of the glial tissue, which are generally slow-growing, but have the potential to undergo anaplastic progression into more aggressive tumours. Diffuse low-grade gliomas (LGG) represent a heterogeneous group of primary brain tumour arising from supporting glial cells. The role of surgery in the management of human low- gliomas has been controversial. The current adjuvant therapies have facilitated treatment of patients, and have rendered neurosurgical removal without morbidity or mortality more commonplace than ever before. Here, we investigated the role of neurosurgery in the management of adults with low-grade gliomas. The management of low- grade glioma is one of the most controversial areas in clinical neuro-oncology. The concept of management of low-grade gliomas is not unitary but much more a composite of different challenges depending on the clinical presentation, signs, neuroradiology, perspectives of neurologists, the opinion of the neurosurgeon, and perhaps most importantly, the aspirations of the patient. It is true therefore that in many patients there will be a dilemma about what is considered optimal management since there is no good evidence base to underpin any single management. Even though there is substantial evidence which claims that surgery have a role to play in extending patient survival.

1. Introduction

Low-grade Gliomas are the common primary tumors of the central nervous system (CNS), representing approximately 50% of the newly diagnosed brain tumors. In the past, these diffuse gliomas were classified into different subtypes and grades based on histopathology such as a diffuse astrocytoma, oligodendrogliomas, or mixed gliomas/oligoastrocytomas. Recently, gliomas were classified based on molecular and genetic markers[1]. These advances have more specific prognostic and therapeutic benefits for patients with gliomas. In addition to molecular and genetic markers, gliomas are classified in grade I to IV based on the degree of proliferation indicated by the mitotic index and the presence or absence of necrosis.

There are three common types of gliomas, which are classified based on the phenotypic cell characteristics: astrocytomas, ependymomas, and oligodendrogliomas. These cell gliomas are further classified to low grade, atypical, and high-grade tumors based on cell morphology, mitotic activities, and molecular marker. The World Health Organization (WHO) grading system utilizes molecular markers that have shown to have significant prognostic and therapeutic implications.

1. **Astrocytomas**: Originated from astrocytes and can be encapsulated, preserving clear borders between normal and tumor cells, or infiltrative, indicating advanced grade. Low grades are common in children while high grades are common in young adults and older patients.

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2. **Oligodendrogliomas**: Originated from oligodendrocyte cells. These are less infiltrating than astrocytomas and are common in adults.
3. **Ependymomas:** Originated from ependymal cells which are found lining the ventricular cavities and the central canal of the spinal cord. These are common in the paediatric patient population.

2. Materials and Methods

This study was conducted at Neurosurgery department LLRM Medical College Meerut, CNS Hospital (Neuro super speciality hospital, Meerut) and nearby hospitals of Meerut city. The patients admitted to SVBP Hospital neurosurgery department for treatment from January 2020 to December2021 included on the basis of radiological finding suggestive of low grade glioma (GLL).

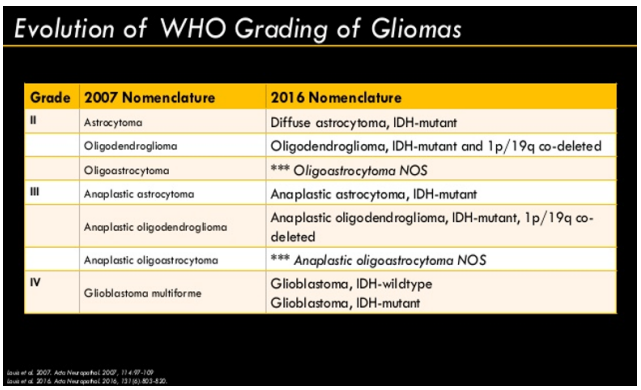
3. Review of Literature

Gliomas account for the great majority of primary tumours that arise within the brain parenchyma. The term "glioma" refers to tumours that have histologic features similar to normal glial cells (i.e., astrocytes, oligodendrocytes, and ependymal cells). For each of these types of gliomas, there are neoplasms that span a broad spectrum of biologic aggressiveness.

Historically, the slower-growing lesions, corresponding to World Health Organization (WHO) grades I and II, have been commonly referred to as low-grade gliomas, while the more rapidly progressive tumours are referred to as high-grade gliomas.

Classification and grading of gliomas have evolved over time, beginning in 1926 with a system devised by Bailey and Cushing and later revised by Kernohan, Ringertz, and others. The resulting classification, published by Bailey and Cushing in 1925, demonstrated that the cellular structure of a tumour can guide treatment and prognosis. And it laid the groundwork for the system presented by the World Health Organization in 2016 to describe and diagnose gliomas: tumours that arise from glia, the various types of supportive cells of the central nervous system. Modern classification of gliomas is based on the World Health Organization (WHO) Classification of Central Nervous System Tumors, first published in 1979 and revised four times since then, most recently in 2016.

As of the 2016 edition of the WHO classification, gliomas are classified based not only on histopathologic appearance but also on well-established molecular parameters. The identification of distinct genetic and epigenetic profiles in different types of gliomas has revealed novel diagnostic, prognostic, and predictive molecular biomarkers for refinement of glioma classification and improved prediction of therapy response and outcome. Therefore, the new (2016) World Health Organization (WHO) classification of tumors of the central nervous system breaks with the traditional principle of diagnosis based on histologic criteria only and incorporates molecular markers. This will involve a multilayered approach combining histologic features and molecular information in an "integrated diagnosis". We review the current state of diagnostic molecular markers for gliomas, focusing on isocitrate dehydrogenase 1 or 2 (IDH1/IDH2) gene mutation, α-thalassemia/mental retardation syndrome X-linked (ATRX) gene mutation, 1p/19q co-deletion and telomerase reverse transcriptase (TERT) promoter mutation in adult tumors, as well as v-raf murine sarcoma viral oncogene homolog B1 (BRAF) and H3 histone family 3A (H3F3A) aberrations in pediatric gliomas.



The international classification of human tumours published by the World Health Organization (WHO) was initiated through a resolution of the WHO Executive Board in 1956 and the World Health Assembly in 1957. Its objectives have remained the same until today: to establish a classification and grading of human tumours that is accepted and used worldwide. Without clearly defined histopathological and clinical diagnostic criteria, epidemiological studies and clinical trials could not be conducted beyond institutional and national boundaries.

The first edition on the histological typing of tumours of the nervous system was edited by Zülch and published in 1979. The second edition reflected the advances brought about by the introduction of immunohistochemistry into diagnostic pathology; it was edited by Kleihues et al. The third edition, edited by Kleihues and Cavenee and published in 2000, incorporated genetic profiles as additional aids to the definition of brain tumours.

4. Nomenclature of Glioma

Combining histopathological and molecular features into diagnoses necessarily results in portmanteau diagnostic terms and raises the need to standardize such terminology in as practical a manner as possible. In general, the 2016 CNS WHO decision was to approximate the naming conventions of the hematopoietic/lymphoid pathology

community, which has incorporated molecular information into diagnoses in the past. As detailed below, CNS tumour diagnoses should consist of a histopathological name followed by the genetic features, with the genetic features following a comma and as adjectives, as in: Diffuse astrocytoma, IDH mutant and Medulloblastoma, WNT-activated.

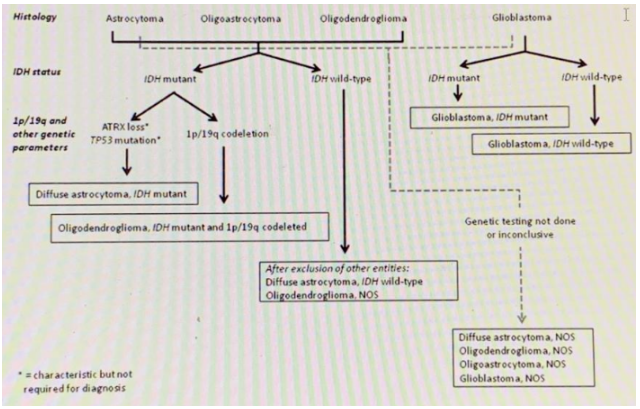
For those entities with more than one genetic determinant, the multiple necessary molecular features are included in the name: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted.

For a tumour lacking a genetic mutation, the term wildtype can be used if an official "wildtype" entity exists: Glioblastoma, IDH-wildtype. However, it should be pointed out that in most such situations, a formal wildtype diagnosis is not available, and a tumour lacking a diagnostic mutation is given an NOS designation.

For tumour entities in which a specific genetic alteration is present or absent, the terms "positive" can be used if the molecular characteristic is present: Ependymoma, RELA fusion–positive.

For sites lacking any access to molecular diagnostic testing, a diagnostic designation of NOS (i.e., not otherwise specified) is permissible for some tumour types. These have been added into the classification in those places where such diagnoses are possible. An NOS designation implies that there is insufficient information to assign a more specific code. In this context, NOS in most instances refers to tumours that have not been fully tested for the relevant genetic parameter(s), but in rare instances may also include tumours that have been tested but do not show the diagnostic genetic alterations. In other words, NOS does not define a specific entity; rather it designates a group of lesions that cannot be classified into any of the more narrowly defined groups. An NOS designation thus represents those cases about which we do not know enough pathologically, genetically and clinically and which should, therefore, be subject to future study before additional refinements in classification can be made.

With regard to formatting, italics are used for specific gene symbols (e.g., ATRX) but not for gene families (e.g., IDH, H3). To avoid numerous sequential hyphens, wildtype has been used without a hyphen and en-dashes have been used in certain designations (e.g., RELA fusion–positive). Finally, as in the past, WHO grades are written in Roman numerals (e.g., I, II, III and IV; not 1, 2, 3 and 4)



Simplified algorithm for classification of the diffuse gliomas based on histological and genetic features

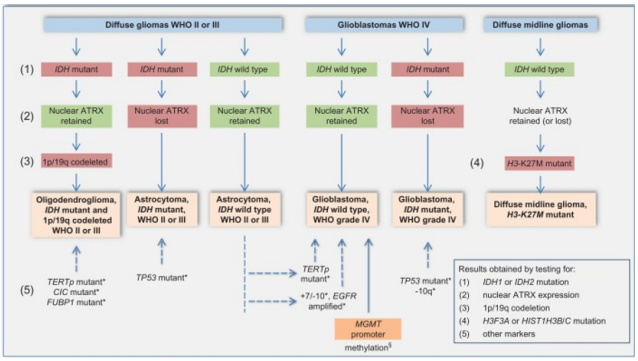
The WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into IDH-mutant, IDH-wildtype and NOS categories. For both grade II and III tumors, the great majority falls into the IDH-mutant category if IDH testing is available. If immunohistochemistry for mutant R132H IDH1 protein and sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations are both negative, or if sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations alone is negative, then the lesion can be diagnosed as IDH-wildtype. Finally, in the setting of a diffuse astrocytoma or anaplastic astrocytoma, if IDH testing is not available or cannot be fully performed (e.g., negative immunohistochemistry without available sequencing), the resulting diagnosis would be diffuse astroctyoma, NOS, or anaplastic astrocytoma, NOS, respectively.

4.1. Glioblastomas

Gliomatosis cerebri has also been deleted from the 2016 CNS WHO classification as a distinct entity, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendroglial tumors as well as IDH-wildtype glioblastomas. Thus, widespread brain invasion involving three or more cerebral lobes, frequent bilateral growth and regular extension to infratentorial structures is now mentioned as a special pattern of spread within the discussion of several diffuse glioma subtypes

Glioblastomas are divided in the 2016 CNS WHO into (1) glioblastoma, IDH-wildtype (about 90 % of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age (2) glioblastoma, IDH-mutant (about 10 % of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients and (3) glioblastoma, NOS, a diagnosis that is reserved for those tumors for which

full IDH evaluation cannot be performed. The definition of full IDH evaluation can differ for glioblastomas in older patients relative to glioblastomas in younger adults and relative to WHO grade II and grade III diffuse gliomas: in the latter situations, IDH sequencing is highly recommended following negative R132H IDH1 immunohistochemistry, whereas the near absence of non-R132H IDH1 and IDH2 mutations in glioblastomas from patients over about 55 years of age suggests that sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry in such patients



5. Discussion

5.1. Low grade gliomas

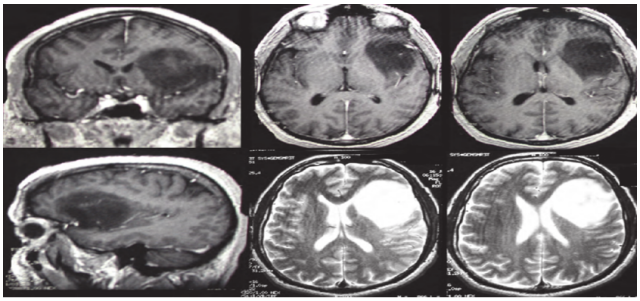
In the classic literature, the vast majority of authors considered LGG as a “stable” and “benign” brain tumour. Therefore, the “wait and see” approach was advocated for many years. Second, it was traditionally thought that this infiltrative tumour cannot be removed without generating functional consequences Third, mainly based on the subjective estimation of the extent of resection by the neurosurgeon, it was argued that surgical removal had no impact on the natural history of LGG. Thus, it was common to perform only a biopsy in order to obtain samples for neuropathological examination, and then to choose between a single follow-up or radiotherapy according to the morphological criteria established by the WHO classification.

5.2. Clinical presentation

LGG usually affects young adults. After an asymptomatic period that lasts several years seizures are the most common presentation and may be partial or generalized. They occur in about 80 to 90% of patients and are intractable in 50%. Seizures are mainly due to cortical invasion, there is no clear association between severity of epilepsy and behaviour of the tumour. Focal neurologic deficits due to mass effect, haemorrhage, and intracranial hypertension are not common presenting features.

5.3. Imaging

On magnetic resonance imaging (MRI), LGG is characteristically homogeneously isointense to hypointense on T1-weighted images and hyperintense on T2/fluid-attenuated inversion recovery (FLAIR)-weighted images.



Recent advances in MRI sequence development and use provided a new conceptual approach to diagnosis and follow-up of LGG based on a multipara metrical and dynamic study of metabolism enabled by spectroscopy (even multinuclear) and perfusion-weighted imaging, namely, oncological bio metabolic imaging. Dynamic susceptibility contrast MRI (DSC-MRI) enables the measurement of relative cerebral blood volume (r CBV), which is associated with vascularity. In astrocytoma, increase in r CBV in LGG predicts malignant transformation before contrast enhancement occurs. From a functional point of view, advances in functional neuroimaging, for example, functional MRI (fMRI), magnetoencephalography, diffusion tensor imaging (DTI), and, more recently, transcranial magnetic stimulation, have enabled us to perform a non invasive mapping of the whole brain. These techniques estimate the location of the eloquent areas (e.g., regions involved in sensorimotor, language, visual, and even higher cognitive functions) in relation to the glioma, and provide information with regard to the hemispheric language lateralization. Correlations with intraoperative electrophysiology have recently demonstrated that the sensitivity of fMRI is currently 59 to 100% for language (specificity, 0% to 97%).[1]

5.4. Impact of surgical resection in LGG

In all the recent series based on an objective postoperative evaluation of Extent of resection on T2/FLAIR-MRI, a more aggressive resection predicted a significant improvement in Overall survival compared with a simple debulking. In a series examining 216 LGGs, after adjusting for the effects of age, KPS score, tumour location, and tumour subtype, Extent of Resection remained a significant predictor of Overall Survival (hazard ratio [HR], 0.972; 95% confidence interval [CI], 0.960–0.983; $p < 0.001$), with 98% of patients with complete resection having an Overall survival of 8 years.[2] In another series of 156 LGGs, patients who

underwent incomplete resection were at 4.9 times the risk of death relative to patients with total resection.[3] In a study of 130 LGGs, extended surgery was shown to significantly prolong Overall Survival.[4]

It was also reported that, in an experience with 314 LGG patients, adverse prognostic factors for Overall Survival identified by multivariate analysis were tumor size 5 cm or larger, presentation with sensory motor symptoms, pure astrocytoma histology, Kernohan grade 2, and less than subtotal resection.[5] In 190 LGGs, it was demonstrated that patients with an EOR of 90% or greater had an estimated 5-year OS rate of 93%, those with EOR between 70% and 89% had a 5-year OS rate of 84%, and those with EOR less than 70% had a 5-year OS rate of 41% ($p < 0.001$).[6] Recently, one study investigated survival in population-based parallel cohorts of LGGs from two Norwegian university hospitals with different surgical treatment strategies.[7] The study found that treatment at a center that favored early surgical resection was associated with better OS (median survival not reached) than treatment at a center that favored biopsy and watchful waiting (median survival 5.9 years; 95% CI, 4.5-7.3). Finally, the French Glioma Network published the largest surgical series of LGG ever reported, 1,097 patients, and found that Extent of Resection as well as the postsurgical residual volume were independent prognostic factors significantly associated with a longer Overall Survival.[8]

5.5. Adjuvant therapy

Adjuvant therapy could be considered in high-risk patients—those with partial resection (with a residual volume > 10–15 cc) or with rapid progression calculated on regular postoperative MRIs performed every 6 months (or every 3 months in LGGs with foci of malignant transformation on pathological examination). Postoperative intractable seizures can also be an indication for adjuvant treatment.

5.6. Chemotherapy

Chemotherapy has shown clinical benefits against tumor progression for patients who cannot be ooperated or re-operated on due to a diffuse involvement of eloquent structures by the tumor. Procarbazine, chloroethylcyclohexylnitrosourea (CCNU; lomustine), and vincristine (PCV) and temozolomide (TMZ) yield similar objective response rates on MRI, with more than 90% of patients experiencing initial decrease of the mean tumor diameter.[9] However, a toxicity profile favors TMZ in terms of better tolerability (reduced myelotoxicity) and Quality of Life. Patients more likely to respond have oligodendroglial tumors, but mixed or astrocytic tumors may respond as well. A stronger role for chemotherapy with surgery has been discussed more recently in unresectable tumors, by allowing glioma shrinkage due to neoadjuvant chemotherapy and thus making surgery (with total or at least subtotal removal) possible.[10]

5.7. Radiotherapy

Two phase 3 randomized trials demonstrated no advantage for high versus low radiation doses, with increased toxicity for higher doses (EORTC 22844 and North Central Cancer Treatment Group [NCCTG]). Regarding the timing of radiotherapy (RT), one study demonstrated that early RT had no impact on overall survival (despite an improved PFS; EORTC 22845).[11] Recently, Radiation Therapy Oncology Group (RTOG) trial 9802 compared RT alone with RT plus PCV, the probability of Overall Survival for an additional 5 years was 74% with RT + PCV versus 59% with RT alone (HR, 0.52; 95% CI, 0.30–0.90; log-rank p = 0.02).[12]

5.8. Observation

In this study total 56 patients were included who were presented with features of headache, vomiting, seizures and focal neurological deficit and CTSCAN Brain or MRI brain showing SOL suggestive of glioma.

Age distribution: Age of patients ranges from 15 years to 80 years.

Table 1: Age distribution of patients having intracranial SOL.

Age group in years	No. of patients (N)	Percentage %
15 yrs to 25 yrs	2	3.57%
26 yrs to 35 yrs	05	8.92%
36 yrs to 45 yrs	10	17.85%
46 yrs to 55 yrs	12	21.42%
56 yrs to 65 yrs	15	26.79%
66 yrs to 75 yrs	10	17.85
76 yrs and more	02	3.57%
Total	N=56	100%

Sex distribution: Total 56 patient were studied in which 32 were male and 24 were female.Table 1

Table 2: Sex distribution

Total no. patients	Male no. and %	Female no. and %
N= 56	N= 32 and 57.14%	N=24 and 42.86%

5.9. Clinical features

Head ache and vomiting, seizures and weakness are common presentation of these patients.

Investigation: Studies investigating the growth rate of LGG have consistently demonstrated that LGG grow continuously prior to anaplastic progression, despite often appearing static on the subjective visual analysis of interval

Table 3: Showing Sign and symptoms of patients presented with ICSOL.

Sign and Symptoms	No. (N)of patients
Headache	N=48
Vomiting	N=40
Seizures	N=46
Vertigo	N=10
Altered sensation in limbs	N=8
Visual disturbances	N=5
Weakness (focal neurological deficit)	N=18
Speech difficulty/Aphasia	N=6

imaging examinations, demonstrating that LGG are actually not "stable" as initially thought. The majority of studies use velocity of diametric expansion 3(VDE) as a measure of growth rate.[13] This is obtained from a series of measurements and calculations: the tumour volume is measured using axial images and manual segmentation.

Table 4: Number of patients showing high grade and low grade radiological features.

Number of patients	Low grade	High grade
N=56	N=26	N=30

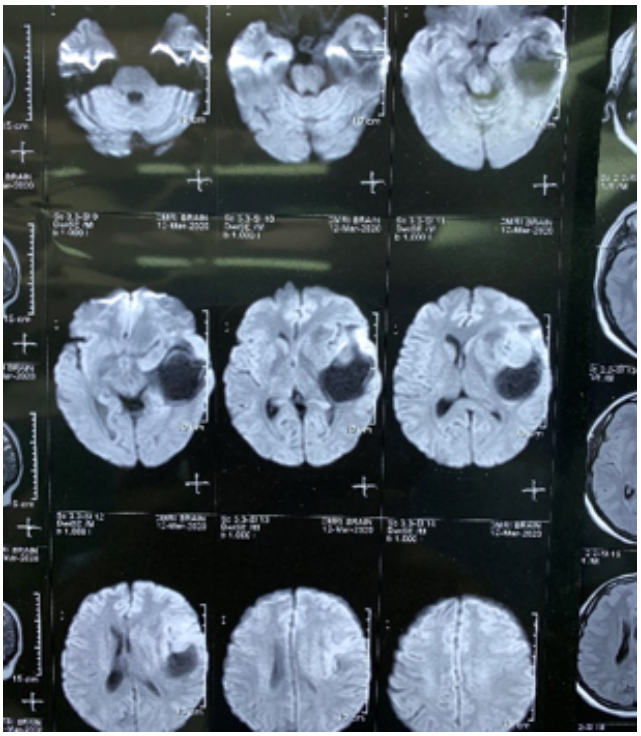


Fig. 1: MRI T1weighted image

5.10. Treatment and management

Out of 26 patients only12 patients were operated and rest were treated conservatively due to some patients well manage conservatively and some cases consent weren't given. Mostly patients having persistent features of raised ICP, having high growth rate and having mass effects i.e. mid line shift more than 5mm or uncontrolled seizures were operated. CUSA was used to resect the tumour near to allocate area of brain.

Table 5: Showing number of patients treated conservatively and surgically.

Number of patients	Treated surgically	Treated conservatively
N=26	N=12	N=14

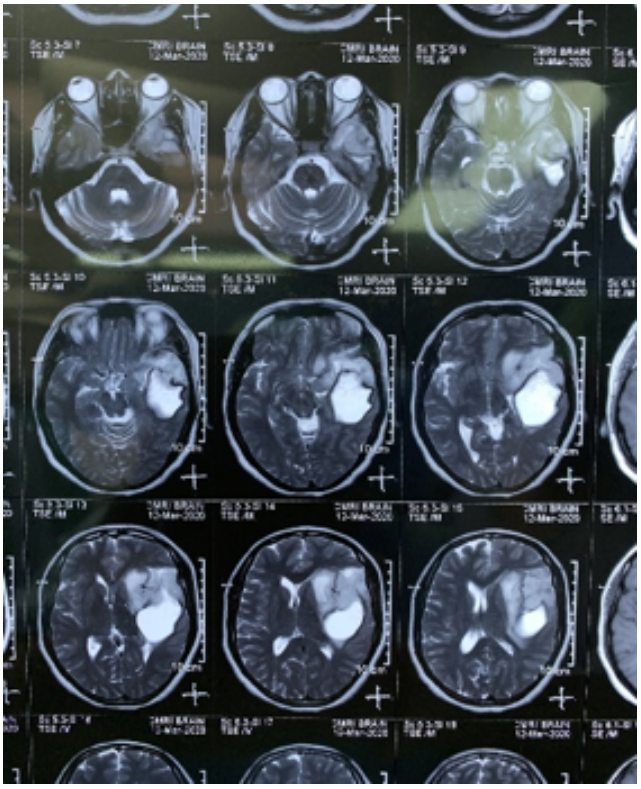


Fig. 2: T2 weighted image

6. Conclusion

Our review investigated numerous reports in the literature supporting the importance of surgery for the treatment of low- and high-grade gliomas. Many articles showed the impact of more extensive and aggressive resections. However, most of the studies are retrospective or multivariate and nonrandomized in nature. Today, the management of these patients relies on combined therapies, which have been evolving over the last two decades. Concerning the role of surgery in patients with LGGs and

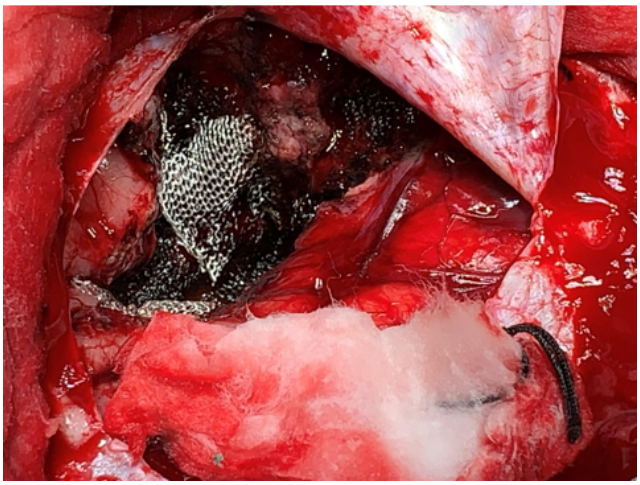


Fig. 3: Intraoperative photograph after near total excision of lesion.

HGGs, it is hoped that definitive trials lie just ahead. For the moment, clinicians should continue to individualize the management of their patients, taking into account the patient's age, tumour location, imaging studies, pathology of the tumour, and prognostic molecular markers.[14]

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.

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