BRAIN TUMORS - 2 -

Based on the fifth-year curriculum for medical students at the University of Jordan, class of 2022

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--- Brain tumors represent a complex and heterogeneous group of neoplasms arising from the intracranial contents or their coverings, and they are broadly categorized into primary and secondary (metastatic) tumors. Primary brain tumors originate from within the central nervous system (CNS) itself, including the brain parenchyma, meninges, cranial nerves, and pituitary gland, and they can be either benign (non-cancerous) or malignant (cancerous) based on their histological characteristics and biological behavior. In contrast, secondary brain tumors, or brain metastases, are far more common in adults and result from the hematogenous spread of systemic cancers, most frequently originating from the lung, breast, kidney, and melanoma, highlighting the brain's vulnerability as a sanctuary site for metastatic disease due to the unique properties of the blood-brain barrier which can also impede the delivery of therapeutic agents.

--- The epidemiological landscape of brain tumors reveals significant variations based on age, gender, and geography. Globally, CNS tumors are a leading cause of cancer-related mortality, ranking as the second most common cause of cancer death in children and the third in adults, accounting for approximately 1.9% of all cancers and resulting in 246,253 deaths worldwide in 2019. The Western Pacific Region, including countries like China, bears the highest burden of both incidence and mortality. A notable gender disparity exists, with a male-to-female ratio of 1.8:1 in adult malignant tumors, suggesting potential hormonal or genetic influences on tumorigenesis. In the pediatric population, brain and other CNS tumors constitute approximately 20% of all childhood cancers, making them the second most frequent malignancy after leukemia and the most common solid tumor in this age group.

--- The age-adjusted incidence of malignant brain tumors in children is 3.55 per 100,000, whereas in adults, the paradigm shifts dramatically with non-malignant tumors (age-adjusted incidence 22.38 per 100,000) being far more prevalent than malignant ones (8.5 per 100,000), which has profound implications for treatment strategies and prognostic counseling.

--- The clinical presentation of brain tumors is fundamentally dictated by two pathophysiological mechanisms: the generalized effects of increased intracranial pressure (ICP) and the focal neurological deficits resulting from the direct compression or invasion of specific neural structures by the tumor mass. The skull is a rigid compartment with a fixed volume, and any space-occupying lesion—whether a tumor, surrounding edema, hemorrhage, or obstructive hydrocephalus—will elevate ICP, leading to the classic triad of headache, nausea, and vomiting, which are often projectile in nature and most pronounced in the morning or upon awakening. Papilledema, or swelling of the optic disc observed on fundoscopy, is a critical sign of chronically elevated ICP. Focal symptoms are highly dependent on the tumor's location within the CNS. Supratentorial tumors, which are more common in adults, frequently involve the cerebral hemispheres and present with seizures, which may be the inaugural symptom in up to 50% of patients, as well as progressive hemiparesis, aphasia, visual field cuts, or cognitive and personality changes that can be insidious and easily misattributed to psychiatric conditions.

--- Conversely, infratentorial tumors, which predominate in the pediatric population, arise in the posterior fossa and typically manifest with cerebellar dysfunction such as ataxia, dysmetria, and nystagmus, brainstem signs including multiple cranial nerve palsies, and obstructive hydrocephalus due to compression of the fourth ventricle, leading to acute symptoms of raised ICP.

--- The diagnostic workup for a suspected brain tumor is anchored by neuroimaging, with magnetic resonance imaging (MRI) being the undisputed gold standard due to its superior soft tissue resolution and multiplanar capabilities. MRI with gadolinium-based contrast agents is essential for delineating the tumor margins, assessing its vascularity, identifying areas of necrosis or hemorrhage, and detecting leptomeningeal spread. Computed tomography (CT) may be utilized in acute settings to rapidly identify hemorrhage or large mass effects, but it is less sensitive for small tumors or isodense lesions. Advanced MRI techniques, such as magnetic resonance spectroscopy (MRS) and perfusion imaging, provide valuable metabolic and hemodynamic information that can help narrow

the differential diagnosis and guide biopsy targets. However, definitive diagnosis and tumor grading, which are paramount for prognostication and treatment planning, rely on histopathological examination of tissue obtained via stereotactic or open biopsy. The integration of molecular markers, such as isocitrate dehydrogenase (IDH) mutation status, 1p/19q codeletion, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, has revolutionized the classification of gliomas, moving beyond pure histology to a more precise, molecularly-informed taxonomy that also predicts therapeutic response and overall survival.

--- The management of brain tumors is inherently multidisciplinary, necessitating close collaboration between neurosurgeons, neuro-oncologists, radiation oncologists, neuropathologists, and specialized support services. The primary therapeutic modality for most accessible tumors is maximal safe surgical resection, which serves to establish a tissue diagnosis, alleviate mass effect and symptoms of raised ICP, and potentially improve survival by cytoreduction. In cases where gross total resection is not feasible due to eloquent location, subtotal resection or biopsy may be performed. Adjuvant radiotherapy is a cornerstone of treatment for malignant gliomas and is typically delivered using conformal techniques to minimize damage to surrounding healthy brain tissue. Chemotherapy, particularly with the alkylating agent temozolomide, is often administered concurrently with and adjuvant to radiotherapy for high-grade gliomas, and its efficacy is significantly influenced by the MGMT promoter methylation status of the tumor. For metastatic disease, treatment is generally palliative, focusing on whole-brain radiotherapy, stereotactic radiosurgery, or surgical resection in select cases to control symptoms and improve neurological function. Crucially, the management of brain tumor patients extends beyond direct anti-tumor therapies to encompass aggressive symptom control and supportive care. Corticosteroids, primarily dexamethasone, are indispensable for rapidly reducing peritumoral vasogenic edema and improving neurological symptoms, albeit with significant long-term side effects. Anticonvulsants are prescribed for seizure control or prophylaxis, and newer agents like levetiracetam are often preferred due to their

favorable side-effect profile and fewer drug interactions. The treatment of obstructive hydrocephalus may require emergency cerebrospinal fluid diversion procedures, such as a ventriculoperitoneal shunt or an endoscopic third ventriculostomy, underscoring the need for timely and decisive intervention in the face of acute neurological deterioration.

--- The field of neuro-oncology is characterized by its complexity, spanning from the intricate molecular pathogenesis of primary brain tumors to the pragmatic challenges of managing metastatic disease in a confined cranial space. The prognosis remains grim for many high-grade gliomas, such as glioblastoma multiforme (GBM), which has a median survival of approximately 14 months despite aggressive multimodal therapy, driven by its infiltrative nature, therapeutic resistance, and intratumoral heterogeneity.

--- However, ongoing research into novel therapeutic targets, immunotherapeutic strategies, and advanced drug delivery systems across the blood-brain barrier holds promise for improving outcomes in the future. For the clinician, a high index of suspicion for brain tumors, coupled with a systematic approach to diagnosis and a thorough understanding of the principles of neuro-oncology, is essential for providing optimal care to this vulnerable patient population.

--- The etiology of primary brain and central nervous system tumors remains largely enigmatic, representing a complex interplay between genetic susceptibility and environmental exposures that has eluded definitive elucidation despite decades of intensive research. Unlike many other solid tumors, no single dominant risk factor accounts for a substantial proportion of cases, with the vast majority of patients presenting without any identifiable predisposing condition. This fundamental uncertainty is a critical piece of information to convey to patients, as it helps alleviate unwarranted guilt or self-blame, which are unfortunately common psychological burdens associated with a cancer diagnosis. However, a small but well-defined subset of cases arises in the context of recognized hereditary cancer predisposition syndromes or following documented exposure

to specific environmental agents, most notably ionizing radiation. These established risk factors, while accounting for a minority of overall brain tumor incidence, provide crucial insights into the molecular pathogenesis of these neoplasms and are essential for identifying high-risk individuals who may benefit from enhanced surveillance or preventative strategies.

--- Inherited cancer syndromes constitute approximately 5-10% of all primary brain tumor cases and are characterized by germline mutations in specific tumor suppressor genes that increase an individual's lifetime risk of developing various neoplasms, including those of the CNS.

--- Neurofibromatosis type 1 (NF1), caused by mutations in the NF1 gene, is one of the most common of these syndromes and predisposes to pilocytic astrocytomas, particularly along the optic pathway, as well as other low-grade gliomas. In contrast, Neurofibromatosis type 2 (NF2), resulting from mutations in the NF2 gene, is classically associated with bilateral vestibular schwannomas, which are benign nerve sheath tumors of the eighth cranial nerve, and also carries an increased risk for meningiomas and spinal ependymomas. Tuberous sclerosis complex (TSC), linked to mutations in TSC1 or TSC2, is another important pediatric syndrome that predisposes to subependymal giant cell astrocytomas (SEGAs), which are low-grade astrocytic tumors that typically arise in the walls of the lateral ventricles. Li-Fraumeni syndrome, caused by germline mutations in TP53, is a highly penetrant cancer predisposition syndrome associated with a markedly elevated risk of early-onset high-grade gliomas, among many other malignancies. These hereditary syndromes often present with distinctive clinical stigmata beyond the CNS tumors themselves, such as café-au-lait macules and neurofibromas in NF1, or cardiac rhabdomyomas and seizures in TSC, which can provide critical diagnostic clues. A thorough family history and awareness of these syndromes are therefore imperative for clinicians managing brain tumor patients, as their identification has profound implications for genetic counseling, cancer surveillance in the patient and at-risk relatives, and occasionally for tailoring specific therapeutic approaches.

--- Among environmental risk factors, exposure to high-dose ionizing radiation is the only unequivocally established causal agent for primary brain tumors.

--- This risk is most clearly documented in survivors of childhood cancers who received therapeutic cranial irradiation, where the relative risk of developing a subsequent glioma or meningioma can be elevated several-fold compared to the general population, with the risk increasing with higher radiation doses and younger age at exposure. The latency period between radiation exposure and tumor development can extend for decades, necessitating long-term follow-up for these vulnerable individuals. In contrast, the risk associated with diagnostic medical radiation, such as standard X-rays or CT scans, is considered to be extremely low based on current epidemiological data, and the benefits of these essential diagnostic tools far outweigh the minimal potential risk. Other purported environmental risk factors, such as exposure to non-ionizing electromagnetic fields from mobile phones or residential power lines, have been extensively studied but have not yielded consistent evidence of a causal association with brain tumors. Similarly, the relationship between lifestyle factors like smoking, diet, and alcohol consumption and brain tumor risk remains inconclusive, with most studies failing to demonstrate significant links. Emerging areas of research include the potential roles of birth weight (high birth weight may be associated with a slightly increased risk of certain pediatric brain tumors) and non-chromosomal structural birth defects, though these associations require further validation in larger, well-designed studies.

--- Immune-related factors represent another intriguing area of investigation, with some epidemiological studies suggesting an inverse association between a history of allergies or autoimmune conditions and the risk of glioma, possibly indicating a role for immune surveillance in modulating tumor development. However, these observations are primarily hypothesis-generating at this stage and do not have established clinical utility for risk stratification or prevention.

--- The most transformative advancement in the field of neuro-oncology in recent years has been the integration of molecular genetics into the diagnostic classification of CNS

tumors, culminating in the 5th edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS5), published in 2021.

--- This paradigm shift recognizes that tumors with seemingly identical histological appearances can exhibit vastly different biological behaviors and clinical outcomes based on their underlying molecular profiles. Consequently, WHO CNS5 mandates an integrated diagnostic approach that combines traditional histopathological assessment with molecular testing for specific genetic alterations that are now considered essential diagnostic criteria for many tumor types.

--- This "histomolecular" classification has led to a more precise and biologically relevant taxonomy that better predicts prognosis and guides therapeutic decision-making. A key innovation in this system is the concept of a "layered diagnosis," which provides a comprehensive framework for reporting all relevant diagnostic information in a structured format.

--- This layered approach typically includes: (1) an integrated diagnosis that synthesizes histology and molecular findings into a single, definitive diagnostic entity (e.g., "Diffuse astrocytoma, IDH-mutant, CNS WHO grade 2"); (2) the traditional histological diagnosis; (3) the WHO CNS grade; and (4) a listing of the specific molecular alterations identified. This multi-layered reporting ensures clarity and precision in communication among pathologists, neuro-oncologists, and radiation oncologists.

--- The impact of WHO CNS5 is particularly profound in the classification of diffuse gliomas, which are now stratified primarily based on their molecular features rather than solely on histological criteria. In adult-type diffuse gliomas, the single most important molecular distinction is the mutation status of the isocitrate dehydrogenase (IDH) genes. IDH-mutant gliomas constitute a distinct biological entity with a significantly better prognosis compared to their IDH-wildtype counterparts. IDH-mutant astrocytomas are now graded as CNS WHO grade 2, 3, or 4, with the term "anaplastic" being discarded in favor of a purely grade-based nomenclature.

--- Oligodendrogliomas, in contrast, are defined by the presence of both an IDH mutation and combined loss of chromosomal arms 1p and 19q (1p/19q-codeletion), a molecular signature that is associated with a particularly favorable prognosis and heightened sensitivity to chemotherapy. The most common and most aggressive adult primary brain tumor, Glioblastoma (GBM), is now defined molecularly as "Glioblastoma, IDH-wildtype" to distinguish it from other high-grade astrocytomas that may harbor IDH mutations. This molecular precision is crucial, as it directly influences treatment selection and patient counseling.

--- In the pediatric population, diffuse gliomas are now recognized as biologically distinct from adult counterparts and are classified separately based on recurrent molecular alterations. A seminal discovery in pediatric neuro-oncology was the identification of recurrent mutations in genes encoding histone H3 variants, which define two major clinico-pathological entities. Diffuse midline glioma, H3 K27-altered, is an aggressive tumor that arises in midline structures such as the thalamus, brainstem, and spinal cord, and is characterized by a lysine-to-methionine substitution at position 27 (K27M) in histone H3.3 or H3.1.

--- In contrast, diffuse hemispheric glioma, H3 G34-mutant, typically occurs in adolescents and young adults and involves the cerebral hemispheres, harboring a glycine-to-arginine or valine substitution at position 34 (G34R/V) in histone H3.3.

--- These histone mutations are driver events that fundamentally alter the epigenetic regulation of gene expression, leading to tumorigenesis. Their identification has not only refined classification but has also opened new avenues for targeted therapeutic development, as these mutations create unique neoepitopes that could potentially be targeted by immunotherapeutic strategies.

--- Meningiomas, the most common primary intracranial tumors in adults, have also undergone significant revision in WHO CNS5. While histological grading (grades 1-3) based on features such as mitotic count, brain invasion, and anaplasia remains central to risk stratification, the 2021 update

incorporates molecular markers to further refine prognostic assessment. Notably, specific molecular alterations, such as TERT promoter mutations and homozygous deletion of the CDKN2A/B locus, are now considered sufficient criteria for assigning a grade 3 designation to a meningioma, even in the absence of overt histological anaplasia.

--- This reflects the growing understanding that these molecular features are associated with a significantly higher risk of recurrence and poorer clinical outcomes. Furthermore, the concept of "brain-invasive otherwise benign (BIOB) meningioma" has been clarified, with recommendations to assign a grade based on the presence of brain invasion in conjunction with other histological features.

--- These molecular updates underscore the evolution towards a more biologically grounded classification system that transcends traditional morphology.

--- The modern understanding of brain tumor etiology and classification is characterized by a sophisticated integration of epidemiological risk factors, hereditary cancer syndromes, and, most importantly, a detailed molecular characterization of the tumors themselves. The WHO CNS5 classification represents a watershed moment in neuro-oncology, establishing a new diagnostic standard that is far more clinically relevant than its predecessors. For the practicing clinician, this means that a comprehensive diagnostic workup for a patient with a brain tumor must now include not only expert neuropathological review but also a battery of molecular tests that are essential for accurate classification, prognostication, and the selection of targeted therapies. This integrated approach, while complex, ultimately serves the paramount goal of delivering more personalized and effective care to patients with these challenging diseases.

--- The clinical manifestation of brain tumors is fundamentally governed by two distinct pathophysiological mechanisms: the generalized effects of increased intracranial pressure and the focal neurological deficits resulting from local mass effect, tissue infiltration, or vascular compromise. It is a foundational anatomical principle that the brain parenchyma itself is entirely insensitive to pain; therefore, tumor-related

headaches are exclusively generated by the distortion, stretch, or invasion of pain-sensitive intracranial structures. These structures include the dura mater (particularly the basal dura and the dural sinuses), the major pial vessels at the base of the brain, and the cranial nerves conveying general sensation, such as the trigeminal, glossopharyngeal, and vagus nerves. As a tumor expands within the rigid, non-compliant skull, it disrupts the delicate equilibrium of the intracranial contents—brain tissue, cerebrospinal fluid, and blood volume—leading to a rise in intracranial pressure (ICP). This elevated ICP transmits mechanical stress to the aforementioned pain-sensitive structures, producing a headache that is classically progressive, worse in the morning or upon Valsalva maneuvers, and frequently accompanied by nausea and projectile vomiting. Furthermore, this headache can be indirectly exacerbated by secondary visual disturbances, as chronically elevated ICP causes papilledema, leading to ocular strain and transient visual obscurations. Recognizing the specific characteristics of a tumor-related headache is paramount, as it serves as a critical red flag distinguishing a structural intracranial pathology from far more common benign primary headache disorders.

--- Beyond headaches, the consequences of raised intracranial pressure can rapidly progress to life-threatening neurological emergencies, specifically brain shift and herniation syndromes. As a mass lesion expands, it creates a pressure gradient that forces brain tissue to migrate from one intracranial compartment to another. Uncal herniation, perhaps the most classic and clinically tested scenario, occurs when the medial temporal uncus is displaced over the tentorial edge, compressing the ipsilateral oculomotor nerve (CN III) against the petroclinoid ligament. This initially produces a "blown pupil"—a unilaterally dilated and unreactive pupil due to parasympathetic fiber disruption—followed by an inability to adduct the eye, and subsequently, compression of the ipsilateral cerebral peduncle, resulting in contralateral hemiparesis. If the pressure gradient continues to force tissue downward, tonsillar herniation through the foramen magnum compresses the medulla oblongata, leading to sudden cardiorespiratory arrest, a phenomenon often preceded by Cushing's triad of hypertension, bradycardia,

and irregular respirations, which represents a late, desperate physiological response to extreme brainstem ischemia.

--- Another cardinal presentation of supratentorial brain tumors is the development of new-onset epilepsy, which serves as a vital diagnostic clue in clinical practice. The cerebral cortex, when normal, maintains a delicate balance of excitatory and inhibitory neurotransmission. A tumor acting as an irritative focus disrupts this equilibrium, leading to abnormal, synchronized neuronal depolarization. A fundamental clinical pearl is that any adult presenting with a first-time seizure, particularly above the age of 20, must be evaluated for an underlying structural brain lesion, as approximately 30% of patients with brain tumors will present with seizures. In the pediatric population, idiopathic or genetic epilepsy syndromes are far more common, making a new seizure less specific for a tumor, whereas in adults, a structural cause such as a low-grade astrocytoma, oligodendroglioma, or a meningioma must be rigorously excluded using advanced neuroimaging. The semiology of the seizure often localizes the tumor, for instance, focal impaired awareness seizures pointing to the temporal lobe, or focal motor seizures indicating the precentral gyrus.

--- In addition to seizures, tumors can cause subtle, insidious changes in personality, behavior, and executive function, which are frequently misattributed to psychiatric conditions, leading to significant diagnostic delays. These deficits are highly characteristic of tumors involving the frontal lobes, particularly the prefrontal cortex, which governs higher-order cognitive functions, judgment, impulse control, and social appropriateness. A patient with a slow-growing frontal lobe tumor, such as an olfactory groove or a convexity meningioma, may present with apathy, disinhibition, or a profound lack of motivation long before any focal motor weakness manifests. Conversely, progressive neurological deficits depend strictly on the anatomical location of the tumor; a lesion in the corticospinal tract causes contralateral hemiparesis, a tumor in the dominant temporal lobe causes fluent aphasia, an occipital lobe lesion produces a contralateral homonymous hemianopia, and a posterior fossa tumor causes ataxia, nystagmus, and cranial nerve palsies due to compression of the cerebellum and brainstem.

--- The diagnostic workup for a suspected brain tumor is strategically designed to confirm the presence of a mass, delineate its anatomical boundaries, identify its pathological nature, and determine if it is a primary tumor or a metastasis. While plain skull X-rays are largely obsolete in modern clinical practice due to the superiority of cross-sectional imaging, they remain a frequent subject on board examinations due to their ability to reveal characteristic secondary signs of intracranial pathology. Specific patterns of calcification can strongly suggest certain tumor histologies; for example, oligodendrogliomas frequently exhibit stippled, clumped calcifications, craniopharyngiomas often present with amorphous, "eggshell" calcifications, meningiomas may show psammoma body calcifications, and ependymomas can calcify. Skull X-rays can also demonstrate hyperostosis, a classic sign of a meningioma that provokes an osteoblastic reaction in the adjacent bone, or lytic bone destruction, which is more suggestive of aggressive lesions like metastases, chordomas, or invasive craniopharyngiomas. Erosion of the sella turcica points toward an expanding pituitary macroadenoma, while an enlarged pineal gland calcification shifted away from the midline suggests a contralateral mass effect pushing the pineal body.

--- In acute clinical settings, a non-contrast computed tomography (CT) scan of the head is the initial investigation of choice due to its rapid acquisition and high sensitivity for detecting acute hemorrhage, acute hydrocephalus, and critical bone involvement. However, to truly characterize a brain tumor, a contrast-enhanced CT is necessary, as it highlights areas where the blood-brain barrier has been disrupted. High-grade gliomas, such as glioblastoma multiforme (GBM), typically demonstrate an irregular, heterogeneous ring-like enhancement surrounding a central area of necrosis. Meningiomas, being extra-axial tumors, show intense, homogeneous, and well-circumscribed enhancement with a broad dural base, often accompanied by a "dural tail" sign. Brain metastases usually appear as multiple, well-defined, spherical enhancing lesions located at the gray-white matter junction, where the vascular lumen narrows, trapping tumor emboli. Acoustic neuromas (vestibular schwannomas) enhance in the cerebellopontine

angle, and large pituitary macroadenomas will enhance suprasellarly, often compressing the optic chiasm.

--- Despite the utility of CT, Magnetic Resonance Imaging (MRI) is the undisputed gold standard for the evaluation of brain tumors, offering vastly superior soft tissue resolution and multiplanar capabilities without the beam-hardening artifacts that degrade CT images of the posterior fossa and skull base. MRI protocols for brain tumors must include pre- and post-contrast T1-weighted sequences to assess enhancement, T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) sequences to identify peritumoral vasogenic edema, and critically, Diffusion-Weighted Imaging (DWI) to help differentiate tumors from other ring-enhancing lesions. A classic diagnostic dilemma is differentiating a cystic/necrotic neoplasm from a brain abscess; on DWI, an abscess will exhibit marked restricted diffusion (appearing bright) due to the high viscosity and cellular debris of pus, whereas the necrotic center of a tumor or metastasis will show facilitated diffusion (appearing dark). Furthermore, while GBM typically presents as a solitary, irregularly enhancing lesion with significant surrounding edema, brain metastases are often multiple with smoother rim enhancement and less perilesional edema relative to their size.

--- Additional diagnostic modalities are utilized based on specific clinical questions. Magnetic Resonance Angiography (MRA) or conventional digital subtraction angiography (DSA) may be employed to evaluate the vascular supply of highly vascular tumors like meningiomas, allowing for preoperative embolization to reduce intraoperative blood loss. Positron Emission Tomography (PET) scans are particularly useful in differentiating tumor recurrence from radiation necrosis, as recurrent tumor exhibits high metabolic activity while necrotic tissue does not. Cerebrospinal fluid (CSF) cytology can be instrumental in diagnosing leptomeningeal carcinomatosis or primary CNS lymphoma, but it is absolutely contraindicated in any patient with known or suspected raised intracranial pressure or mass effect on imaging, as the sudden decrease in lumbar CSF pressure during a lumbar puncture can create a pressure gradient that precipitates fatal tonsillar herniation. Finally, a definitive histopathological diagnosis is required to guide treatment, which is obtained via a biopsy—either a

stereotactic needle biopsy guided by MRI for deep-seated or inaccessible lesions, or an open or endoscopic biopsy at the time of surgical resection. Tumor markers, such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (Beta-hCG), are also drawn, particularly in pediatric and young adult populations, to diagnose and monitor germ cell tumors of the central nervous system.

--- The medical management of brain tumors is primarily palliative and symptomatic, as pharmacological interventions do not directly eradicate the neoplastic cells but rather mitigate the devastating physiological consequences of the tumor's presence. The paramount indication for medical therapy is the reduction of peritumoral vasogenic edema, a pathological state driven by the tumor's secretion of vascular endothelial growth factor (VEGF), which disrupts the tight junctions of the blood-brain barrier and leads to the extravasation of plasma proteins into the extracellular space of the brain parenchyma. Glucocorticoids, with dexamethasone being the undisputed agent of choice due to its minimal mineralocorticoid activity and high potency, exert their therapeutic effect by restoring the integrity of the blood-brain barrier, downregulating VEGF expression, and reducing capillary permeability. This results in a rapid, often dramatic, clinical improvement within 24 to 48 hours, making dexamethasone an indispensable lifesaving intervention in patients presenting with acute symptomatic raised intracranial pressure secondary to metastases, meningiomas, or glioblastomas. However, clinicians must be acutely aware that prolonged high-dose corticosteroid therapy carries significant morbidity, including severe steroid myopathy, hyperglycemia, and immunosuppression, necessitating prompt tapering to the lowest effective dose once definitive surgical or radiation therapies are initiated.

--- Surgical intervention remains the cornerstone of definitive brain tumor management, serving multiple critical objectives that extend beyond mere tumor debulking. The primary goals of surgery include obtaining a histopathological diagnosis via biopsy, achieving cytoreduction through either gross total or subtotal resection, and alleviating life-threatening complications such as obstructive hydrocephalus through cerebrospinal fluid diversion procedures like external

ventricular drains or ventriculoperitoneal shunts. The contemporary neurosurgical paradigm for tumor resection is defined by the principle of "maximal safe resection," which aims to remove the greatest possible volume of the tumor while meticulously preserving eloquent cortical and subcortical structures responsible for motor, sensory, linguistic, and visual functions, often utilizing intraoperative neurophysiological monitoring and awake craniotomy mapping. The choice of surgical approach is strictly dictated by the tumor's anatomical location relative to the skull and meninges. A standard craniotomy, where the bone flap is replaced at the end of the procedure, is employed for the majority of supratentorial and posterior fossa tumors. In contrast, a craniectomy, where the bone flap is deliberately left out, is reserved for situations where massive postoperative cerebral edema is anticipated, allowing the swollen brain to herniate outward rather than compressing critical deep structures. For sellar and parasellar lesions, such as pituitary adenomas, a trans-sphenoidal approach through the nasal corridor provides direct access without disturbing the cerebral parenchyma, while a trans-oral approach is utilized for ventral skull base and upper cervical pathologies like clival chordomas.

--- The application of radiation therapy in neuro-oncology requires a strict conceptual distinction between conventional fractionated radiotherapy and stereotactic radiosurgery, as their biological mechanisms and clinical indications differ fundamentally. Conventional radiotherapy utilizes multiple small fractions of radiation delivered over several weeks, exploiting the differential DNA repair capacity between normal brain tissue and tumor cells, and serves primarily as an adjuvant treatment following surgical resection to eradicate microscopic residual disease. The radiosensitivity of a tumor is directly proportional to its mitotic activity and inability to repair sublethal DNA damage; consequently, germinomas and medulloblastomas are among the most exquisitely radiosensitive primary brain tumors, often achieving dramatic responses. Conversely, stereotactic radiosurgery, exemplified by the Leksell Gamma Knife Icon, does not involve surgical incisions but instead delivers a highly concentrated, single-fraction dose of radiation precisely conforming to the three-dimensional contours of the tumor, thereby acting as an

ablative tool. This modality is ideal for small, well-circumscribed lesions, such as brain metastases, vestibular schwannomas, or deep-seated benign tumors that are surgically inaccessible. However, radiation is not without severe long-term sequelae. Acute effects include the exacerbation of peritumoral edema, while late effects, which can manifest months to years later, include irreversible demyelination from oligodendrocyte loss, radiation necrosis characterized by coagulative infarction of white matter, profound neurocognitive decline particularly in the pediatric population, and a theoretically elevated risk of inducing secondary neoplasms, such as radiation-induced meningiomas.

--- Chemotherapy for brain tumors faces unique pharmacokinetic and biological hurdles that severely limit the efficacy of conventional systemic agents. The primary obstacle is the intact blood-brain barrier (BBB), a highly selective permeability interface formed by endothelial tight junctions, a dense basement membrane, and active efflux transporters like P-glycoprotein, which collectively prevent the penetration of large, hydrophilic chemotherapeutic molecules. Furthermore, the low growth fraction of many primary brain tumors, where a significant proportion of cells remain in the quiescent G0 phase of the cell cycle, renders them inherently resistant to traditional cell-cycle-specific chemotherapeutics. To circumvent the BBB, historical strategies included the iatrogenic osmotic disruption of the barrier by infusing hypertonic mannitol prior to chemotherapy administration, which transiently shrinks endothelial cells and opens tight junctions, or the design of lipid-soluble drugs capable of passive diffusion across the lipid bilayer. Today, the cornerstone of medical oncology for gliomas is Temozolomide (TMZ), an oral alkylating agent with excellent CNS bioavailability, approved for the treatment of high-grade gliomas and oligodendrogliomas. TMZ functions by methylating DNA at the O-6 position of guanine, leading to mismatch errors during replication and eventual apoptosis. Crucially, the efficacy of TMZ is heavily influenced by the epigenetic silencing of the MGMT (O6-methylguanine-DNA methyltransferase) DNA repair gene via promoter methylation; tumors with MGMT promoter methylation are unable to repair TMZ-induced DNA damage and thus exhibit significantly

prolonged survival compared to unmethylated, chemoresistant tumors.

--- The prognosis of brain tumor patients exists on a vastly heterogeneous spectrum, dictated primarily by the histomolecular classification of the tumor according to modern WHO criteria and the feasibility of achieving maximal safe surgical resection. Clinical outcomes are evaluated not merely by overall survival metrics—such as median survival and five-year survival rates—but increasingly by the preservation of neurocognitive function and overall quality of life, which are profoundly impacted by both the disease and the neurotoxicity of the treatments. At one extreme of the prognostic spectrum are low-grade meningiomas (WHO grade 1); if completely resected, these extra-axial tumors carry a near 100% cure rate with excellent long-term quality of life. At the diametrically opposite end lies glioblastoma, IDH-wildtype (WHO grade 4), an aggressively infiltrative tumor with diffuse boundaries that preclude curative resection. Despite the current standard of care encompassing maximal safe resection, concurrent radiotherapy with temozolomide, and adjuvant TMZ—often referred to as the Stupp protocol—the median overall survival for GBM remains approximately 15 months, underscoring the desperate need for novel therapeutic paradigms such as immunotherapy, tumor-treating fields, and targeted molecular inhibitors to alter the natural history of this devastating disease.

All praise is due to Allah for the successful beginning of my fifth year of studying Medicine.

The first days of clinical rotations have truly been enjoyable in every way. Before anything else, I want to express my sincere gratitude to the physicians and residents I had the privilege of meeting. Their encouragement, advice, and confidence in me left a lasting impact, especially during the beginning of my Obstetrics and Gynecology rotation. To every one of you who took the time to know my ambition, believed in it, and supported me—I promise that I will do everything I can to live up to your expectations. Your words were never just words; they helped shape my determination.

My goal has been clear from the very first day, and it has never changed: to become the very best I can be in

Neurosurgery. By the will of Allah, I aspire to reach the highest level possible. I will dedicate my time, effort, energy, and every part of myself to this dream. I'm not walking this path to impress anyone or to prove anything to anyone. I'm walking it for myself, for my dream, and even if I have to walk it alone, because in the end, Allah and I are all I truly need.

The road here, however, has not been easy. I went through one of the hardest periods of my life. I lost many people—some for understandable reasons, and others without any real explanation. I won't deny that it hurt. But I learned one important lesson: life never stops for anyone. I've made peace with the belief that once someone chooses to leave my life, they leave, and I don't give second chances. It's not hatred, nor resentment; it's simply how I protect my heart and keep moving forward. On the other hand, those who entered my life at the right time, believed in me and my dream before it became reality, stood beside me, and supported me—they will always have a permanent place in my heart and memory, and I will never forget them.

As long as there is breath in my body, nothing will stop me from pursuing this dream except death. Every obstacle before that is simply another challenge that, by Allah's permission, I will overcome. And I don't intend to stop at one specialty. I want to continue growing into a polymath—someone whose knowledge extends across multiple disciplines. I truly believe that excellence has no boundaries and that learning is a lifelong journey.

To my future self...

This is a promise between who I am today and who I will become—a promise that will never be broken:

By the will of Allah, I will become one of the world's leading neurosurgeons.

When the days become difficult, remember these words. The future is waiting, and I have complete faith that Allah never lets sincere effort go to waste.

O Allah, bless my journey and my knowledge. Make me a means of healing for those who suffer, allow me to benefit humanity, and write for me the honor of becoming one of the distinguished neurosurgeons in the world—if that is good for my faith, my life, and my Hereafter.

This is not merely a wish.

It is a covenant I have made with myself, and I will remain faithful to it for as long as I live.

And Allah is the Best of Witnesses.

As my first step on this journey, I will begin explaining the Fifth-Year Neurosurgery course. All lecture files and educational materials will be uploaded to my Facebook page, which you can find below: https://www.facebook.com/share/1EwknsrycZ/

The journey ahead is long, but I am walking it with unwavering determination.