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Prognostic Factors for Survival in Adult Patients with Cerebral Low-Grade Glioma

Systematic Review Submitted for Partial Fulfillment of Master Degree in Neurosurgery

By

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List of Abbreviations

Abb.	Full term
DLGG.....	Diffuse low grade glioma.
IDH	Isocitrate dehydrogenase.
G	Grade.
GBM.....	Glioblastoma multiforme.
GFAP.....	Glial fibrillary acidic protein.
H&E.....	Hematoxylin & eosin stain.
ATRX.....	Alpha thalassemia mental retardation X-linked gene.
TP53.....	Tumor protein 53 gene.
MRS	Magnetic resonance spectroscopy.
rCBV.....	Relative cerebral blood volume.
PET.....	Positron Emission Tomography.
OS	Overall survival.
PFS.....	Progression-free survival.
GTR	Gross total resection.
NTR.....	Near total resection.
STR.....	Subtotal resection.
SEER	Surveillance, Epidemiology, and End Results.
RT.....	Radiotherapy.
KPS	Karnofsky Performance Scale.
PCV.....	procarbazine, CCNU, and vincristine.
TMZ.....	Temozolomide.
TERT	Telomerase Reverse Transcriptase.

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Introduction

Low grade gliomas (LGGs) account for approximately 5-10% of the primary CNS tumors diagnosed in USA each year [1]. Historically, histological classification of these tumors was either pure/mixed astrocytomas, or oligodendrogliomas.

In 2021, WHO revised 5th edition classification groups IDH-mutant diffuse astrocytic tumors together in one type (*Astrocytoma, IDH-mutant*), and oligodendrogliomas into (*Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted*).

Also, the new classification system uses the category "*Circumscribed astrocytic gliomas*" for other circumscribed astrocytic tumors (pilocytic astrocytomas, pleomorphic xanthoastrocytomas and subependymal giant cell astrocytomas) [2].

Molecular biology and genetics helped understanding the tumor behavior for better defining subgroups at increased risk of recurrence, WHO grade II tumors are subdivided into three classes [3]:

1) oligodendroglioma (1p/19q codeleted tumors)
2) IDH-mutated non-1p/19q codeleted astrocytoma
3) IDH wild-type astrocytoma

IDH mutations are frequently identified in WHO grade 2 and 3 oligodendrogliomas and astrocytomas. Grade 1 gliomas, such

as gangliogliomas and pilocytic astrocytomas, do not express IDH mutations [4].

The presence of an IDH mutations in a glioblastoma defines a secondary glioblastoma that evolved from a lower-grade tumor, rather than a primary Grade 4 glioblastoma, which is IDH wild-type.

Whilst CT and PET, respectively, play adjunct roles in detecting calcifications in the pre-operative diagnosis of oligodendroglioma and identifying 'hot' spots as a potential sign of tumor hyperactivity and/or progression [5], the mainstay of radiological diagnosis of LGG is enhanced MRI.

Typically, LGG is identified as a non-enhancing, T1-hypointense, T2- and FLAIR hyperintense mass lesion; contrast enhancement of as little as 1.2 cm3 may be enough to distinguish Grade 4 glioblastoma from LGG, with very high specificity [6].

However, the controversy in LGG management, with regards to imaging, lies not in diagnosis; rather, what's the next step after diagnosis.

Historically, LGG has been considered to be inactive or 'benign', at least on radiological grounds, however, consecutive MRI studies, coupled with a deeper understanding of biological behavior, has led to the development of a four step framework proposing to model the true natural history of LGG, all the way from MR silence, (with presumed occult glioma stem cell

proliferation), to frank malignant transformation of LGG to glioblastoma [7, 8].

Conservative management, watchful waiting and serial MRI scans are used specially for incidentally discovered lesions or eloquent tumors. Surgical resection is associated with low morbidity and mortality [9], especially in high volume quaternary hospitals, maximizing extent of resection is likely to convey significant progression-free survival and overall survival benefit [10, 11].

Aim of work

The reason for this investigation is to analyze the collective data from studies to define prognostic factors for overall survival in adult patients with cerebral low grade gliomas.

Our primary goal is to assess survival in adult patients with cerebral low grade glioma, and define prognostic factors with its relative importance.

Also, to evaluate the best plan of management for each patient with benefits of improvement and recovery, incidence of complications, symptoms recurrence and patient's quality of life.

Literature review

Embryology

Cortex and neurons development start as early as the 5th week of gestation and complete by 28 weeks [12], there are three major stages: proliferation, migration and organization.

Neurons proliferate and develop from glial stem cells at the surface of ventricles and ganglionic eminence [12].

The migration of neurons has been traditionally categorized into two types, radial and tangential. In radial migration (*Pia-directed migration*), neurons follow a radially oriented glial scaffold directly to the cortical surface, with later-forming neurons passing through early layers to pial surface [13].

This regular development pattern is disturbed with malformations, infections (such as CMV) and migrational disorders [12].

In tangential migration, GABAergic cells from ganglionic eminence take a tangential route through the cortex and provide centers with controlling functions [12].

The cortex undergoes folding into gyri to accommodate more extra cells, finally neurons in cortex organize to form local connections and send large tracts with remote axons such as corpus callosum to connect both hemispheres [12]. This development requires normally functioning genes and is easily