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Role of surgery in the management of low grade glioma

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ROLE OF SURGERY IN THE MANAGEMENT OF LOW GRADE GLIOMA

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Management of low grade glioma (LGG), particularly with regards to the role of surgery, is not clear to most clinicians. LGG constitutes only a small subset of gliomas, the most common type of primary brain tumors. Primary brain tumors, in turn, make up two-thirds of all brain tumors, and half of all primary brain tumors are gliomas (Figure 1).[1] As the name implies, gliomas originate from glial cells, primarily astrocytes and oligodendrocytes. They are classified, based on their cell of origin, into astrocytomas and oligodendrogliomas. Histopathological features determine the degree of biological malignancy, which is not divided into discrete categories but actually forms a biological continuum (Table 1).

It is not uncommon to find gliomas that seem to be a combination of astrocytoma and oligodendroglioma cells - these are called oligoastrocytomas. Those astrocytomas that show all the features of malignancy, particularly necrosis, are termed glioblastoma multiforme (GBM), which is the most malignant variant of astrocytoma. Oligodendrogliomas, as they undergo anaplastic de-differentiation, acquire histopathologic features and clinical behavior indistinguishable from GBM.

TABLE 1

Histopathological Features of Glioma

- Nuclear atypia and pleomorphism
- Mitotic figures
- Endothelial proliferation
- Necrosis
- Cellularity and cellular pleomorphism

LOW GRADE GLIOMA COMPRISES ASTROCYTOMA AND OLIGODENDROGLIOMA LACKING MALIGNANT HISTOLOGICAL FEATURES

According to the World Health Organization (WHO) classification, astrocytomas range from grades I through IV,[2] with grade IV corresponding to GBM whereas grade I corresponds to a subset of biologically benign tumors of which pilocytic astrocytoma is the most common. This latter variant is considered by some experts to be a different pathological entity altogether, even though it seems to represent the benign end of the astrocytoma histopathology spectrum. Prognosis in grade I astrocytoma

Figure 1(a)

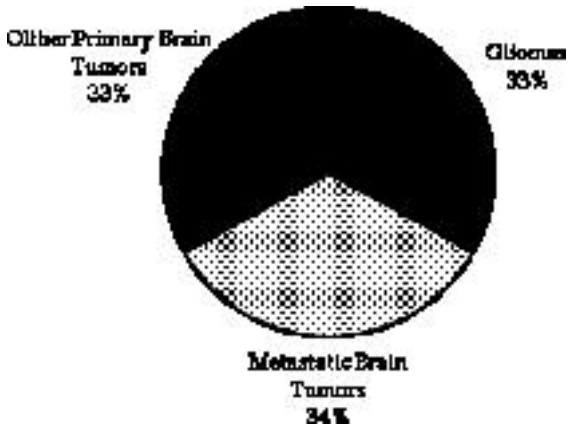

Figure 1(b)

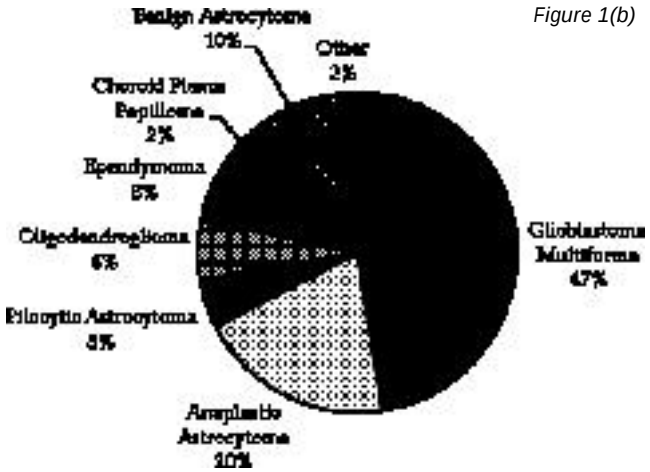

Figure 1. Incidence of primary brain tumors versus secondary brain tumors (metastasis) is shown in (a) along with the fraction of primary brain tumors that consists of glioma; (b) shows further distribution of the types of glioma. (Modified from Osborne1)

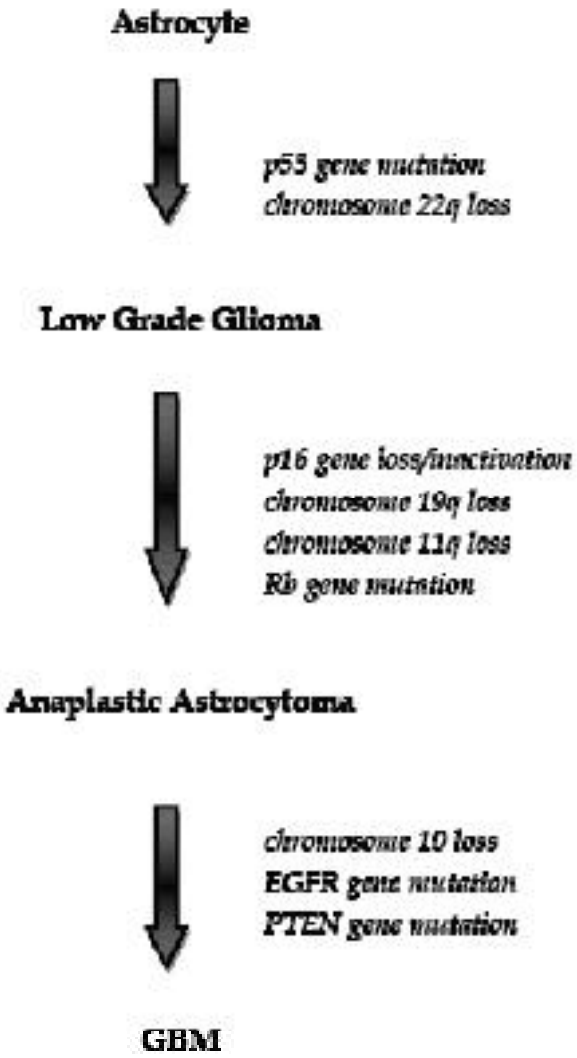

Figure 2. Progression of genetic changes that lead to malignant progression from a normal astrocyte to GBM. These include genetic and epigenetic changes and vary widely. This is a general pattern and progression may not always follow precisely the sequence presented. (Modified from Kaye and Walker4)

is excellent and gross total resection results in cure. Grade I astrocytomas also show certain unique histopathologic features and display distinct imaging findings, such as intense contrast enhancement, hence the reluctance to group the together with other astrocytomas. Another widely used classification is the St. Anne/Mayo system. Grades in this classification do not correlate with the WHO classification and can be a source of some confusion. Table 2 compares these two classification systems.

Anaplastic astrocytoma, anaplastic oligodendroglioma, and GBM are grouped together as high grade gliomas (HGG), whereas benign variants of astrocytoma and oligodendroglioma are grouped together as low grade gliomas (LGG). For clinicopathologic purposes, only WHO grade II astrocytoma and WHO grade II oligodendroglioma (the lowest grade, as there is no grade I oligodendroglioma in the WHO classification) comprise LGG. WHO grade I astrocytomas (such as pilocytic astrocytoma), although technically a part of LGG, have a much better prognosis; they are thus clinically distinct, and not discussed in the prognosis and treatment of LGG. Other primary brain tumors such as pleomorphic xanthoastrocytoma (an astrocytoma variant) and neurocytoma are classified as WHO grade II, and other entities such as dysembryoblastic neuro-epithelial tumors and gangliogliomas are classified as grade I along with pilocytic astrocytoma.

MORBIDITY IN LGG RESULTS FROM MALIGNANT PROGRESSION

LGG in general have a much better prognosis than HGG. Table 3 compares overall survival in LGG versus HGG patients. Oligodendrogliomas have a better prognosis than astrocytomas. In gliomas with cells derived from both glial lineages, the overall behavior of the tumor resembles oligodendroglioma.

Morbidity from LGG results from their invasive nature and, more importantly, from de-differentiation into higher grade gliomas over time. The propensity for LGG to transform

TABLE 2
A comparison of astrocytoma classification

St. Anne/Mayo Classification	WHO Classification	Low or High Grade
Astrocytoma grade 1	Pilocytic Astrocytoma (Grade I)	Low grade gliomas (LGG)
Astrocytoma grade 2	Astrocytoma (WHO Grade II)	
Astrocytoma grade 3	Anaplastic Astrocytoma (WHO Grade III)	High grade gliomas (HGG)
Astrocytoma grade 4	Glioblastoma Multiforme	

TABLE 3
Median Survival in Glioma Patients

Glioblastoma	1-1.5 years
Anaplastic Astrocytoma	2-3 years
Anaplastic Oligodendroglioma	3-7 years
Low Grade Astrocytoma	6-7 years
Low Grade Oligodendroglioma	8-12 years

into HGG seems to correlate with its vascular density and expression of vascular endothelial growth factor.[3] It appears that although most GBMs arise de-novo, approximately 5% of GBM are secondary with histopathological evidence of a precursor low grade or anaplastic astrocytoma. Many GBMs actually result from accumulation of progressive genetic mutations that occur in lower grade gliomas (Figure 2).[4,5]

SEIZURES ARE THE MOST COMMON PRESENTATION

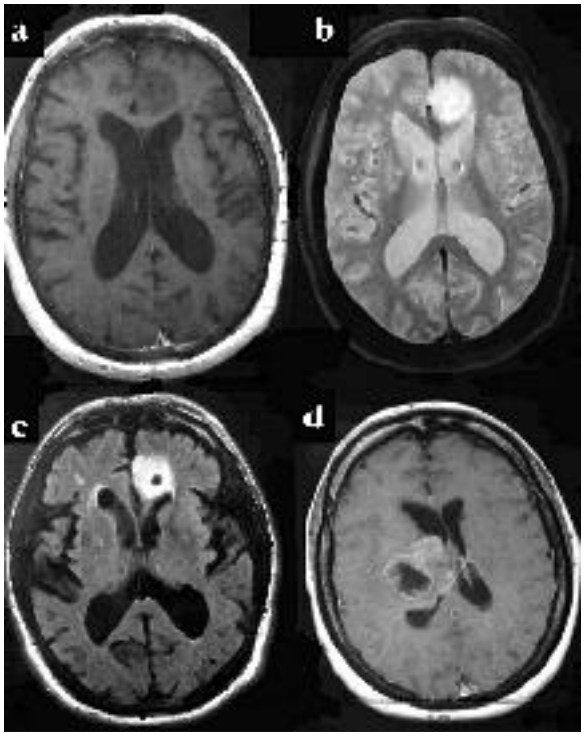

Figure 3. MR image of a typical LGG lesion (a-c) and a typical HGG lesion (d). The tumor is hypointense and non-enhancing on a T1 weighted contrast-enhanced image (a), and shows hyperintensity on T2 weighted (b) and FLAIR (c) images. In this lesion, FLAIR imaging brings out a cystic portion in the center of the LGG mass which is not evident on T1 weighted or T2 weighted images; (d) shows a ring-enhancing mass which is extending subependymally; this is a biopsy-proven GBM.

LGG usually present with seizures. Headaches and slowly progressive neurologic deficits such as paresis or sensory symptoms may also be the presenting symptoms. Increased intracranial pressure, either because of mass effect or from hydrocephalus due to obstruction of cerebrospinal fluid flow, is an uncommon presentation for LGG. Seizures associated with LGG can be focal, complex partial, or generalized. As a rule, all new onset seizures (particularly adult onset seizures) should be investigated by brain imaging; the study of choice is MRI with and without contrast. An initial CT scan offers no additional advantage.

MRI REVEALS LGG AS A LOCALIZED, NON-ENHANCING MASS

The characteristic MRI appearance of LGG is a space-occupying lesion that is hyperintense on T2-weighted and FLAIR images but hypo-intense on T1-weighted images (Figure 3). A consistent feature of LGG is the lack of contrast enhancement on MRI. HGG, on the other hand, usually enhance markedly with contrast, typically in an irregular ring-like pattern (Figure 3). LGG usually occur supra-tentorially, with the most common site being frontal and then temporal lobes. Rarely, LGG are found in the cerebellum, brainstem, or spinal cord. It should be noted, though, that not all LGG present as non-enhancing lesions on MRI, and not all HGG enhance. The MRI characteristics can occasionally be confusing. In cases where a non-enhancing lesion is assumed to be an LGG and the patient and the neurosurgeon decide to follow the patient without any biopsy, any new enhancement or any change in the size of the lesion suggests progression to HGG. Malignant progression in these cases should be assumed unless proven otherwise.

AGE, SIZE AND NEUROLOGIC DEFICIT ARE IMPORTANT PROGNOSTIC INDICATORS

An understanding of factors predicting survival in LGG comes from a prospective study conducted by the EORTC (European Organization for Research and Treatment of Cancer). Only a few factors were found to be associated with good outcome.[6] Of these, age at initial presentation (less than 40 years), size of tumor (less than 6 cm), extent of tumor across the midline (nil), histological type (oligodendroglioma or oligoastrocytoma), and extent of neurologic deficit (none) were most significant in predicting survival (Table 4). These indicators were noted to have an additive effect.

TABLE 4

Positive Prognostic Indicators in Adult Patients with Cerebral LGG

- Age less than 40 years
- Size of tumor less than 6 cm
- Tumor not crossing the midline
- Oligodendroglioma or oligoastrocytoma on hisotology
- Absence of any neurologic deficit

After Pignatti et al[6]

INITIAL MANAGEMENT

Since patients usually present with seizure, the first step is to start anti-epileptic medication. Valproic acid, phenytoin, and carbamzepine are reasonable choices. In recalcitrant cases, toparimate, or polytherapy with more than one anti-epileptic medication, can be considered. The role of corticosteroid therapy such as dexamethasone is not clearly defined in LGG. Typically, these lesions are not associated with any substantial vasogenic edema. Anecdotal experience suggest that patients who present with headache and have a large lesion on MRI may experience relief from headaches with dexamethasone, which has a dose-related effect on vasogenic edema. Use of corticosteroids should always be combined with gastric ulcer/gastritis prophylaxis. Proton pump inhibitors (PPI) seem to work better in these situations than H2 histamine receptor blockers. Antacids or combination of PPI and H2-blockers do not have any additive effect. The use of steroids is limited by the risk of long-term side-effects resulting from prolonged use.

BETTER SURVIVAL IS SEEN WITH >90% TUMOR RESECTION

Surgical management of LGG cannot yet be encapsulated in the form of a guideline. It is still considered optional by many neurosurgeons. Extent of resection ranges from a simple biopsy to almost complete removal of tumor tissue. It is impossible to claim total tumor resection as these tumors are typically very invasive and the margins cannot be definitively ascertained due to lack of a defining capsule. In non-excisional biopsy, only a small part of the tumor (typically just 1 or 2 square cubic millimeters) is removed through a burr hole with or without the help of stereotactic navigation technology. Tumor may be described as gross total resection, near total resection, subtotal resection, and partial resection (Table 5). Many a time more than 90% resection, which technically is a near total resection, is called gross total resection.

TABLE 5

Definition of Extent of Intervention during Surgery of Glioma

Biopsy (non-excisional)	Few mm of tissue
Partial resection	< 50% of tumor mass
Subtotal resection	50%-90% of tumor mass
Near total resection	>90% of tumor mass
Gross total resection	Complete resection of tumor visible by naked eye or a surgical microscope

Confusion about the role of surgery in LGG stems from a lack of adequate randomized controlled trials. Several studies have suggested that surgery plays a central role in the treatment of LGG (Table 6).[7-14] The most extensive prospective data comes from an EORTC study,[15] which was randomized for the efficacy of two different doses of radiation. Patients were enrolled after surgery and, based on the type of surgery, were stratified into three groups - biopsy or less than 50% resection; 50% or more but less than 90% resection; and 90% or greater resection. Extent of resection was estimated by the operating neurosurgeon; logistical complexity precluded precise volumetric assessment through imaging. Despite this caveat, the data show an impressive trend toward higher survival with greater resection. Both survival and progression-free survival at 5 years after resection are higher by 40% in those undergoing gross total (or near total) resection, compared with those who underwent biopsy or less than 50% resection (Figure 4).

TABLE. 6

Debate about Surgery in Low Grade Glioma

In Favor of	Not in Favor of
• Histopathological diagnosis	• Rsik of neurological deficits
• Alleviating the symptoms due to mass effect	• Lack of any randomized controlled trial proving the efficacy of surgery for LGG
• Reducing the chance of malignant progression	
• Reducing the number of cells innately resistant to chemotherapy or radiation therapy	

CLINICAL REASONING FAVORS SURGICAL RESECTION

Apart from increased life expectancy, several other objectives support surgical resection of LGG (Table 7), including relief of neurologic deficit, control of medically intractable seizures, or reduction in raised intracranial

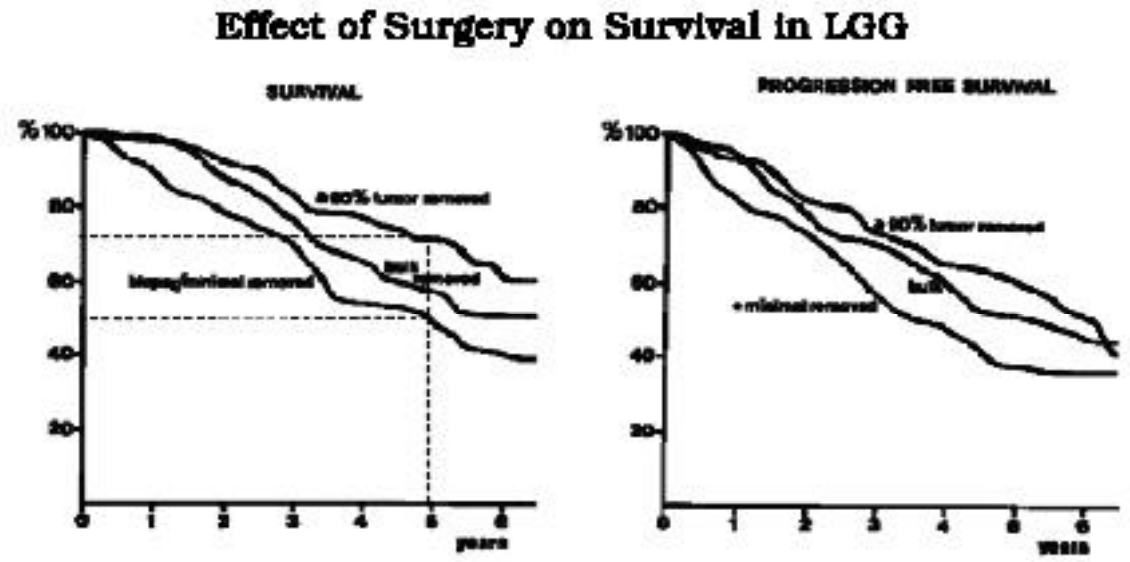

Figure 4. Data as presented in a graph by Karim et al[15] highlighting the beneficial effect of >90% tumor resection on progression-free survival or overall survival in patients with LGG.

pressure. Contrast enhancement in a mass lesion otherwise consistent with LGG is suggestive of malignant transformation; similarly a presumed or biopsy-proven LGG that demonstrates a new pattern of contrast-enhancement or an increase in size also needs attention. These cases should be considered for surgical intervention.

Arguments against surgery mainly focus on two points: (i) lack of any randomized controlled trial establishing the benefit of surgery; and (ii) risk of neurological deficits in patients who are intact or have minimal deficits pre-operatively. Although more evidence has come forth supporting the role of surgery in the management of LGG, the debate continues. Several points favor surgical intervention (Table 7). An imaging diagnosis of LGG requires histological confirmation; rarely, even a GBM can mimic LGG as a non-enhancing mass on MRI. For lesions causing mass effect, debulking the tumor is desirable. The pool of cells constituting the LGG eventually gives rise to a focus that transforms into HGG; therefore, decreasing the cellular population of the LGG will decrease the chance of a focus turning malignant. Theoretically, resection of more than 90% of tumor (near total or gross total resection) should decrease the chance of malignant progression to one-tenth. Decreasing the number of proliferating cells by debulking the tumor should also decrease the growth rate and decrease the number of cells that are resistant to radiation therapy or chemotherapy.

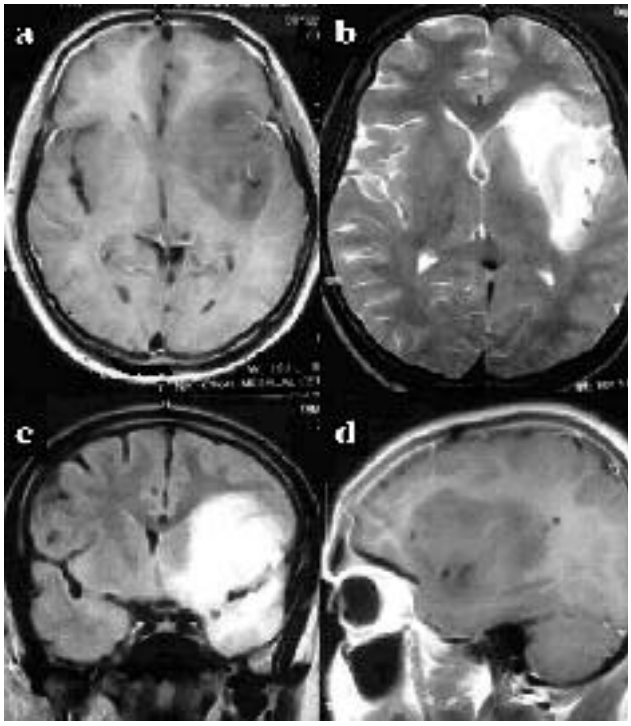

Figure 5. MRI of LGG present in the dominant hemisphere of a right-handed male, mainly in the insular and sub-insular region. The lesion does not enhance on contrast: (a) T1 weighted contrast-enhanced axial image; (b) T2 weighted axial image; (c) FLAIR coronal image; and (d) T1 weighted contrast-enhanced sagittal image.

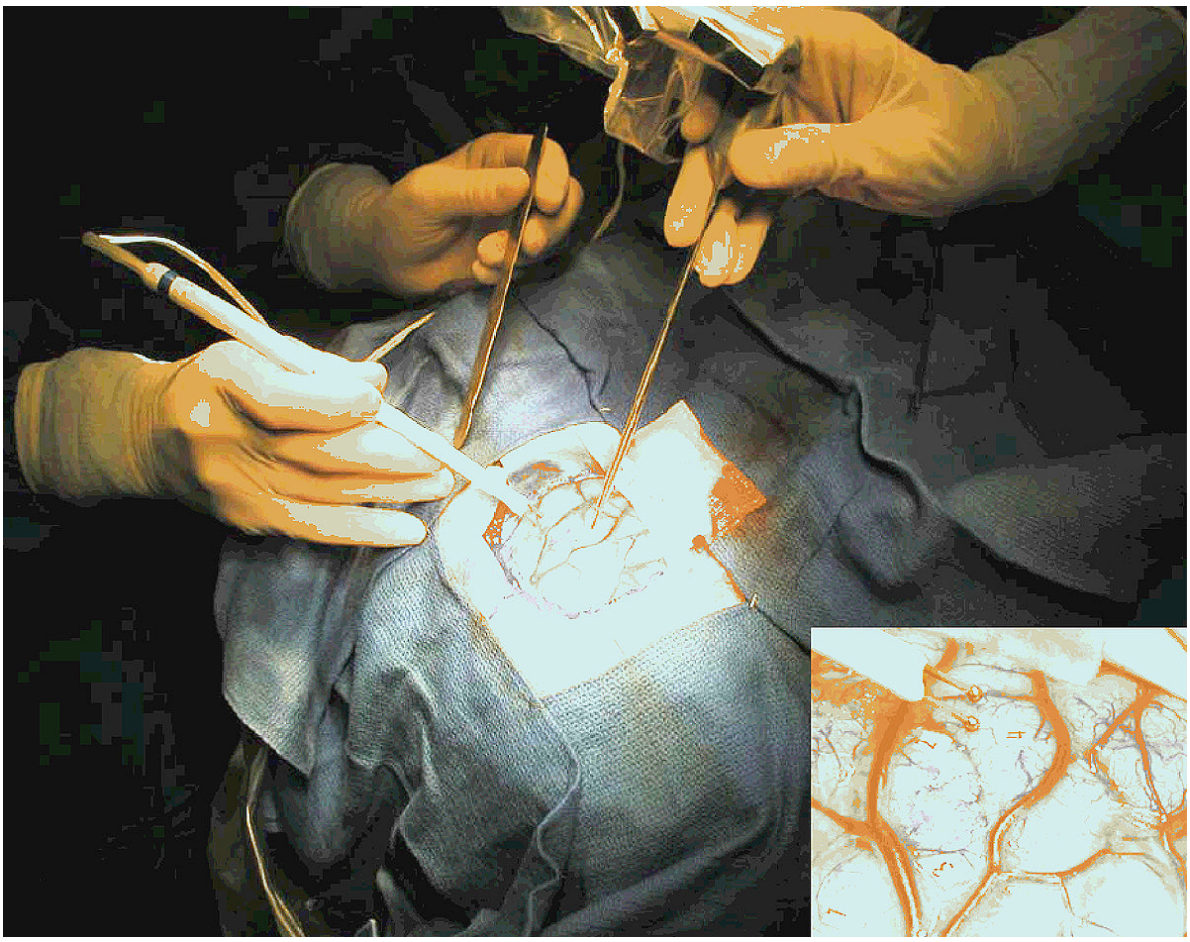

Figure 6. Craniotomy for a grade II oligodendroglioma in the right motor cortex. Surgery is being done with the assistance of cortical mapping with the patient awake, along with assistance provided by neuro-navigation. Inset shows a close-up of the motor cortex with temporary labels placed on the cortex to delineate the motor area.

Neurosurgical imperatives in LGG are offset by safety concerns. Surgical manipulation of lesions in or near eloquent or sensitive areas of the brain may lead to profound postoperative deficits. These cases are better off with observation alone or, at most, a biopsy (stereotactic or otherwise) with serial follow-up imaging studies. Advanced age or other medical conditions, particularly cardiopulmonary feebleness, are other relative contraindications for surgical resection of LGG (Table 7).

In situations where a non-enhancing LGG mass is located in an eloquent or deep region of the brain, observation alone is the most judicious option (Figure 5). If the LGG is located in eloquent cortex and displays an increase in size over time, appearance of new enhancement, change in the pattern of enhancement, or worsening neurological symptoms, careful surgical excision is necessary. A computerized neuro-navigation system as well as intra-operative cortical mapping while keeping the patient awake should be used to minimize the chance of post-operative deficits (Figure 6). The natural tendency of patients and families is to shy away from surgical intervention. At a minimum, however, biopsy of the mass lesion should be done, particularly where features suggest a higher grade (Figure 7).

Although the options of biopsy, resection, and observation are available whether the lesion is in eloquent cortex or not, aggressive management should be pursued for masses in non-eloquent areas that harbor features of higher grade tumor. Serial imaging is necessary in all cases, and should be continued after resection to monitor for recurrence. There is no consensus about decision making in the treatment of LGG, but the flow diagram shown in Figure 8 conforms to generally accepted practice.

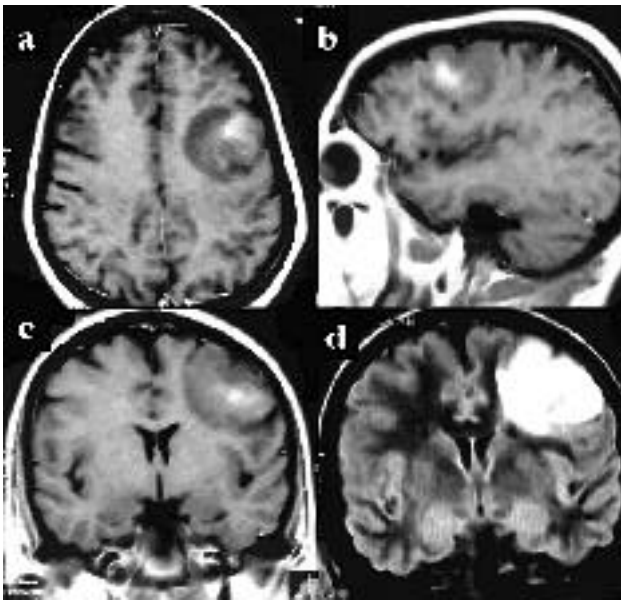

Figure 7. MRI of a patient that showing a contrast-enhancing mass that turned out to be LGG on resection.

TABLE 7

Indications for Surgical Resection in LGG

- Neurologic deficit
- Seizures
- Mass effect
- Contrast enhancement
- Recent change in size or contrast enhancement pattern of tumor
- Cytoreduction to diminish the chances of malignant progression
- Histopathological diagnosis

Relative Contra-Indications

- Proximity of eloquent area of brain eloquent area
- Deep location or difficult accessibility
- Advanced age
- Poor medical condition

TEMOZOLAMIDE IS THE MOST APPROPRIATE CHEMOTHERAPY BUT OPTIMAL TIMING IS UNKNOWN

Although the efficacy of chemotherapy in the treatment of LGG is unproven, several choices are available for use in both the pediatric and adult populations.[16-19] Temozolamide, an alkylating agent, has been used more recently as the drug of choice. Nitrosurea-based chemotherapy is an alternative. The timing of chemortherapy is not established. Chemotherapy soon after surgical resection is a valid option. Alternatively, chemotherapy can be held until there is evidence of progression on follow-up scans, with or without resection. For pediatric patients, the chemotherapy of choice is a combination of etoposide, cisplatin, procarbazine, vincristine, lomustine, and carboplatin. Evidence also supports adequate response and tolerance of temozolamide in the pediatric population.

Specific genetic alterations predict higher chemosensitivity
Genetic studies on LGG have shown that low grade oligodendroglioma carrying certain genetic aberrations responds very well to chemotherapy. These include loss of heterozygosity of chromosome 1p and 19q.[4] Another genetic alteration shown to make the tumor susceptible to the alkylating action of chemotherapeutic agents is methylation of the promoter of the methylguanine-DNA methyltransferase (MGMT) gene.[4] MGMT is a DNA repair enzyme and hyper-methylation of its promoter restricts its expression. There is evidence to suggest that these genetic and epigenetic changes confer chemosensitivity in some patients with low grade astrocytoma as well. Perhaps genetic analysis to detect these genetic/epigenetic changes will be used on a more routine basis in the future to assess chemo-susceptibility of LGG subgroups.

RADIOTHERAPY IS A VALUABLE ADJUNCT BUT OPTIMAL TIMING IS UNKNOWN

Radiation therapy (RT) plays an adjunctive role in the management of LGG. EORTC trials have shown that the timing of RT (immediately after surgical resection versus upon neuro-imaging evidence of malignant progression) does not affect overall survival.[20] Early institution of RT, however, does increase progression-free survival, although overall life expectancy does not change. Based on these findings, it seems advisable to delay RT in all cases, whether they have undergone tumor resection or not. The risk of toxicity from RT, including dementia and other encephalopathic changes, tip the risk-benefit ratio in favor of avoiding early RT. A phase III randomized controlled trial conducted in North America also showed that higher doses of RT (65 Gray) actually decreased survival and increased the incidence of radiation necrosis, when compared with lower dose RT (50 Gray) for LGG.[21]

CONCLUSION

LGG have benign histological features but possess inherent propensity for malignant transformation. They are associated with seizures (which are controlled by anticonvulsants) and sometimes headache (which may respond to dexamethasone). Definitive treatment is based on surgical resection (if feasible), to be followed up by RT and possibly chemotherapy. Chemotherapy is especially advisable in oligodendroglioma.

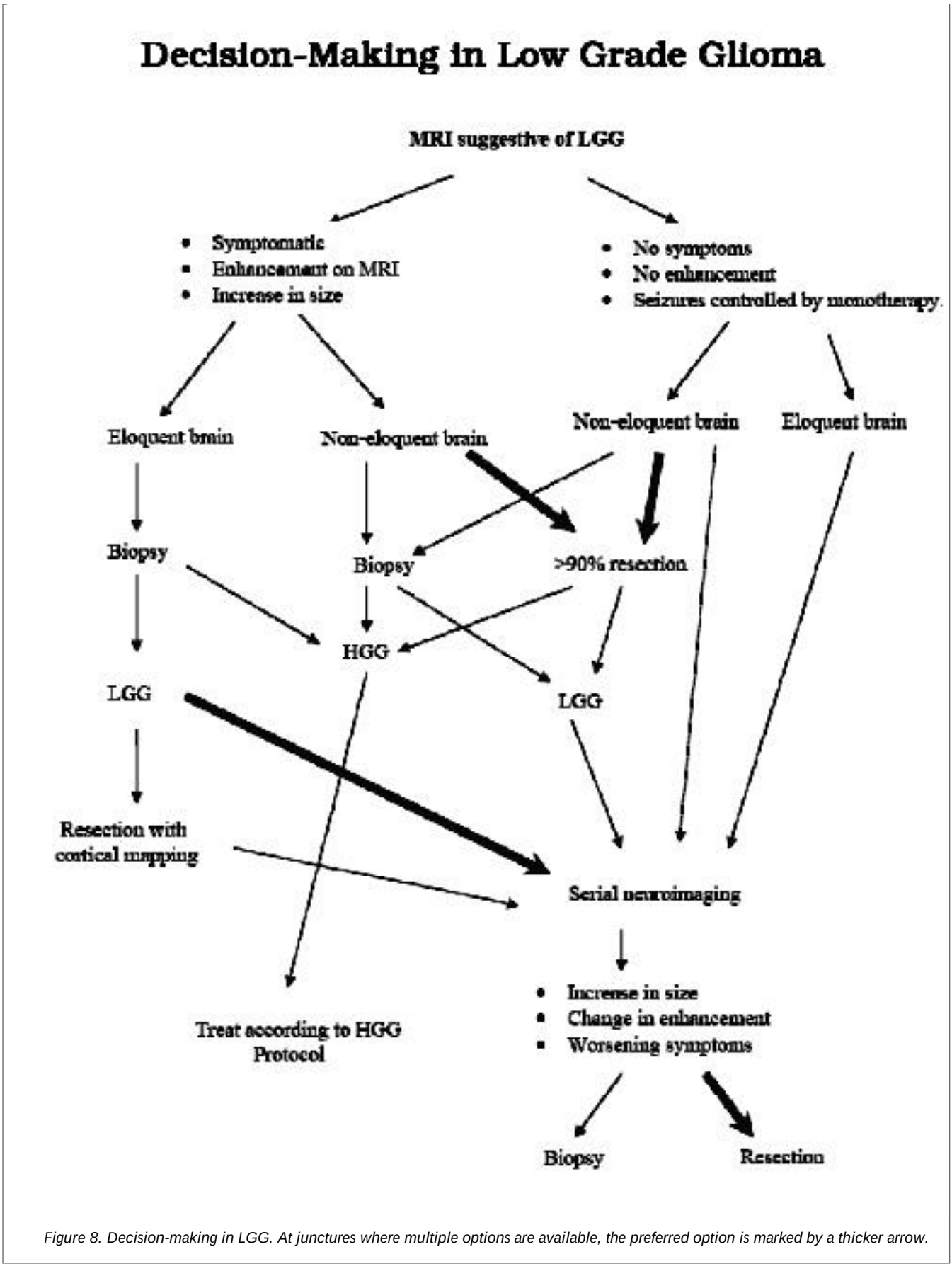

Figure 8. Decision-making in LGG. At junctures where multiple options are available, the preferred option is marked by a thicker arrow.

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