



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكرو فيلم

# بسم الله الرحمن الرحيم



**HANAA ALY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



**HANAA ALY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**HANAA ALY**

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

Systematic Review Submitted for Partial Fulfillment of Master Degree in  
Neurosurgery

By

**Michael Zohney Zakhary Johnny**

*M.B.B.Ch., Faculty of Medicine, BeniSuef university.*

Under supervision of

**Prof.Dr. Ashraf Gamal Eldin Al-Abyad**

*Professor of Neurosurgery*

*Department of Neurosurgery, Ain Shams University.*

**Prof.Dr. Hesham Anwar Abdelraheem**

*Professor of Neurosurgery,*

*Department of Neurosurgery, Ain Shams University.*

**Dr. Hesham Mohamed Abouelela Abdelmawla  
Radwan**

*Lecturer of Neurosurgery,*

*Department of Neurosurgery, Ain Shams University.*

**Faculty of Medicine, AIN SHAMS UNIVERSITY**

**2021**

## Table of contents

Table of contents.....	2
Table of figures.....	4
List of Abbreviations .....	6
List of Tables.....	7
Introduction .....	8
Aim of work.....	11
Literature review .....	12
Embryology.....	12
Anatomy .....	13
Molecular aspects .....	18
The new 2021 WHO Classification.....	20
Epidemiology .....	23
Clinical Presentation.....	24
Natural History of the disease.....	24
Symptoms.....	24
Symptoms according to location.....	25
Frontal lobe .....	25
Parietal lobe.....	26
Temporal lobe .....	26
Disconnection syndromes.....	27
Radiological Features.....	28
Magnetic Resonance Images (MRI) .....	28
Magnetic resonance spectroscopy (MRS).....	30

Perfusion MRI.....	31
Positron Emission Tomography (PET) .....	32
Functional MRI (fMRI) .....	33
Management & treatment .....	34
Anti-epileptic drug treatment .....	34
Surgical management of LGG.....	34
Post-surgical management of LGG:.....	36
Role of radiotherapy .....	37
Role of chemotherapy .....	39
Systematic review .....	41
Materials and methods.....	41
Literature search .....	41
Eligibility criteria .....	42
Data extraction .....	43
Results .....	45
Result of literature search .....	45
Characteristics of included studies .....	45
Patient-related factors .....	46
Tumor-related factors .....	55
Treatment-related factors.....	65
Prognostic evaluations .....	77
Discussion.....	116
Conclusion.....	123

## Table of figures

Figure 1 - Normal glia. <sup>[14]</sup> .....	14
Figure 2 - Normal brain cortex <sup>[15]</sup> .....	14
Figure 3 - Reactive glia. (A, B) <sup>[14]</sup> .....	15
Figure 4 - Schematic presentation for astrocytes.....	16
Figure 5 - Normal brain-CSF barrier <sup>[16]</sup> .....	17
Figure 6 - Diffuse astrocytoma histology <sup>[17]</sup> .....	17
Figure 7 - MRI showing non-enhancing LGG <sup>[50]</sup> .....	30
Figure 8 - Enhancement in LGG <sup>[39]</sup> .....	30
Figure 9 - Astrocytoma G. II MRS <sup>[53]</sup> .....	31
Figure 10 - MRI DWI of ganglioglioma <sup>[39]</sup> .....	32
Figure 11 - fMRI of LGG <sup>[39]</sup> .....	33
Figure 12 - Etzaniz 2017 graphs acc. to age, KPS .....	47
Figure 13 - Wahl 2017 graphs acc. to age, KPS.....	48
Figure 14 - Shaw 2012 graph acc. to age .....	48
Figure 15 - Daniels 2011 graphs acc. to age .....	49
Figure 16 - Houillier 2010 graphs acc. to age, KPS.....	49
Figure 17 - El-hateer 2009 graph acc. to Age, KPS, Seizures.....	50
Figure 18 - Shaw et al. 2002 graphs acc. to age.....	51
Figure 19 - Lo 2001 graphs acc. to Age, KPS, Seizures .....	52
Figure 20 - Leighton 1997 graphs acc. to Age, KPS, Seizures .....	53
Figure 21 - Nicolato 1995 graphs acc. to Age, KPS .....	54
Figure 22 - Breen 2020 graph acc. to tumor diameter .....	56
Figure 23 - Etzaniz 2017 graphs acc. to subtype,tumor volume.....	57
Figure 24 - Wahl 2017 graphs acc. to subtype, tumor volume .....	58
Figure 25 - Youland 2013 graphs rates acc. to subtype.....	58

Figure 26 - Shaw 2012 graphs acc. to subtype .....	59
Figure 27 - Daniels 2011 graphs acc. to subtype, tumor diameter .....	60
Figure 28 - Houillier et al. 2010 graphs acc. to subtype .....	61
Figure 29 - El-hateer 2009 graph acc. to tumor diameter.....	61
Figure 30 - Schomas 2009 graph acc. to subtype .....	61
Figure 31 - Shaw 2002 graphs acc. to subtype, tumor diameter .....	62
Figure 32 - Lo 2001 graphs acc. to subtype, enhancement.....	63
Figure 33 - Leighton 1997 graphs acc. to subtype .....	64
Figure 34 - Nicolato 1995 graphs acc. to tumor diameter.....	64
Figure 35 - Breen 2020 graphs acc. to EOR, RT dose .....	66
Figure 36 - Etxaniz 2017 graphs acc. to EOR, Post-op RT .....	67
Figure 37 - Youland 2017 graphs acc. to EOR.....	67
Figure 38 - Youland 2017 graphs acc. to EOR, Adj therapy.....	68
Figure 39 - Buckner 2017 graphs acc. to EOR, Adj therapy .....	69
Figure 40 - Youland 2013 graphs acc. to EOR, RT Dose .....	70
Figure 41 - Shaw 2012 graph acc. To EOR, adj therapy.....	71
Figure 42 -Daniels 2011 graphs acc. to EOR.....	71
Figure 43 - Houillier 2010 graphs acc. to EOR, RT timing .....	72
Figure 44 -Schomas 2009 graphs acc. to EOR .....	72
Figure 45 -McGirt 2008 graphs acc. to EOR .....	72
Figure 46 - Shaw 2002 graphs acc. to EOR, RT dose .....	73
Figure 47 - Lo 2001 graphs acc. to EOR, RT dose.....	74
Figure 48 - Leighton 1997 graphs acc. to EOR, Post-op RT.....	75
Figure 49 - Nicolato 1995 graphs acc. to EOR, RT dose .....	76
Figure 50 - PRISMA flow diagram .....	78



## 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.

## List of Tables

Table 1: Characteristics of included studies .....	79
Table 2: Cochrane risk of bias for randomized trials .....	82
Table 3: Newcastle-Ottawa scale for cohort studies.....	83
Table 4: Patient-related factors (Age) .....	87
Table 5: Patient-related factors (KPS). .....	90
Table 6: Patient-related factors (Seizures) .....	93
Table 7: Tumor-related factors (Histological subtype).....	95
Table 8: Tumor-related factors (IDH-mutatton).....	98
Table 9: Tumor-related factors (1p/19q codeletion) .....	99
Table 10: Tumor-related factors (size) .....	101
Table 11: Treatment-related factors (surgery) .....	104
Table 12: Treatment-related factors (Adj. therapy).....	107
Table 13: Summary of each prognostic factor in OS.....	110
Table 14: Summary of each prognostic factor in PFS .....	112
Table 15: Each factor and associated studies .....	114

## 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 cm<sup>3</sup> 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 <sup>[12]</sup>, 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 <sup>[12]</sup>.

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 <sup>[13]</sup>.

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

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

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 <sup>[12]</sup>. This development requires normally functioning genes and is easily