



AN UPDATED REVIEW ON BRAIN TUMOUR

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Abstract

A cluster of irregular brain cells referred to as a brain tumor. Early detection of brain tumours is crucial for enhancing treatment options and raising patient survival rates, hence it is a crucial responsibility of medical practitioners. This review's goal is to give comprehensive information about brain tumours, including their categorization, risk factors, associated symptoms, diagnoses, and treatment regimens. Each form of brain tumour has its own biology, course of therapy, and high chance of development in relation to certain risk factors. The indications and symptoms of a brain tumour might include localised brain invasion, compression of nearby tissues, and elevated intracranial pressure (ICP). A thorough neurologic examination, extensive history taking, and the appropriate diagnostic neuroimaging procedures are all necessary for the accurate assessment of the patient with a suspected brain tumour. Treatment plans, based on a number of variables, include surgery, radiation, chemotherapy, and immunotherapy

Keywords: Brain Cells, Intracranial Pressure, Neuroimaging Procedures, Chemotherapy, Immunotherapy, Radiation.

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following:

- The location in which the tumor/cancer develops
 - The type of brain cells from which they originates
- The biological diversity of these tumors, however, makes classification difficult [5].

Based on location:

Primary brain tumors: A primary brain tumor is a tumor that starts in the brain. A primary brain tumor is often described as "low grade" or "high grade." A low-grade tumor generally grows slowly, but it can turn into a high-grade tumor. A high-grade tumor is more likely to grow faster[6].Healthcare providers categorize primary tumors as glial (composed of glial cells in your brain) or non-glial (developed on or in the structures of your brain, including nerves, blood vessels and glands) and benign (noncancerous) or malignant (cancerous).Many types of brain tumors can also form in your spinal cord.

Benign brain tumors.

- ❖ Chordomas: These slow-growing tumors typically begin at the base of your skull and the bottom part of your spine. They're mostly benign.
- ❖ Craniopharyngiomas: These tumors usually arise from a portion of your pituitary gland. They're difficult tumors to remove because of their location near critical structures deep in your brain. Gangliocytomas, gangliomas and anaplastic gangliogliomas: These are rare tumors that form in neurons (nerve cells).
- ❖ *Glomus jugulare*: These tumors are typically located just under the base of your skull at the top of your

Introduction

A brain tumor is a collection, or mass, of abnormal cells in your brain. Your skull, which encloses your brain, is very rigid. Any growth inside such a restricted space can cause problems [1]. These brain tumors are a group of neoplasms, each of which has its own biology, prognosis, and course of treatment; these tumors are more accurately known as "intracranial neoplasms," as some of them do not develop from brain tissue (e.g., meningiomas and lymphomas)[2]. BTs can be broadly classified as two types of brain tumors: Benign and Malignant. In fact, the World Health Organization [WHO] has implemented the most widely used grading scheme. Under the microscope, it ranks brain tumors from I to IV. In general, grades I and II are benign (low-grade) brain tumors, while grades III and IV are malignant (high-grade) brain tumors (high –grade). If a low-grade brain tumour is not treated, it is likely to progress to a high-grade brain tumour [3]. These tumors are also located behind the blood–brain barrier (BBB) — a system of tight junctions and transport proteins that protect delicate neural tissues from exposure to factors in the general circulation, thus also impeding exposure to systemic chemotherapy [4].

TYPES: *Brain tumors named and classified according to the*

jugular vein (neck vein). They're the most common form of glomus tumor.

- ❖ *Meningiomas*: These are the most common type of primary brain tumors. Meningiomas typically develop slowly. They form in the meninges, the layers of tissue that protect your brain and spinal cord. In rare cases, a meningioma can be malignant.
- ❖ *Pineocytomas*: These slow-growing tumors form in your pineal gland, which is located deep in your brain and secretes the hormone melatonin.
- ❖ *Pituitary adenomas*: These tumors form in your pituitary gland, which is located at the base of your brain. Your pituitary gland makes and controls hormones in your body. Pituitary adenomas are usually slow growing and they may release excess pituitary hormones.
- ❖ *Schwannomas*: These are common benign brain tumors in adults. They develop from the Schwann cells in your peripheral nervous system or cranial nerves. Schwann cells assist the conduction of nerve impulses. Acoustic neuromas are the most common schwannoma. These tumors occur on your vestibular nerve (the nerve that leads from your inner ear to your brain).

Cancerous (malignant) brain tumors

Approximately 78% of cancerous primary brain tumors are gliomas. These tumors develop in glial cells, which surround and assist nerve cells. Types of gliomas include:

Astrocytoma: These tumors are the most common type of glioma. They form in the star-shaped glial cells called astrocytes. They can form in many parts of your brain, but most commonly occur in your cerebrum.

- ❖ *Ependymomas*: These tumors often occur near the ventricles in your brain. Ependymomas develop from ependymal cells (called radial glial cells).
- ❖ *Glioblastoma (GBM)*: These tumors form in glial cells called astrocytes. GBMs are the fastest-growing astrocytoma.
- ❖ *Oligodendroglioma*: These uncommon tumors begin in cells that create myelin (a layer of insulation around nerves in your brain).
- ❖ *Medulloblastoma*: is another type of cancerous brain tumor. These tumors are fast growing and form at the base of your skull. They're the most common cancerous brain tumor in children [7].

Based on brain cells : Essential mind cancer classifications attributable to cell type from which they begin are: gliomas; having their relationship with glial cells, meningiomas; unusual development of meninges, ependymomas; start from cells (ependymocytes) coating the CSF filled ventricles, astrocytomas; creating from star-formed glial cells (astrocytes)etc, Since the majority of primary brain tumors are gliomas, a class of tumors evolving from supporting cells of the nervous system (glial cell/neuroglia), with an integer of nearly 33%[9].

Under the current WHO classification

gliomas are divided into four histological grades. Grade I gliomas, such as pilocytic astrocytomas, are very slow-growing tumours that are potentially curable if completely resected.

Grade II gliomas (astrocytomas, oligodendrogliomas and oligoastrocytomas) and the more aggressive.

Grade III gliomas (including anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas) have an intermediate clinical course, whereas Grade IV gliomas (glioblastoma) have the most aggressive clinical course (median survival between 14.5 and 16.6 months[15].

Secondary brain tumors: Cancer that begins elsewhere and spreads to the brain. Secondary (metastatic) brain tumors are tumors that result from cancer that starts elsewhere in your body and then spreads (metastasizes) to your brain. Secondary brain tumors most often occur in people who have a history of cancer. Rarely, a metastatic brain tumor may be the first sign of cancer that began elsewhere in your body. In adults, secondary brain tumors are far more common than are primary brain tumors.

Any cancer can spread to the brain, but common types include:

- Breast cancer
- Colon cancer
- Kidney cancer
- Lung cancer
- Melanoma [8].

This Focus issue highlights current research into the unique biology of brain tumours and brain metastasis and how this research might improve therapy of these often devastating diseases:

Survival for many types of malignant primary brain tumours has not improved much in the past 10 years, despite the introduction of some new treatments and despite our improved understanding of the biological bases of brain tumour development. In addition, most malignant brain lesions are actually secondary brain tumours (brain metastases), and it is estimated that brain metastases will develop in up to 30% of adults who have a malignant primary tumour at another site. Furthermore, brain tumours are the most common type of solid tumour in children and are the leading cause of cancer-related deaths in this population. These statistics all indicate that better treatments for brain tumours and brain metastasis are a pressing need. A prime example of both the unique biology and the anatomical challenges of treating brain tumours is the blood-brain barrier (BBB), the neurovascular unit that maintains brain homeostasis and acts as a 'gatekeeper', controlling the crossing of molecules and cells from the blood into the brain. Although the BBB is often disrupted in brain tumours, effective delivery of anticancer therapeutics through this blood-tumour barrier remains a challenge. Gliomas account for ~80% of malignant brain tumours, and the highest grade glioma, glioblastoma, is one of the most lethal cancers in adults.

Interestingly, genomic sequencing efforts more than 10 years ago jump-started the field of glioma metabolism with their finding of recurrent mutations in the genes encoding the tricarboxylic acid cycle enzymes IDH1 and IDH2, but the role of metabolism in glioma pathogenesis goes beyond IDH. Medulloblastoma is one of the most common paediatric brain tumors. Our understanding of this disease was advanced substantially by genomic studies reported in 2012. Since then, as discussed by Hovestadt et al. [8], more genomic studies, as well as epigenomic, transcriptomic and proteomic profiling efforts, have provided new insights into medulloblastoma biology that will hopefully lead to improved diagnosis and therapy [10].

Risk factor:

BRAIN TUMORS ARE A HETEROGENEOUS GROUP OF TUMORS THAT VARY SIGNIFICANTLY IN INCIDENCE BY AGE, SEX, AND RACE/ETHNICITY.

THE ONLY WELL-VALIDATED RISK FACTORS FOR BRAIN TUMORS ARE IONIZING RADIATION (WHICH INCREASES RISK IN ADULTS AND CHILDREN) AND HISTORY OF ALLERGIES (WHICH DECREASES RISK).

GENOME-WIDE ASSOCIATION STUDIES HAVE IDENTIFIED 32 HISTOLOGY-SPECIFIC INHERITED GENETIC VARIANTS ASSOCIATED WITH INCREASED RISK OF THESE TUMORS

Age: Incidence of BTs overall increases with age. For malignant glioma in particular, the incidence is bimodal, with highest incidence in the youngest and oldest ages. The age distribution also varies by histologic type. Embryonal tumors, a group that includes medulloblastoma and primitive neuroectodermal tumors, occur most frequently in children less than 10 years old. Incidence of pituitary tumors is also bimodal, with peaks in adolescence/young adulthood, and again in older adulthood. The most common BTs, such as GBM, vestibular schwannoma, and meningioma, have the highest incidence in individuals in their late 60s and early 70s, with a decreasing incidence thereafter. This may be due to competing causes of mortality, different diagnostic patterns in the oldest age group, or true differences in BT incidence.

Sex: Incidence of BTs varies by sex, with malignant tumors occurring much more frequently in males and nonmalignant tumors generally occurring more frequently in females. This sex difference varies significantly by histology, with some histologies showing little or no variation in incidence by sex. The largest sex difference is observed in non-malignant meningioma (which is nearly twice as common in females), and high-grade gliomas (particularly GBM, which is ~60% more common in males). Sex differences are smaller or nonexistent in many tumors that are common in children, such as pilocytic astrocytoma and medulloblastoma.

- **Race/Ethnicity:** Incidence of different histologies of BTs varies by race/ethnicity. Neuroepithelial tumors, including gliomas, are much more common in individuals of European ancestry (white non-Hispanics) compared with other groups. Meningiomas and pituitary adenomas occur more frequently in black non-Hispanics compared with other groups. Nerve sheath tumors and germ cell tumors have the highest incidence in Asian/Pacific Islanders [11].
- **Allergic diseases:** The relation of allergic diseases to neoplasia is controversial. In general, retrospective and descriptive studies have tended to show protective effects of asthma, hay-fever, eczema and other allergic diseases (Vena et al., 1985), as found in the present study. In their own retrospective, questionnaire-based study of over 17,000 subjects, Vena et al. found decreased risks for many different types of cancer and for all cancer sites combined associated with a history of allergic diseases, especially hives. An exception, also reported by Reynolds and Kaplan (1987), was lung cancer associated with asthma, for which an increased risk was found. Analysis of a cohort of 6,913 adults in the First National Health and Nutrition Examination Survey (NHANES I), designed to overcome weaknesses of previous studies (discussed by Vena et al.), showed that risk of malignancy was increased by pre-existing allergic disease (McWhorter, 1988). None of these studies considered brain tumors separately, and previous studies of brain tumors in adults have not specifically considered allergic disease as a possible risk factor. The present results suggest that overstimulation of the immune system, reflected in a history of atopy or allergic phenomena, may be associated with a decreased risk of glioma [12].

Exposure to radiation

- People who have been exposed to ionizing radiation have an increased risk of brain tumors. You can be exposed to ionizing radiation through high-radiation cancer therapies. You can also be exposed to radiation from nuclear fallout.
- The nuclear power plant incidents in Fukushima and Chernobyl are examples of how people can be exposed to ionizing radiation [13]. Cohort studies of nuclear industry workers, radiologists and X-ray technologists report effects of ionizing radiation occupational exposure with leukemia, but not BT, risk. A study of US radiology technologists from 1983–1998, found 53 cases of BT, yielding a SIR of 0.95. A case-control study of 60 newly diagnosed CNS tumors, aged 25–74, reported a RR of 2.1 (95% CI: 1.0–4.3) for meningioma development in subjects receiving dental radiography at least annually, compared with less than every 5th year.
- **Non-Ionizing Radiation:** Electromagnetic Fields and Radio Frequency Cell Phones

The association of exposure to non-ionizing radiation, specifically exposures in the radio frequency range (RF) or electromagnetic fields in the extremely low frequency range (EMF ELF) and development of primary BTs remains unresolved. Of particular interest is the questionable relationship between both gliomas and meningiomas and cellular phone use.⁶⁶ These exposures are ubiquitous, and recent research focuses principally on mobile phones because these RF exposures occur near the head and brain. The possible influence of currently acceptable low-level RF exposures on carcinogenesis has been suggested by some studies and warrants further investigation.⁶⁷ While the relative rarity of primary BTs necessitates a case-control study

genes *TP53* and *CHEK2*. Turcot's syndrome is caused by mutations in genes involved in introduction DNA repair. It is likely that in Li-Fraumeni syndrome and Turcot's syndrome the risk for brain tumors is increased by an increased rate of DNA mutation leading to uncontrolled growth. Neurofibromatosis is caused by mutations in *NF1* or *NF2* and tuberous sclerosis is caused by mutations in *TSC1* or *TSC2*. *NF1*, *NF2*, *TSC1* and *TSC2* are all involved in down regulation of growth promoting signal transduction pathways in the cell. It is therefore likely that in neurofibromatosis and tuberous sclerosis, the risk for brain tumors is increased because brain cells are primed for excessive growth and then develop additional mutations allowing cancer to form.

In addition to known familial cancer predisposition syndromes, it has also been observed that brain tumors can cluster within families. Familial clustering can be because of both genetic and environmental factors, as families often share common environmental exposures in addition to common genes. Modeling of the inheritance pattern of familial glioma suggests that at least in some cohorts, genetic factors play a role in susceptibility. Segregation analysis of 297 families in Sweden suggested that recessive genes may contribute to familial glioma, although a multifactorial model was not excluded. However, homozygosity mapping in a study of seven glioma families in Sweden did not identify any common homozygous alleles. Segregation analysis of 639 families in the United States and Canada found evidence for a multifactorial Mendelian model, and suggested that familial glioma is affected by multiple low penetrance genes. In contrast, a study of 396 families in Iceland found no evidence for increased risk of gliomas in families, although the authors cite several limitations to the study including small sample size [14].

Table 1: Risk Factors associated with brain tumor [9]

Validated Risk Factors	Unverified Risk Factors
Environmental Prior exposure to high-dose Ionizing radiations Genetic Neurofibromatosis types 1 & 2 Li-Fraumeni syndrome Von Hippel-Lindau disease Tuberous sclerosis Turcot syndrome Cowden disease Gorlin syndrome	Environmental Cell phones Alcohol Virus- induced Infections Smoking Exposure to Vinyl chloride, Pesticides, Rubber etc. Dietary N-nitroso compounds Exposure to Aspartame Exposure to Electromagnetic fields Genetic Genetic polymorphisms (e.g. XRCC1)

design, these studies experience severe limitations with exposure assessment due to reliance of personal recall of cases and controls of their RF exposures (i.e., cell phone use)[39].

Genetic risk factor for BT:

Although very little is known about the genetic risk factors for brain cancer, a few factors have been identified thus far. Brain tumors are associated with several familial cancer predisposition syndromes. These include Li-Fraumeni syndrome, neurofibromatosis, tuberous sclerosis and Turcot's syndrome. In these syndromes, individuals inherit a germline mutation in a tumor suppressor gene.

Tumors initiate when the remaining copy of the tumor suppressor is mutated or silenced, giving rise to cells with a growth advantage. Because tumorigenesis requires the accumulation of multiple mutations in cells, these individuals have an increased tumor risk because all cells carry an initial mutation. Li-Fraumeni syndrome is caused by mutations in the cell checkpoint

Clinical signs and symptoms of brain tumors :

Signs and symptoms in patients with primary brain tumors can be generalized or focal. In the initial stages of disease (low-grade tumors), most symptoms are focal. Generalized symptoms occur with increased tumor size. Common generalized symptoms include headache, nausea, vomiting, seizures, and altered mental functions (e.g., personality changes)[16]. Focal symptoms and signs occurring during brain tumor clinical presentation are dependent on a number of factors. Location and rate of growth are the most critical, followed by overall lesion size and nature, whether infiltrating or causing the displacement of neural structures, but also the presence or extent of associated pathology, including edema, hemorrhage, vascular compromise, and cerebrospinal fluid obstruction. Tumor can damage neural tissue or displace it by compression, leading to focal symptoms. Direct invasion of the tumor typically occurs in infiltrating gliomas or lymphomas, whereas meningiomas and metastases displace brain tissue. The disruption of the blood-brain barrier by the tumor leads to vasogenic

edema that is probably one of the main causes of clinical impairment. Edema favors an increased mass effect and thus further compression of the surrounding brain. Furthermore, presenting symptomatology can be often attributed to more generalized symptoms and signs, including headache, altered mental status, seizure and symptoms of increased intracranial pressure, including papilloedema, nausea, and vomiting[17]. Patients with brain tumors commonly have symptoms caused by the tumor or treatment. Treatment approaches for these symptoms will help the patient cope with those impairments caused by the symptoms[21].

In children : Headaches (41%), vomiting (12%), shakiness (11%), visual problems (10%), behavioural or academic issues (10%), and seizures (9%), were the most frequently reported initial symptoms. Headache (56%), vomiting (51%), behavioural or educational issues (44%), shakiness (40%), and visual impairments (38%) were the most prevalent symptoms at any given time. 88% of patients exhibited neurological symptoms at the time of diagnosis: 38% had papilloedema, 49% had abnormalities of the cranial nerves, 48% had cerebellar signs, 27% had long tract indications, 11% had somatosensory abnormalities, and 12% had a decreased state of consciousness. The median time between symptoms was 2.5 months (range 1 day to 120 months). High grade tumours and patient ages of 3 years or less were substantially correlated with a brief symptom interval[18].

In Adult : Patients have described the following as the primary brain tumor's initial signs: Generalized seizures (21.3%), generalised headaches (23.5%), unilateral weakness (7.1%), unsteadiness (6.1%), expressive language disorder (5.8%), visual issues (3.2%), confusion (4.5%), unilateral numbness (2.3%), personality issues (1.6%), diplopia (0.3%), and other symptoms (24.2%) like anosmia, apraxia, cognitive delay, drowsiness, dysphagia, hallucinations, memory loss, nausea and vomiting[19].

Psychiatric symptoms may be early indicators for primary brain tumors, and these tumors are up to ten-times more common in psychiatric patients . Infrequently, psychiatric manifestations are the only presenting symptoms of a brain tumor . The reported incidence of psychiatric symptoms in brain tumors varies from 50% [4] to 78% . Primary intracranial tumors occur in approximately ten per 100,000 adults and exhibit an age-related increase. Gliomas account for approximately 50% of primary brain tumors . Metastatic brain tumors may be associated with a greater incidence of mental symptoms than primary brain tumors, most likely due to the diffuse distribution of the tumors scattered throughout the brain parenchyma. This leads to the additive effects of the constitutional symptoms of the primary tumor itself, such as lethargy and apathy. No well designed, large-scale studies have been conducted with the purpose of examining the association between clinical psychiatric symptoms and tumor location/histology [20].

DIAGNOSIS

Early tumor diagnosis plays a significant role in enhancing treatment possibilities[22]. Diagnosis of a suspected brain tumor is dependent on appropriate brain imaging and histopathology[23].

Brain imaging : Brain imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS), are used to provide information about the location, size, shape, and type of brain tumor to assist in the diagnosis. The main goal of computerized brain tumor diagnosis is to obtain important clinical information regarding the tumor presence, location, and type. The information obtained through clinical imaging can guide and control any future interventions and thus leads to the correct diagnosis and treatment of the tumor[22].

PET: Positron Emission Tomography (PET) is used in monitoring of brain activities in a live view. This method is developed by observing the absorption rate of glucose by a tumor. A radioactive marked deoxyglucose is injected to patient and the scanning observes the activity of brain based on the processing of glucose by the tumor[24].

Single-photon emission computed tomography

Similar to a gamma camera, SPECT is a nuclear medicine tomographic imaging technique utilizing gamma rays that provide three-dimensional (3D) information. SPECT has a rather poor spatial resolution of 8–10 mm, but is more sensitive and somewhat cheaper, and SPECT is available at every nuclear medicine department. At present the quantization of tissue function with SPECT is not a routine procedure. Four nuclides are used currently in SPECT imaging: thallium 201, technetium 99m, iodine 123, and indium 111. Several radioisotope-labeled compounds including 201Tl, technetium-99m-hexakis-2-methoxyisobutyl isonitrile (99mTc-MIBI), and 3-[123I]iodo- α -methyl-L-tyrosine (IMT) have been developed and utilized for glioma imaging, and several reviews have discussed these tracers[40].

CT: CT remains more widely available and can provide important complementary information(5, 6). CT remains the current gold standard imaging modality to diagnose the presence of acute intracranial hemorrhage, calcifications, and osseous anatomy. In select cases, the information provided by CT may be helpful for narrowing the differential diagnosis of a newly diagnosed intracranial mass lesion. For example, coarse calcifications may be observed in oligodendrogliomas(7), whereas hyperdensity on CT suggests a densely cellular tumor such as lymphoma(8). CT is frequently obtained prior to MRI for the initial work-up of a suspected intracranial mass lesion, and it is often obtained immediately following stereotactic biopsy. Despite these situational advantages, limitations of CT compared to MRI include inferior soft tissue characterization, posterior fossa beam hardening artifact and the use of ionizing radiation[25].

MRI: Magnetic Resonance (MR) imaging produces images of the human tissues in a noninvasive manner, revealing the structure, metabolism, and function of tissues and organs. The impact of this image technique in diagnostic radiology is impressive, due to its versatility and flexibility in joining high-quality anatomical images with functional information [2]. MRI is attracting more and more attentions for the brain tumor diagnosis in the clinical. Four standard MRI modalities used for glioma diagnosis include T1-weighted MRI (T1), T2-weighted MRI (T2), T1-weighted MRI with gadolinium contrast enhancement (T1-Gd) and Fluid Attenuated Inversion Recovery (FLAIR)[3]. Generally, T1 images are used for distinguishing healthy tissues, whereas T2 images are used to delineate the edema region which produces bright signal on the image. In T1-Gd images, the tumor border can easily be distinguished by the bright signal of the accumulated contrast agent (gadolinium ions) in the active cell region of the tumor tissue. Since necrotic cells do not interact with the contrast agent, they can be observed by hypo intense part of the tumor core making it possible to easily segment them from the active cell region on the same sequence. In FLAIR images, signal of water molecules are suppressed which helps in distinguishing edema region from the Cerebrospinal Fluid (CSF)[26].

Histopathological diagnosis: imaging diagnosis of intracranial lesions may lead to a considerable proportion of misdiagnosis, and therefore it is important to obtain a histopathological diagnosis[27]. histologic assessment and confirmation is essential to determine biology, grade, and genetic alternations of the tumor . However, in some conditions such as brain stem gliomas, diagnosis is generally based on the clinical presentation and imaging findings because of the substantial risk of mortality and morbidity of tissue sampling in such cases [28]. The tumor location and age of the patient are considered in the histological differential diagnosis[29].The specific cell type, or histology, comprising a CNS tumor is a critical piece of information in the determination of an appropriate treatment plan and the estimation of a patient's prognosis[30]. Surgical intervention is required to remove the lesion and obtain tissue for histopathological evaluation; therefore, it is incumbent upon the neurosurgeon to perform a biopsy that is safe and minimally invasive and involves proper handling of specimens for molecular profiling[30].

BIOPSY:A brain biopsy is an established method for obtaining a histopathological diagnosis and for guiding the management of cerebral lesions[31].biopsy is a clinical procedure that facilitates extraction of brain tissue for histological analysis and the subsequent initiation of appropriate treatment based on accurate morphological diagnosis[32].Indication for biopsy was established by the institutional multidisciplinary neuro-oncology team. Major indications for biopsy were as follows: (1) multifocal or diffusely infiltrating tumors not candidate for debulking

surgery; (2) deep-seated tumors not amenable to safe surgical resection; (3) elderly patients harboring large tumors (either multi-centric or deep-seated); and (4) cases with radiological suspicion of PCNSL[33].

Type of Biopsy: Biopsy of intracranial lesions can be performed by

Craniotomy/open biopsy:An open biopsy involves obtaining a chunk of block specimen via craniotomy; it is the most common form of brain biopsy. Craniotomy is performed above the abnormal lesion, and the specimens are obtained using an operating microscope. Te advantages of this approach include a high diagnostic yield and relatively large sample that can be collected from any site of the lesion. Furthermore, most neurosurgeons are familiar with microsurgery. Open biopsy does not require equipment such as a stereotactic brain surgery system and endoscopes. However, this technique is invasive and can be disorientating due to mechanical deviation and brain shif in deeper and smaller lesions. Open biopsy involves a long skin incision, craniotomy, and a large extent of brain retraction and incision; it is a long procedure performed under general anesthesia[30].

Stereotactic needle biopsy: It is commonly used for intraparenchymal tumors. Tis method is minimally invasive; neither a craniotomy nor general anesthesia is required. Te risk of complications such as brain damage due to retraction and corticotomy is low[34].Brain needle biopsies are indicated for deep-seated or multiple brain lesions and for patients with poor prognosis in whom the risks of resection outweigh the potential outcome benefits.biopsy location should be planned based on molecular guidance techniques, such as positron emission tomography, magnetic resonance (MR) spectroscopy, or others in order to provide a reliable molecular diagnosis.

The current standard-of-care method for stereotactic brain needle biopsy involves a 1.6- to 2-mm-diameter needle cannula insertion through a cranial burr-hole aligned to a predetermined trajectory. The two cannulas have overlapping side windows. When the desired position is reached, these windows are aligned, and brain tissue is lodged into cannula using suction and cut by sliding the inner cannula[34].

Neuroendoscopy: Endoscopic neurosurgery encompasses endoscopic endonasal approach to skull base lesions and intraventricular surgery (including third ventriculostomy and intracerebral hematoma evacuation in cylinder surgery). Recently, navigation-guided endoscopic biopsy has been used to overcome the drawbacks of needle and open biopsies. The biggest advantage of this method is that the target lesion and surrounding vessels can be visualized using an endoscope. Operators can resect a larger lesion volume without increasing the risk of bleeding; if bleeding occurs, it can be controlled with monopolar or biopsy forceps. Furthermore, a combination of multi-modal techniques, including intraoperative [34].Endoscopic procedures are performed under general anesthesia. A small incision is made in the location

determined by the safest entry point and trajectory to the tumor. A single burr hole is made, the dura mater is opened, and the pia mater is coagulated and incised. A peel-away sheath or a cannula and obturator are then introduced into the lateral ventricle. The inner cannula of the sheath or the obturator is then removed and the endoscope is introduced. Cerebrospinal fluid may be sampled for routine analysis, malignant cells, and/or tumor markers. For tumors in the lateral ventricle, the lesion is usually immediately visualized. For lesions that cannot be easily reached with a straight trajectory, angled (30 or 70) degree rigid endoscopes or flexible endoscopes can be used[35].

All the brain biopsies sent for histopathological analysis were analyzed. Clinical, radiological, and pathological features were analyzed during the evaluation and examination of a slide of tissue by a neuropathologist. To prepare a permanent specimen, a sample of tissue is fixed in formalin, embedded in wax and stained with hematoxylin and eosin (H&E). Immunohistochemistry was performed wherever indicated, further with immunohistochemical stains and molecular testing for accurate diagnosis and proper classification. Overall, this process of obtaining a final pathologic diagnosis lasts multiple days and is important for specific treatment and prognosis [30,36].

Liquid biopsy: Direct biopsies obtain tissue material from the primary tumor, either via neurosurgical removal of all or most parts of a tumor or via stereotactic tissue biopsy. In contrast, a liquid biopsy uses body fluids collected distant to the brain tumor, such as venous blood from the arm or cerebrospinal fluid (CSF) via lumbar or cisternal. In general, probes from urine, saliva, ascites, bronchial fluid, or vitreous liquid can also serve as material for liquid biopsy, but mainly for other tumors. Within these biofluids, the relevant tumor-derived nucleic acids can be found in different compartments: (1) in single or clustered, intact circulating tumor cells (CTCs), (2) in subcellular parts derived from the tumor, such as extracellular vesicles (EVs), or (3) in even cell-free nucleic acids (cfDNA, RNA). Due to the location, tissue biopsies from brain tumors represent a usually much higher risk for complications than from most other tumors; hemorrhage or brain swelling can harm healthy parts of the brain and endanger life. Repeated tissue biopsies of the brain for follow-ups are difficult; thus, it is tempting to replace or complement them with a less risky procedure, as long as there is high specificity and acceptable sensitivity. Replacing a surgical tissue biopsy by a regrowing brain tumor by obtaining blood or CSF for liquid biopsy instead, while still getting the relevant information of the response to a therapy even more quickly and cheaply, would significantly reduce the individual risk for the patient, especially those with severe comorbidities. Tissue biopsies may miss a relevant part of a tumor, which liquid biopsy may detect, and, vice versa, liquid biopsy may also not represent the whole primary

tumor, but represent a more migratory and aggressive part, thus potentially having some advantage or additional information over classical tissue biopsy[37].

Serum samples were analysed using our spectroscopic liquid biopsy test; a platform technology based upon attenuated total reflectance-Fourier transform IR (FTIR) spectroscopy. Each sample was prepared for spectroscopic liquid biopsy by pipetting 3 µl of serum onto three wells of the optical sample slides. Slides were then dried for 1 h, in an incubator cabinet at 35°C, permitting controlled drying. When dried, each patient slide was then analysed using the attenuated total reflectance-FTIR spectroscopy platform, by placing the slide into the slide carriage on the slide indexing unit. In this study, a Perkin Elmer Spectrum 2 FTIR spectrometer (Perkin Elmer, US) was used to generate spectral data using locked down spectral parameters[38].

Treatment:

The goal of treatment may be curative or focus on relieving symptoms (palliative care). Treatments are often used in combination with one another. The goal is to remove all or as much of the tumor as possible through surgery to minimize the chance of recurrence. Radiation therapy and chemotherapy are used to treat tumors that cannot be removed by surgery alone. For example, surgery may remove the bulk of the tumor and a small amount of residual tumor near a critical structure can later be treated with radiation [41].

Factors they consider include:

THE PERSON'S AGE

- Their general health status
- Their medical history
- The location, size, and type of tumor
- The risk of the tumor spreading
- The person's tolerance for certain treatments

The following are some of the most common treatment methods for brain tumors[42].

Surgery is the primary definitive treatment for patients with low-grade gliomas. In patients with aggressive gliomas or metastatic disease, surgical options are generally offered to patients who have good performance status, to establish the diagnosis, as well as achieve the most reduction in tumor burden. Despite aggressive attempts at surgical resection, complete removal of the tumor is not always possible. This can be especially difficult in patients with primary aggressive GBM or in patients with brain metastases, where other sites of systemic disease are still present. Therefore, additional treatments such as adjuvant radiation or chemotherapy are often employed.

Specific types of tumors warrant tailored treatment options. In low-grade gliomas, maximal surgical resection may be the only treatment required followed by appropriate surveillance. In cases of aggressive GBM, adjuvant chemotherapy and radiation is typically offered after maximal surgical resection as it had been shown to improve overall survival [43].

Radiation therapy: plays a critical role in the management of primary and secondary brain tumors. In the past few decades, radiotherapy (RT) has seen technical advances in all aspects of treatment, with improvement in patient immobilization, imaging, treatment planning and delivery. Advances in imaging and RT technology have enabled more precise tumor localization and dose delivery, leading to a reduction in the volume of normal brain tissue irradiated at high radiation doses. The principal aim of normal tissue sparing is to reduce the potential long-term toxicity of RT while maintaining its effectiveness. Radiation techniques have evolved from 3D conformal radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic techniques, including either stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT). A further improvement in accuracy of radiation delivery has been made with the development of image-guided radiation therapy (IGRT), in which image guidance enables better precision in patient setup and target localization, allowing reduction of planning margins and leading to a smaller volume of healthy tissue irradiated at high doses. Currently, there is interest in the use of particle therapy for treating brain tumors because of the ability to concentrate the dose of protons and ions in the target volume while simultaneously sparing surrounding healthy tissues [44].

Chemotherapy: Treatments for many forms of malignant brain tumors have included various types of chemotherapy. Although the blood-brain barrier tends to protect the brain to some degree, avoidance of toxicity to normal brain tissue and delivery of agents to tumors within functioning brain tissue have been major problems. Single-agent chemotherapy, primarily with nitrosoureas (BCNU and CCNU), has had modest effectiveness in adult malignant gliomas. Combination chemotherapy has been employed with some success in the management of pediatric malignant brain tumors. Unfortunately, the number of effective and nontoxic agents remains limited [45]. The availability of temozolomide, a novel alkylating agent with good penetration in the central nervous system. In the 1990s a series of phase II trials have shown activity of temozolomide (TMZ) against recurrent glioblastoma and anaplastic astrocytoma. After approval in 1999, TMZ has largely replaced nitrosoureas in the treatment of glioma, although a formal comparative trial was never conducted. Recently, a randomized trial has demonstrated a superior survival in newly diagnosed glioblastoma multiforme (GBM) patients, treated with TMZ and radiation. Both PCV combination chemotherapy (procarbazine, CCNU and vincristine) and temozolomide were investigated as treatment for recurrent and newly diagnosed anaplastic oligodendroglioma [46].

Immunotherapy: Immunotherapeutic options for the treatment of solid tumors have rapidly expanded in recent years, and in some cases have produced durable responses without lasting toxicities. Although only a small number of

clinical trials of immunotherapy for the treatment of brain tumors have been completed to date, some early results leave patients and clinicians hopeful. Collectively termed 'immunotherapy,' treatments that modulate immune activity have proven effective for the elimination of several types of cancers, including leukemia, lymphoma, melanoma, non-small cell lung cancer, bladder and kidney cancers, and head and neck cancer. Because they specifically target tumor tissue while sparing healthy tissue, immunotherapies may offer both increased survival of patients with tumors that recur due to incomplete elimination, such as GBM, as well as reduced therapy-related side effects. We will discuss five classes of immunotherapeutic strategies: (1) Direct antitumor activity by endogenous or ex vivo expanded engineered cytotoxic T or NK cells, (2) Antibody blockade of immune checkpoints to prevent exhaustion of T cells, (3) Activation of the innate immune system by peptide or dendritic cell (DC) vaccination, (4) Direct lysis of tumor cells using oncolytic viruses, and (5) Reducing immunosuppression by reprogramming the tumor microenvironment

Conclusion

Our brain is the most protected organ of our body and also very difficult to know what's happening in it. If any deadly disease like brain tumor cancer also it become difficult for its exact treatment due to lack of poor diagnostic in early stage, so diagnosis in early stage necessary by considering its brain imaging (CT, MRI) and histopathological analysis (biopsy) is necessary for determining exact type of tumor and its alternative treatment.

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