FINAL

Lecture 1

Pathology Mind Maps

CNS Tumors-1

Done by: Mas Nafoukh

This file contains the lecture material presented through mind maps to make the information clearer, more organized, and easier to follow. It is designed to simplify studying and make revision more effective.

We truly hope you find it beneficial.
If it helps you in any way, please remember us in your prayers.

Best of luck in your studies !

رَبِّ اشْرَحْ لِي صَدْرِي وَيَسِّرْ لِي أَمْرِي وَاحْلُلْ عُقْدَةً مِّن لِّسَانِي يَفْقَهُوا قَوْلِي

CNS Tumors involve the **brain** or **spinal** cord

ARISE FROM

- **Cells of the coverings = Meningiomas**
- **Brain cells = Gliomas, Neuronal tumors**
- **Other CNS cell populations = Primary CNS lymphoma, Germ cell tumors**
- **Elsewhere in the body = Metastases (more common than primary brain tumors)**

EPIDEMIOLOGY

INCIDENCE: The annual incidence of CNS tumors in the U.S :

- 24 /100,000 for intracranial tumors , 1/3 malignant
- 1-2/100,000 for intraspinal tumors

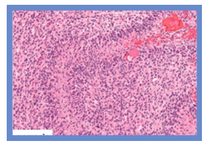
Characteristic features of CNS tumors

1. **No Premalignant stage**: no in situ lesions.
2. **Metastasis is rare!**
   - Even the most **highly** malignant gliomas **rarely** spread **outside** of the CNS.
   - but the brain is **not** comparably **protected** against the spread of distant tumors.
3. **Growth pattern (infiltrative or not) and tumor location strongly influence the prognosis:**

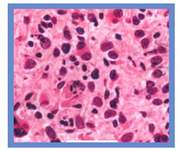
- Even low-grade lesions may **infiltrate** large regions of the brain, leading to serious clinical deficits, inability to be resected, and poor prognosis.
- The **anatomic site** of the neoplasm can influence outcome independent of tumor type or grade due to local effects

HISTOLOGIC GRADING OF CNS TUMORS DEPENDS ON :

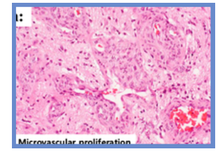
GRADES



Necrosis



Atypia & mitosis



Microvascular proliferation

Grade 1 lesions:

- **low** proliferative activity
- Can be **cured** after **surgical** resection alone.
- Example: pilocytic astrocytoma (PA), subependymal giant cell astrocytoma (SEGA), choroid plexus papilloma, myxopapillary ependymoma

Grade 2 lesions:

- **low** proliferative activity
- usually **infiltrative** and often **recur**
- Some grade II entities tend to **progress** to higher grades of malignancy.
- Examples: astrocytoma, IDH- mutant, grade 2, oligodendroglioma, IDH- mutant and 1p/19q-codeleted, grade 2

Grade 3 lesions:

- **clear histological** evidence of **malignancy** (nuclear **atypia** and Higher proliferative activity (**mitosis**)).
- In **most** settings, patients receive **radiation** and/or **chemotherapy**.
- Examples: astrocytoma, IDH- mutant, grade 3, oligodendroglioma, IDH- mutant and 1p/19q-codeleted, grade 3.

Grade 4 lesions (high grade) :

- **cytologically malignant**, **mitotically active**, **rapid proliferation**, **necrosis**- prone neoplasms
- associated with **rapid** pre- and postoperative disease **evolution** and **fatal outcome**.
- **Widespread infiltration** of surrounding tissue and a risk of craniospinal dissemination.
- examples: Glioblastoma, IDH-wildtype, medulloblastoma, pineoblastoma, and most embryonal neoplasms

WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	II or III
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	I, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I

PEDIATRIC CNS TUMORS **20%** of all pediatric tumors.

Childhood CNS tumors differ from those in adults in:

Location

- 2/3 **infratentorial** in **kids** (posterior fossa)
- 2/3 **supratentorial** in **adults** (cerebral hemispheres above tentorium)

Mutation profile & histologic subtype:

- **Kids**: medulloblastoma, pilocytic astrocytoma, ependymoma
- **Adults**: glioblastoma, metastases, meningiomas, **diffuse gliomas** constitute **most** gliomas in adults (including astrocytomas and oligodendrogliomas).

Classification of CNS tumors According to The 2016 WHO classification of brain tumors; which helped improving treatment protocols and predicting prognosis.

combined phenotype - genotype (integrated diagnoses)

1. **Phenotype**: the **histologic** features and **microscopic** similarities with what's thought to be their cell of origin (based on the light microscopic appearance, the immunohistochemical expression of proteins, and the electron microscopic assessment of ultrastructural features).
2. **Genotype**: tumor **genetic** profile and **molecular** studies

GENETIC ALTERATIONS IN GLIOMAS:

1- Mutations in isocitrate dehydrogenase (IDH) genes:

- observed as an **early** event in **gliomagenesis**
- Seen in **astrocytomas** and **oligodendrogliomas**
- **Gain of function** Mutation affection **IDH1** codon **132** or **IDH2** codon **172**.
- The **most** frequent is **IDH1 R132H** mutation (83-91%) of IDH mutant gliomas
- **IDH2** mutation: **R172K** is the most frequent IDH2 mutation
- Can be **detected** by **immunohistochemical** stains and **molecular** studies: 1. IDH1-R132H immune stain
  2. IDH sequencing for IDH1 codon 132 and IDH2 codon 172
- **Gain of function mutation**→ lead to **increased production of 2- hydroxyglutarate (oncometabolite)**→interferes with the activity of several enzymes that regulate gene expression→**DNA hypermethylation** & maintaining the cells in **stem cell-like** physiological states→**self- renewal and tumorigenesis**

2- whole arm Co-deletion of 1p and 19q chromosomal segments:

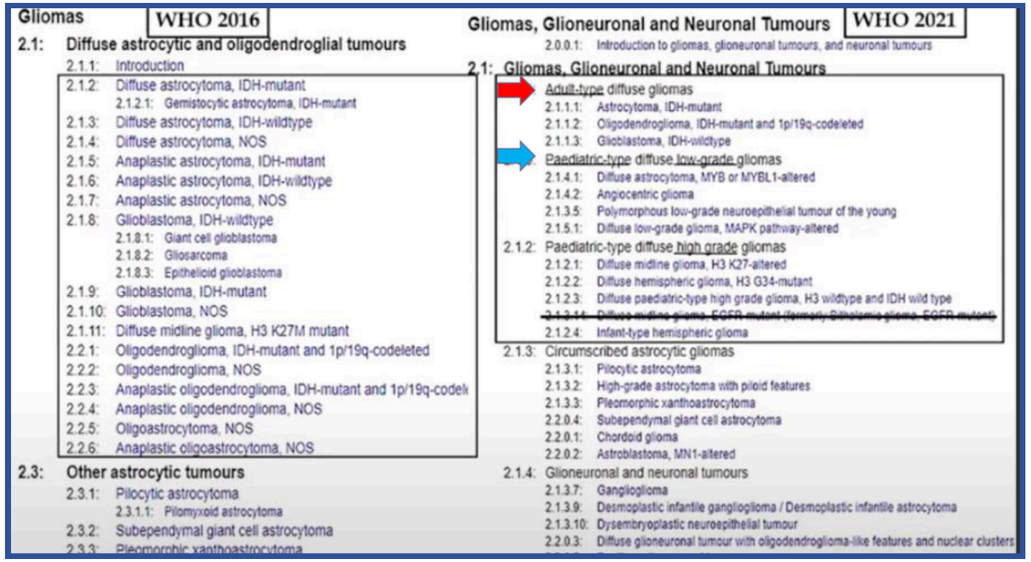
- **Diagnostic** of **oligodendrogliomas** in the **presence** of **IDH** mutation.
- The vast majority of **IDH** mutant and **1p/19q co-deleted** oligodendroglioma →carry **TERT** promotor hotspot mutations
- **TERT** promotor hotspot mutations: **telomerase stabilization**, **cellular immortalization** and **proliferation**

3- ATRX and P53 loss of function mutation:

- Both occur in **IDH** mutant **astrocytomas**
- **ATRX** mutation induces **abnormal telomeres** maintenance mechanism known as "**alternative lengthening of telomeres**"
- ATRX mutation is **Mutual exclusive** with the activating promoter mutation of the **TERT** gene (1p/19q codeletion)
- P53 mutation: enable tumor cell survival :

ATRX→associated with genomic instability→induces P53 dependent cell death→mutation in P53 helps these cells to survive.

WHO CLASSIFICATION



Gliomas — WHO 2016

2.1: Diffuse astrocytic and oligodendroglial tumours

- 2.1.1: Introduction
- 2.1.2: Diffuse astrocytoma, IDH-mutant
  - 2.1.2.1: Gemistocytic astrocytoma, IDH-mutant
- 2.1.3: Diffuse astrocytoma, IDH-wildtype
- 2.1.4: Diffuse astrocytoma, NOS
- 2.1.5: Anaplastic astrocytoma, IDH-mutant
- 2.1.6: Anaplastic astrocytoma, IDH-wildtype
- 2.1.7: Anaplastic astrocytoma, NOS
- 2.1.8: Glioblastoma, IDH-wildtype
  - 2.1.8.1: Giant cell glioblastoma
  - 2.1.8.2: Gliosarcoma
  - 2.1.8.3: Epithelioid glioblastoma
- 2.1.9: Glioblastoma, IDH-mutant
- 2.1.10: Glioblastoma, NOS
- 2.1.11: Diffuse midline glioma, H3 K27M mutant
- 2.2.1: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 2.2.2: Oligodendroglioma, NOS
- 2.2.3: Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codel
- 2.2.4: Anaplastic oligodendroglioma, NOS
- 2.2.5: Oligoastrocytoma, NOS
- 2.2.6: Anaplastic oligoastrocytoma, NOS

2.3: Other astrocytic tumours

- 2.3.1: Pilocytic astrocytoma
  - 2.3.1.1: Pilomyxoid astrocytoma
- 2.3.2: Subependymal giant cell astrocytoma
- 2.3.3: Pleomorphic xanthoastrocytoma

Gliomas, Glioneuronal and Neuronal Tumours — WHO 2021

- 2.0.0.1: Introduction to gliomas, glioneuronal tumours, and neuronal tumours

2.1: Gliomas, Glioneuronal and Neuronal Tumours

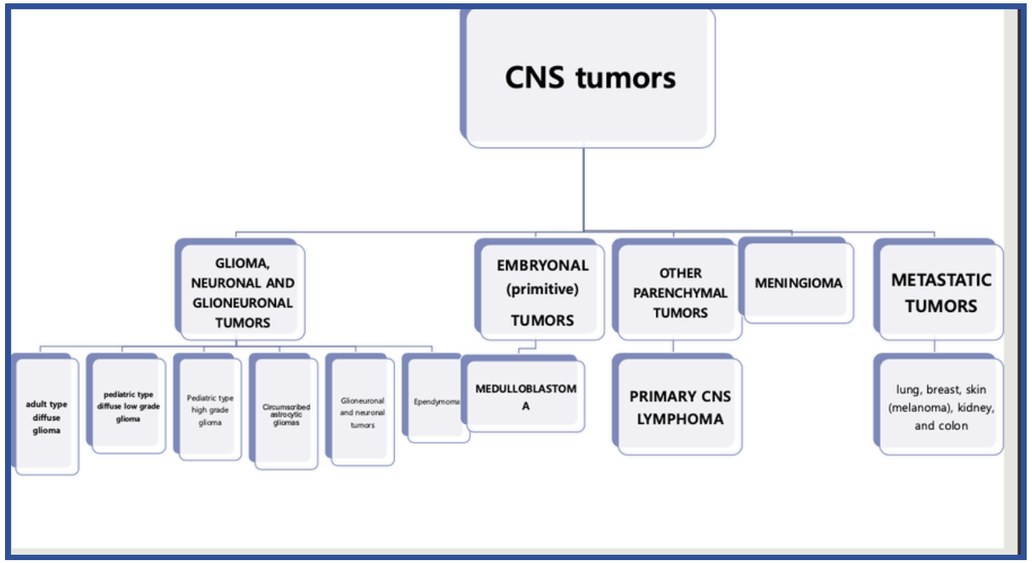
Adult-type diffuse gliomas
- 2.1.1.1: Astrocytoma, IDH-mutant
- 2.1.1.2: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- 2.1.1.3: Glioblastoma, IDH-wildtype

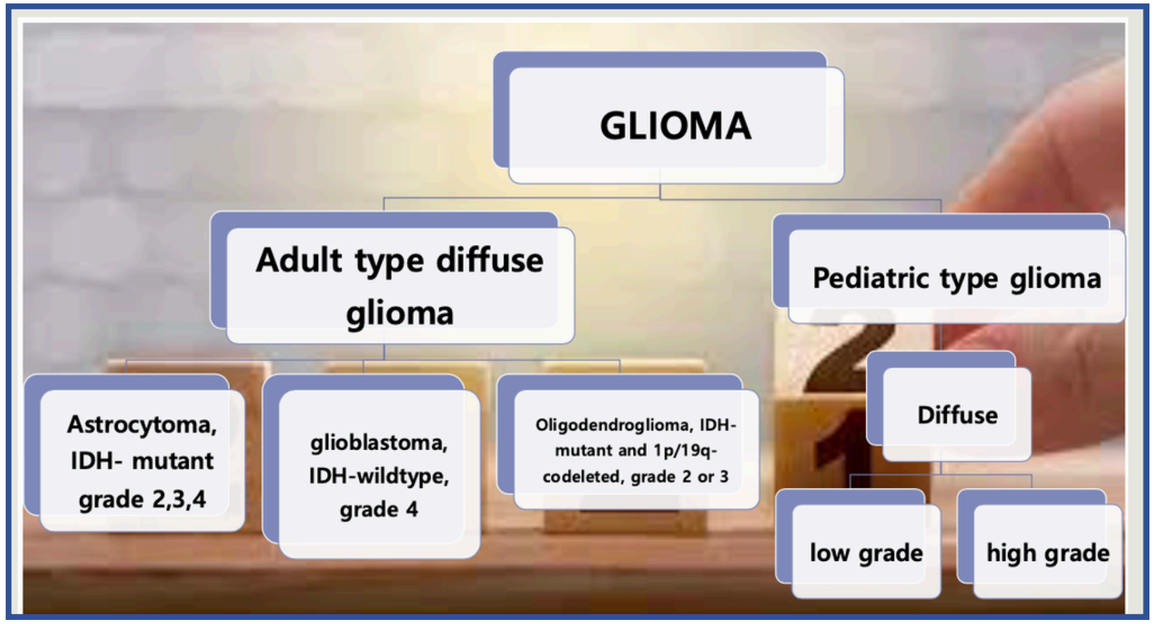
Paediatric-type diffuse low-grade gliomas
- 2.1.4.1: Diffuse astrocytoma, MYB or MYBL1-altered
- 2.1.4.2: Angiocentric glioma
- 2.1.3.5: Polymorphous low-grade neuroepithelial tumour of the young
- 2.1.5.1: Diffuse low-grade glioma, MAPK pathway-altered

2.1.2: Paediatric-type diffuse high grade gliomas
- 2.1.2.1: Diffuse midline glioma, H3 K27-altered
- 2.1.2.2: Diffuse hemispheric glioma, H3 G34-mutant
- 2.1.2.3: Diffuse paediatric-type high grade glioma, H3 wildtype and IDH wild type
- ~~2.1.1.4: Diffuse midline glioma, EGFR mutant (formerly Diffuse glioma, EGFR mutant)~~
- 2.1.2.4: Infant-type hemispheric glioma

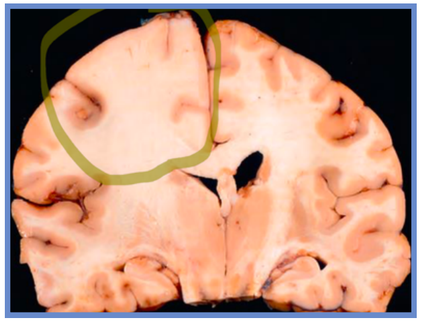
2.1.3: Circumscribed astrocytic gliomas
- 2.1.3.1: Pilocytic astrocytoma
- 2.1.3.2: High-grade astrocytoma with piloid features
- 2.1.3.3: Pleomorphic xanthoastrocytoma
- 2.2.0.4: Subependymal giant cell astrocytoma
- 2.2.0.1: Chordoid glioma
- 2.2.0.2: Astroblastoma, MN1-altered

2.1.4: Glioneuronal and neuronal tumours
- 2.1.3.7: Ganglioglioma
- 2.1.3.9: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma
- 2.1.3.10: Dysembryoplastic neuroepithelial tumour
- 2.2.0.3: Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters





ASTROCYTOMA, IDH-MUTANT



Macroscopic

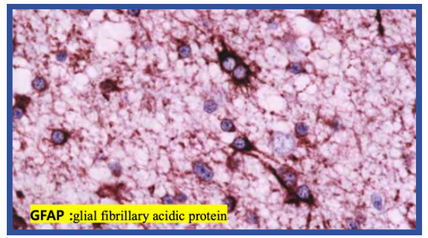
- **Phenotype:** It Is a **diffusely infiltrating glioma**
- **Genotype:**
  1. **IDH1** or less frequently IDH2 mutation.
  2. Inactivating mutation in **TP53** and/or **ATRX**
  3. **absence** of 1p/19q co deletion
- **Age at diagnosis:** 40–60 year old.
- **Location:** cerebral hemispheres +/- cerebellum, brainstem, or spinal cord.
- **Presentation:**
  1. seizures, headaches, and focal neurologic deficits related to the anatomic site of involvement.
  2. Clinically: static for years or Progressive. The prognosis gets poorer as the grade increases
- **On the basis of histologic features astrocytomas, IDH- mutant are stratified into three groups:**
  1. astrocytomas,IDH-mutant,grade **2**,median survival is **>10years**.
  2. astrocytomas, IDH- mutant grade **3**, median survival is **5-10 years**
  3. astrocytomas, IDH- mutant grade **4,** median survival is **3** years.

  NO grade **1** astrocytoma, IDH- mutant, because by convention grade 1 implies benign behavior and all diffuse gliomas are considered malignant
- **Morphology - Macroscopic**

Grade 2 &3: poorly defined, infiltrative tumors \ **expand** and **distort** the invaded brain \ **NO** discrete mass, **Infiltration** beyond the grossly evident margins.
Grade 4: poorly defined, infiltrative tumors \ **lacks** large areas of central necrosis and hemorrhage seen in IDH-wild-type GBM

Microscopic

Diffuse astrocytoma, IDH mutant, WHO **grade 2**



Microscopic

- The transition between neoplastic and normal tissue is indistinct
- tumor cells infiltrate normal tissue many centimeters from the main lesion.

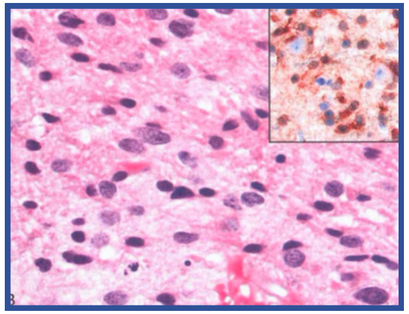
Hypercellular (compared to normal white matter): mild to moderate increase in the number of glial cell nuclei.

Cytologic atypia:

- mild
- enlarged, elongated or irregular hyperchromatic nuclei
- No prominent atypia

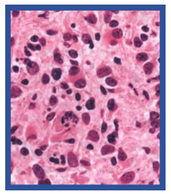
+ **fibrillary background** made of a network of fine astrocytic cell processes

- NO or rare Mitotic activity
- NO necrosis
- NO microvascular proliferation



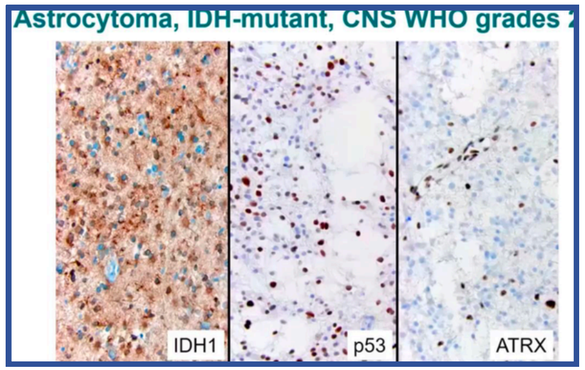
Enlarged irregular nuclei embedded within fbrillar matrix of the brain
Inset: IDH1 immune stain is positive in tumor cells

grade 3



Diffuse astrocytoma, IDH mutant, WHO **grade 3**

- More densely cellular
- More nuclear pleomorphism
- **Mitotic figures are present**
- NO necrosis
- NO microvascular proliferation



Diffuse astrocytoma, IDH mutant, WHO **grade 4**

- Same as grade 3 with **Microvascular proliferation and/or necrosis**
- The presence of **homozygous deletion** of **CDKN2A &/or CDKN2B** → astrocytomas, IDH- mutant, grade 4
- (EVEN IF THE HISTOLOGY SUGGESTS A LOWER GRADE).

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

- اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.
- اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.
- اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.
- اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.
- اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.
- اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.