THE REPUBLIC OF TURKEY
BAHCESEHIR UNIVERSITY

COMPUTATIONAL NEURO-ONCOLOGY: USING MATHEMATICAL MODELS AND MACHINE LEARNING FOR DIAGNOSIS, PROGNOSIS, AND TREATMENT PLANNING OF TUMOURS OF THE HUMAN NERVOUS SYSTEM

Master Thesis

KADIR ÖZEN SÜMERKENT

İSTANBUL, 2019

THE REPUBLIC OF TURKEY

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GRADUATE SCHOOL OF HEALTH SCIENCES

DEPARTMENT OF NEUROSCIENCE

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ABSTRACT

COMPUTATIONAL NEURO-ONCOLOGY:
USING MATHEMATICAL MODELS AND MACHINE LEARNING FOR DIAGNOSIS, PROGNOSIS, AND TREATMENT PLANNING OF TUMOURS OF THE HUMAN NERVOUS SYSTEM

Kadir Özen SÜMERKENT

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In U.S. 70.000 new cases of primary malignant and benign brain and central nervous system, tumours are diagnosed each year, and 14.000 patients die. Brain tumour treatment options depend on several parameters including but not limited with the type, dimensions, and location of the tumour, but obviously, diagnosis of the brain tumour is the first step of treatment.

Because most of the symptoms of brain tumours are shared with other ailments (especially in the first stages), brain tumours are often misdiagnosed. This study proposes the idea of integration of mathematical methods and tools to clinical processes which can support the diagnosis, prognosis, as well as treatment planning and the other services provided by the neuro-oncology clinics. This integration will help clinics to increase diagnosis speed and accuracy and create highly personalized treatment plans for neuro-oncology patients.

In our study, we included the details of a component that we selected for diagnosis within this process, together with our solution suggestion that can be used in the field of neuro-oncology, utilizing machine learning and other computational methods. This project, which has the potential to contribute significantly to the accuracy and speed of diagnosis of brain tumours, is believed to be a decision support system that will make significant contributions to neuro-oncology clinics by developing other components.

Keywords: Brain, Tumour, Cancer, Neurology, Neurosurgery.

ÖZET

COMPUTATIONAL NEURO-ONCOLOGY:
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ABD'de her yıl 70.000 yeni primer malignant ve benign beyin ve santral sinir sistemi tümörü teşhis edilmekte, 14.000 hasta ölmektedir. Beyin tümörlerinde tedavi seçenekleri, tümörün tipi, boyutları ve konumu gibi pek çok parametreye bağlıdır ancak tedavinin ilk ve en önemli aşaması, tümörün mümkün olan en erken evrede teşhisidir.

Beyin tümörlerinin semptomlarının çoğu diğer hastalıklarla (özellikle ilk aşamalarda) paylaşıldığından, beyin tümörleri sıklıkla yanlış teşhis edilir. Bu çalışma, matematiksel yöntemlerin ve araçların tanı, prognoz, tedavi planlaması ve nöro-onkoloji klinikleri tarafından sağlanan diğer hizmetleri destekleyebilecek klinik süreçlere entegrasyonu fikrini önermektedir. Bu entegrasyon kliniklerin tanı hızını ve doğruluk oranını arttırmasına ve nöro-onkoloji hastaları için yüksek oranda kişiselleştirilmiş tedavi planları oluşturmasına yardımcı olacaktır.

Çalışmamıza, bu süreçte teşhis sürecine ilişkin seçtiğimiz bir bileşenin ayrıntılarını, nöro-onkoloji alanında kullanılabilecek çözüm önerimizi, makine öğrenmesini ve diğer hesaplama yöntemlerini kullanarak sunduk. Beyin tümörlerinin tanısının doğruluğu ve hızına önemli ölçüde katkıda bulunma potansiyeline sahip olan bu projenin, diğer bileşenlerin de geliştirilmesi ile birlikte nöro-onkoloji kliniklerine önemli katkılar sağlayacak bir karar destek sistemi olduğuna inanmaktayız.

Anahtar Kelimeler: Beyin, Tümör, Kanser, Nöroloji, Nöroşirürji.

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LIST OF ABBREVIATIONS

AFCM	:	Approximate Fuzzy C Means
ANN	:	Artificial Neural Network
BP	:	Back Propagation
CBF	:	Cerebral Blood Flow
CBV	:	Cerebral Blood Volume
CT	:	Computer Tomography
DNA	:	Deoxyribonucleic acid
DTI	:	Diffusion Tensor Imaging
DWI	:	Diffusion Weighted Imaging
FA	:	Fractional Anisotropy
FCM	:	Fuzzy C-Means
FFBP	:	Feed Forward Back Propagation
FFCC	:	Feed Forward Cascade Correlation
FLAIR	:	Fluid Attenuated Inversion Recovery
GBM	:	Glioblastoma Multiforme
LR	:	Logistic Regression
LVQ	:	Learning Vector Quantization
MDA	:	Multivariate Data Analysis
MLFN	:	Multi-Layer Feed Forward Network
MR	:	Magnetic Resonance
MRI	:	Magnetic Resonance Imaging
MRS	:	Magnetic Resonance Spectroscopy
mTOR	:	Mammalian Target of Rapamycin
PET	:	Positron Emission Tomography
pMR	:	Perfusion-weighted Magnetic Resonance
ROI	:	Region of Interest
rCBV	:	relative Cerebral Blood Volume
SLFN	:	Single Layer Feed Forward Network
SOM	:	Self-Organizing Map
STA	:	Sequential Training Algorithm
VEGF	:	Vascular Endothelial Growth Factor
X-Ray	:	Radiography

LIST OF SYMBOLS

Number of total cases	:	n
Number of categories	:	M
Ith case	:	Xi
Number of total cases	:	N
Signal intensity	:	A_E
Wavelet	:	$\psi_{(t)}$
Coefficients of the approximation components	:	$ca_{j,k}$
Detail components	:	$cd_{j,k}$
Low pass filter	:	$g(n)$
High pass filter	:	$h(n)$
Signal	:	$x(n)$
Approximation component	:	LL
Detail component 1 of the image	:	LH
Detail component 2 of the image	:	HL
Detail component 3 of the image	:	HH
Hyperplanes	:	$H(n)$
Support vectors	:	$S_{(n)}$
Dot Product	:	.
Homogeneous Polynomial	:	HPOL
Inhomogeneous Polynomial	:	IPOL
Gaussian Radial Basis	:	GRB

1. INTRODUCTION

1.1 CONTEXT AND MOTIVATION

Tumours and cancer are often used in the same sense but have two different meanings. A brain tumour is the uncontrolled proliferation of tissue, and not all tumours are cancerous. We can define brain tumours as a mass of abnormal cells within the brain. Some brain tumours begin in the brain (which are called primary brain tumours), but cancer also may arise in another part of the human body and spread to the brain (secondary, or metastatic brain tumours). In U.S. 70.000 new cases of primary malignant and benign brain and central nervous system tumours are diagnosed each year, and 14.000 patients die. 31 percent of these tumours are gliomas, and 37 percent are meningiomas (Selby 1984). Brain tumour treatment options depend on several parameters including but not limited with the type, dimensions, and location of the tumour, but obviously, diagnosis of the brain tumour is the first step of treatment.

Because most of the symptoms of brain tumours are shared with other ailments (especially in the first stages), brain tumours are often misdiagnosed. Misdiagnosis is so common that several law firms are working for the cancer patients of the delayed cancer diagnosis. It is obvious that a physician will never misdiagnose a lesion within the brain intentionally, but some lesions may be misdiagnosed easily due to several reasons. This study proposes the idea of integration of mathematical methods and tools to clinical processes which can support the diagnosis, prognosis, as well as neurosurgical planning and the other services provided by the neuro-oncology clinics. This integration will help clinics to increase diagnosis speed and accuracy and create highly personalized treatment plans for neuro-oncology patients.

Brain tumours are one of the most critical medical issues in the field of neurology. Early diagnosis and treatment are essential for the removal of the symptoms and to extend the survival time of the patients. Despite promising research projects in the field of liquid biopsy and advanced imaging tools we currently use, options in both terms of diagnosis and treatment of the brain tumours are limited. The focus of this study is to propose a

combination of mathematical methods with traditional and advanced neuro-oncology methods under the title: computational neuro-oncology.

Because symptoms of nervous system tumours have a strict relationship with the anatomic location of the tumours, a strong knowledge of nervous system anatomy is important in order to identify the potential location and type of the tumours. Our study starts with an overview of human nervous system. At the last section of our introduction, we summarize the neurologic examination and imaging methods that are available for our use today.

In the second section, we summarize the very basic characteristics of the most common tumours of human nervous system.

In the third section, we summarize the current treatment methods in neuro-oncology and discuss the clinical challenge of patient-specific prognosis and treatment response, surgery, radiation therapies, and systemic therapies. We also discuss the complications of current approach of neuro-oncology on early identification of human nervous system tumours and complications of medical therapies.

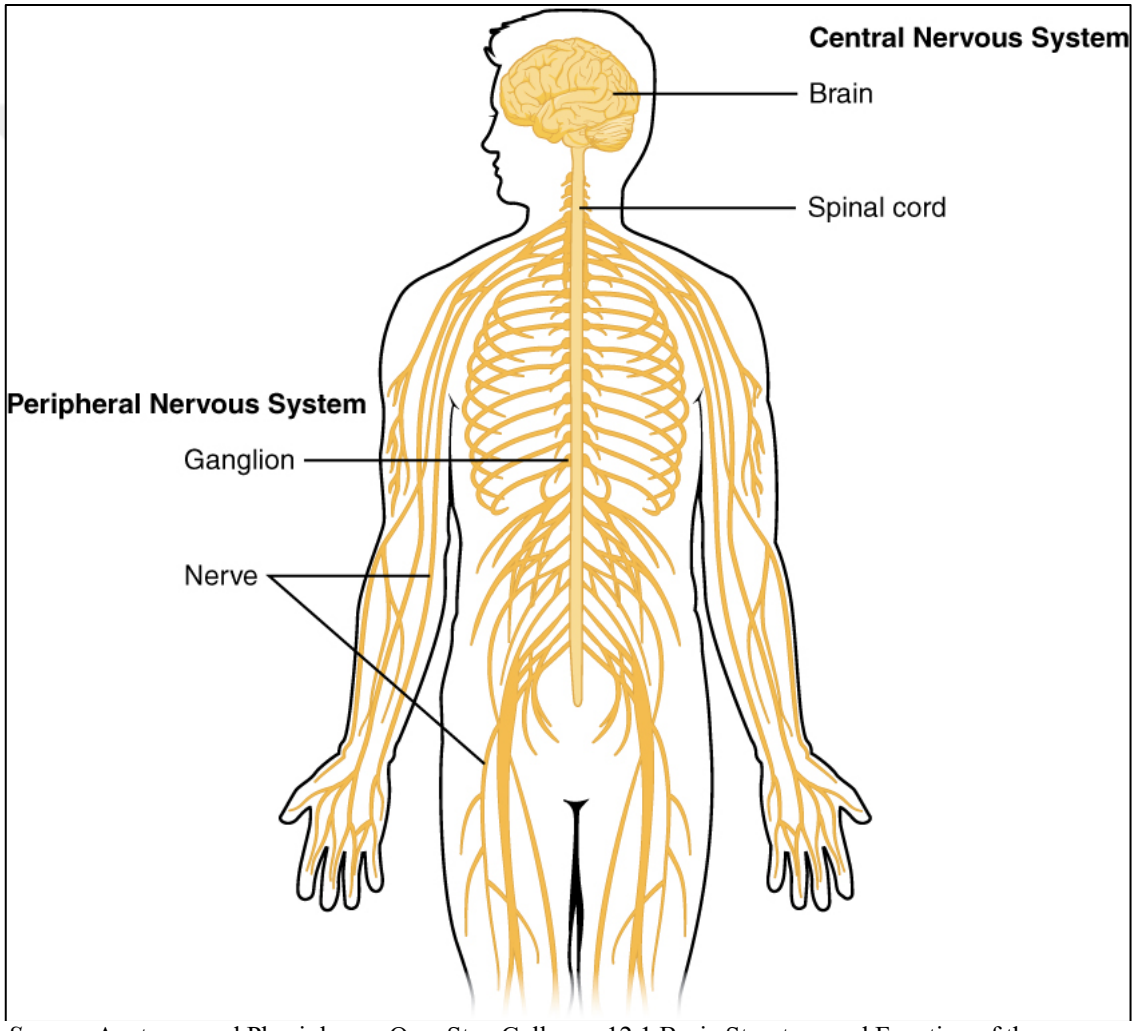
All these discussions will lead us to the question: Why do we need a new approach which empowers us to combine the advantage of advanced mathematical methods with proven traditional tool and methods? At that point, we will propose computational neuro-oncology as a solution for the addressed challenges of today's neuro-oncology clinics.

Finally, we will demonstrate, how computational neuro-oncology can improve clinical processes with an automatic brain tumour identification tool. Implemented decision support system can be both used to analyse the MRI images before clinician’s review of the MRI scan to raise an alert for the clinician or to validate the diagnosis of the clinician to minimize the chance of a misdiagnosis of a tumour that may or may not be surrounded by edema.

1.2 ANATOMICAL OVERVIEW OF THE HUMAN NERVOUS SYSTEM

The nervous system maintains several functions including but not limited to muscle activity, sense, and balance systems, and it is connected with entire organ systems. We study the human nervous system as two separate parts. First part is the central nervous system which consists of the brain and spinal cord where the second part, the peripheral nervous system consists of spinal nerves.

Image 1.1: Overview of Human and Central and Peripheral Nervous System.

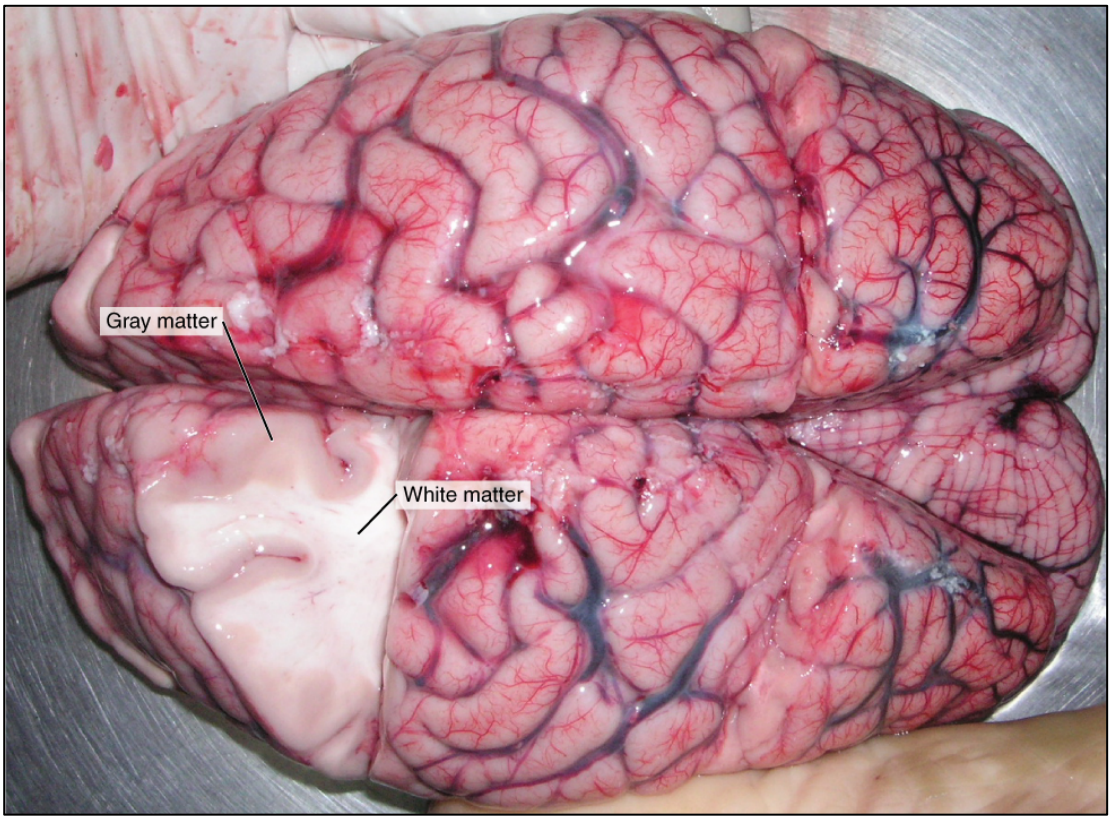


Source: Anatomy and Physiology - OpenStax College - 12.1 Basic Structure and Function of the Nervous System, Page 80

The human brain is approximately 1.500 grams. In an average person, the brain corresponds to 2 percent of the body weight. On the other hand, it uses 20 percent of the energy produced by the body. The human brain consists of the cerebrum, brainstem (midbrain, pons, and medulla) and cerebellum.

The gray matter region of 2-4mm in the outer layer of the cerebrum is called the cerebral cortex. Nerve cell bodies and unmyelinated axons are located in the cerebral cortex where most of the brain activity is formed. The white matter which is formed by the myelinated axons is located right under the gray matter.

Image 1.2: A brain removed during an autopsy, with a partial section removed, shows white matter surrounded by gray matter.



Source: modification of work by "Suseno"/Wikimedia Commons

1.2.1 Cerebrum

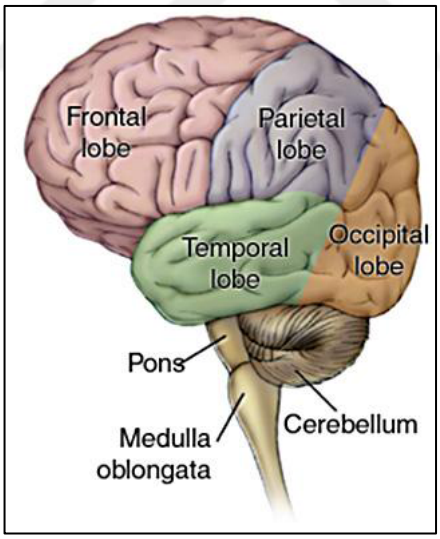
The cerebrum is divided into two hemispheres: right and left. These two hemispheres communicate through the corpus callosum; an anatomical region consists of a highly intense collection of nerve fibers. Corpus callosum contains approximately 200 to 250 million axons.

The right hemisphere controls the left side of the body, and the left hemisphere controls the right side of the body. Each hemisphere contains similar anatomical structures, but

some specialized structures are located (or active) on only one hemisphere. For example, frontal part of the left hemisphere contains the anatomical structures called Broca and Wernicke which consists of the neurons specialized for speech function. The left hemisphere is dominant on 90 percent of the humans.

A specialized group of gray matter located in the deep part of the cerebral hemispheres is called basal ganglia (or basal nuclei). The structures included basal ganglia involves three different anatomic locations. The subthalamic nucleus in the diencephalon, the caudate, globus pallidus, and the putamen in the cerebrum and the substantia nigra in the midbrain forms the basal ganglia. Basal ganglia are associated with several functions including but not limited to eye movements, cognition, emotion, procedural learning, habit learning and control of voluntary motor movements. Basal ganglia is not actually a ganglia, despite its name.

Image 1.3: Central Nervous System



Source: Bright Focus Foundation

Each hemisphere consists of four lobes: frontal, parietal, temporal and occipital lobes.

The frontal lobe is responsible for the control of voluntary movement, reasoning, expressive language, and higher-level cognition. The motor cortex is located at the back

of the frontal lobe which receives information from various lobes of the brain and processes that information to carry out voluntary body movements. Damage to the frontal lobe can lead to changes in several functions including but not limited to socialization, sexual habits and attention.

The parietal lobe is responsible for pain, heat, touch, and pressure. The parietal lobe is located in the middle section of the brain. A part of the somatosensory cortex, which is responsible for processing sensory information is also located in this lobe.

The temporal lobe contains the primary auditory cortex, which processes the sounds and language we hear. The temporal lobe is the home of another important structure called hippocampus, which is associated with memory formation. The temporal lobe also plays an essential role in the functions like speech and understanding. Damage to this lobe can lead impairments with memory, language and speech perception skills of the patient.

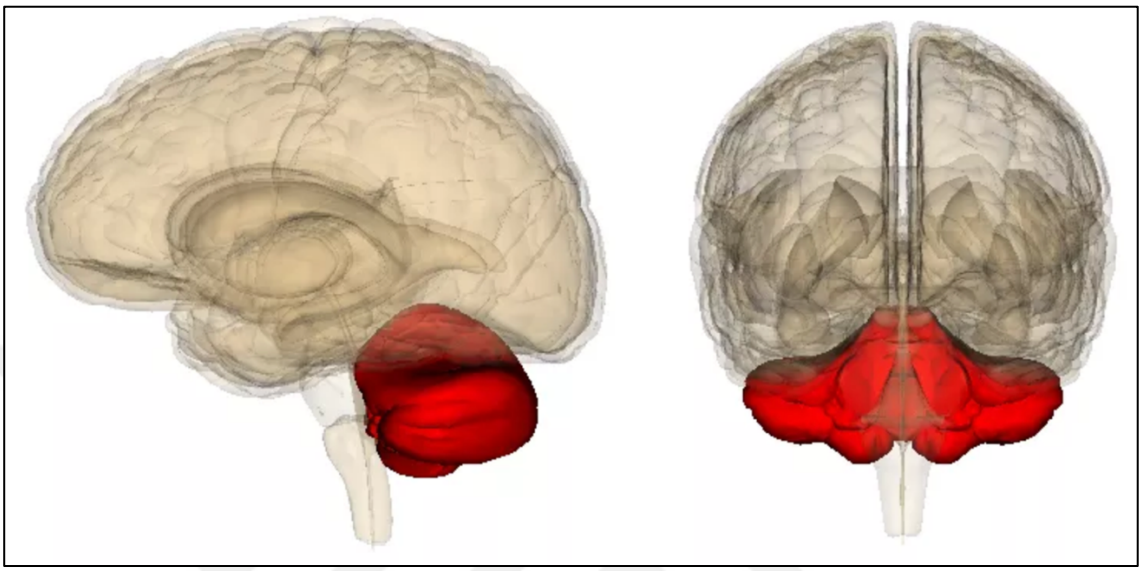
The occipital lobe, which is located at the back portion of the brain contains the primary visual cortex, which receives and interprets information from the retinas of the eyes. Although the occipital lobe has some other functions, interpreting visual stimuli and information are considered the essential functions of this region. Damage to this lobe may cause visual impairments, difficulty recognizing objects, inability to identify colors and issues with recognizing the words.

1.2.2 Cerebellum

Like the cerebrum, cerebellum consists of two hemispheres and these two hemispheres are connected with vermis. The cerebellum is located on top of the pons behind the brain stem. Cerebrum receives information from visual and auditory systems, the balance system of the inner ear and sensory nerves and it is involved in the coordination of motor learning and movements. Physically, the cerebellum is approximately 10 percent of the brain's total size, but it accounts for more than 50 percent of total neurons located in the entire brain. As mentioned, the cerebellum is associated with motor movement and control with primary motor cortex at the frontal lobe. Unlike primary motor cortex, motor commands do not originate at cerebellum, instead, the cerebellum is responsible for the

fine tuning of the motor movements by modifying the posture, balance and the coordination to make them more accurate by coordinating different muscle groups in the body to perform accurate, coordinated and fluid movements.

Image 1.4: The Cerebellum

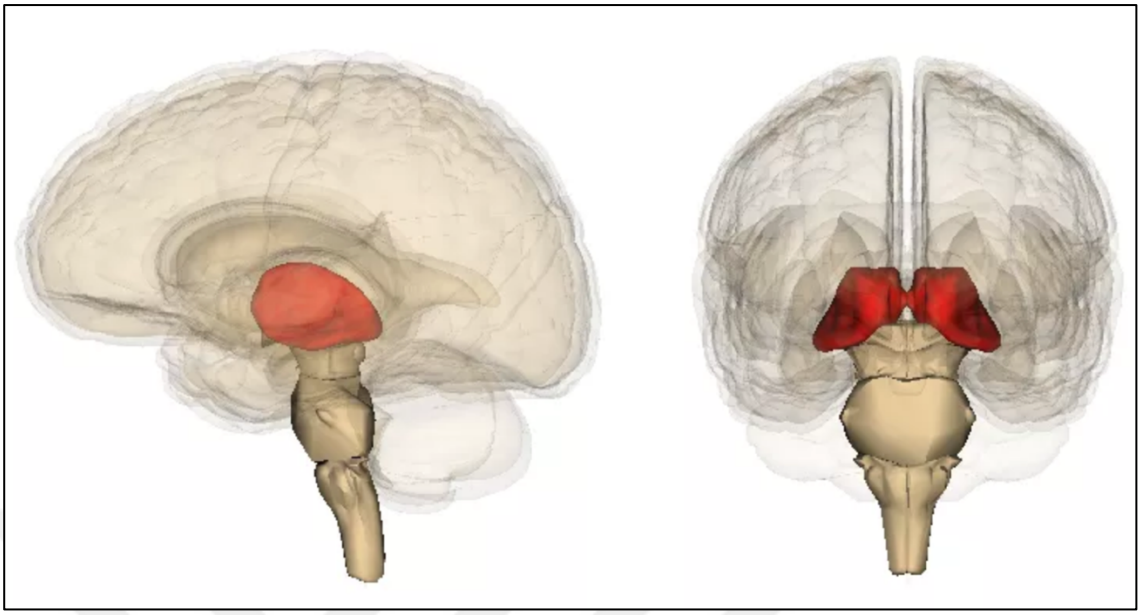


Source: USA Ministry of Education, Culture, Sports, and Technology (MEXT) Integrated Database Project

1.2.3 The Thalamus

Thalamus acts like a relay station and is located above the brainstem. Thalamus is responsible for processing and transmitting the sensory and movement information. There is a bi-directional information transmission between the thalamus and the cerebral cortex. Cerebral cortex sends information to the thalamus, so thalamus relays this information to other systems. Thalamus takes sensory information and passes that information to the cerebral cortex.

Image 1.5: Thalamus



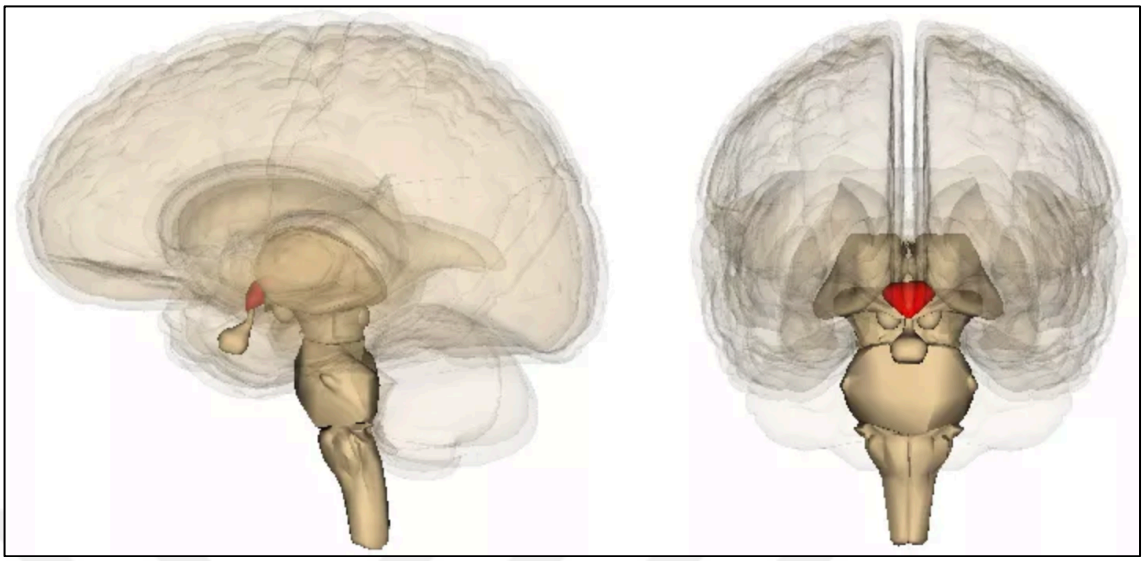
Source: USA Ministry of Education, Culture, Sports, and Technology (MEXT) Integrated Database Project

For example, visual information from retina travels to the lateral geniculate nucleus of the thalamus, which is specialized to process visual information, before being sent on the primary visual cortex. Except smell, all of the signals that pass to the cortex first pass through the thalamus.

1.2.4 The Hypothalamus

The hypothalamus is located along the base of the brain near the pituitary gland and has connections with several other regions of the brain. Main functions of hypothalamus include controlling the hunger, thirst, regulating the body temperature and circadian rhythms. The hypothalamus also plays a significant role in the control of pituitary gland by secreting hormones which means despite its small size; the hypothalamus has significant control over several body functions.

Image 1.6: The Hypothalamus.



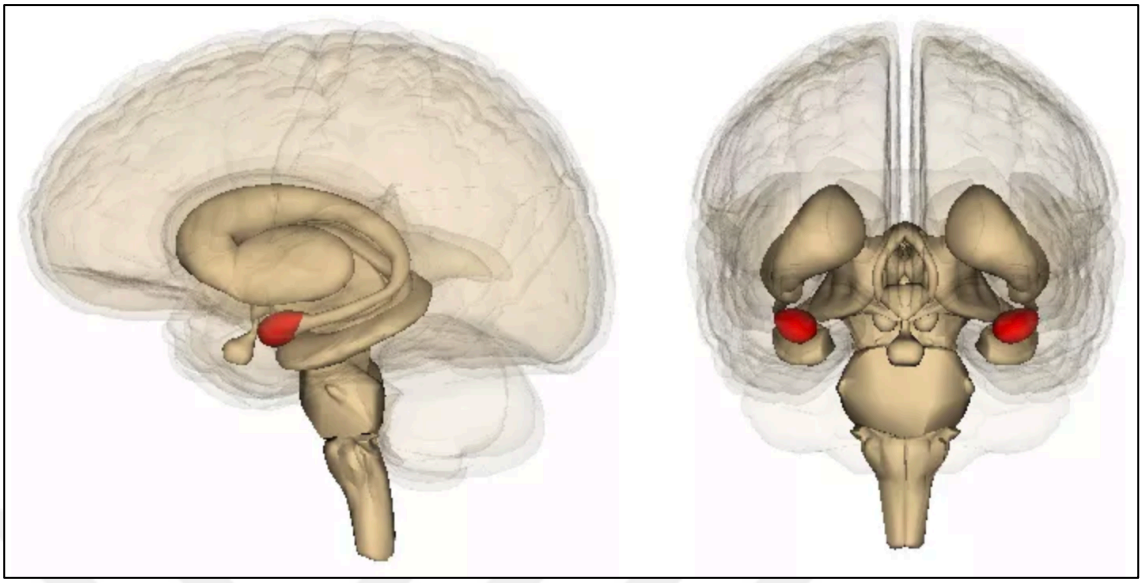
Source: USA Ministry of Education, Culture, Sports, and Technology (MEXT) Integrated Database Project

1.2.5 The Limbic System

The limbic system is not a single region. It is a unique region, which several regions (the amygdala, the hippocampus, some parts of the limbic cortex and the septal area) come together to form, and these structures connect several different regions including the hypothalamus, thalamus, and cerebral cortex. However, there is no consensus on the components of the limbic system.

Many functions can be related with the limbic system because of the unit that forms it, but the essential feature of the limbic system is controlling the emotion.

Image 1.7: Limbic System.



Source: USA Ministry of Education, Culture, Sports, and Technology (MEXT) Integrated Database Project

1.2.6 The Brainstem

The brainstem comprised of three components; medulla, pons, and midbrain.

The pons connects medulla to the cerebellum, and it is a critical component of autonomic functions such as respiration, and sleep cycles.

The medulla is located on top of the spinal cord, in the lower part of the brain stem and controls various vital autonomic functions such as heart rate, respiration, and blood pressure.

The midbrain is one of the tiniest regions of the brain and acts as a relay station for visual and auditory information while controlling various essential functions such as eye movement, auditory and visual systems. Also, the red nucleus and substantia nigra, parts of midbrain are involved in the control of body movement. The substantia nigra contains a vast number of dopamine-producing neurons and damage, or degeneration of this region is associated with Parkinson's disease.

Brainstem regulates several vital functions for the survival of the body including heart rate, blood pressure, respiration rate, sleep.

1.2.7 Other Components of the Human Nervous System

The human nervous system is a very complex structure. Although the entire anatomy of the human nervous system is beyond the scope of this research, we also need to mention that, several arteries, meninges, a highly complex ventricular system, cerebrospinal fluid, spinal cord, spinal nerves, and cranial nerves are some of the other fundamental subjects, when we discuss the anatomy of the human nervous system.

As mentioned, an injury or another abnormality within our nervous system causes some symptoms. Those symptoms depend on the location, type, and severity. Also, in some cases, these symptoms may occur immediately (like traumatic brain injury), or they can also show up hours, days or even months later.

General symptoms of brain-related diseases/injuries are;

i. Headache
ii. Nausea or vomiting
iii. Feeling tired or drowsy
iv. Dizziness
v. Confusion and/or disorientation
vi. Speech problems, including slurring
vii. Seizures
viii. Sensory impairments (blurry vision, double vision, ringing in ears)
ix. Sleeping more or less than usual
x. Dilation of one or both pupils
xi. Fluid draining from nose or ears
xii. Memory impairments
xiii. Concentration impairments
xiv. Mood swings

The following list contains the most common symptoms in the case of a cerebrovascular injury. Symptoms may vary depending on the location and severity of the injury. Also, additional symptoms may appear.

i. A severe headache
ii. Vision impairments (loss of vision, double or blurry vision)
iii. Speech impairments or inability to speak
iv. Dropping face
v. Inability to move or feel one or both sides or one or more than one part of the body
vi. Coma

The following list contains the most common symptoms in the case of neurodegenerative disease;

i. Memory impairments. Forgetfulness
ii. Mood, personality and/or behaviour changes
iii. Motor coordination issues such as problems with walking
iv. Speech impairments such as hesitation before speaking or slurring

Symptoms of the tumours of the nervous system are common with cerebrovascular and brain injury-related symptoms. We will discuss the symptoms of brain tumours in the next section: Diagnosis of Brain Tumours

1.3 OVERVIEW OF BRAIN TUMOURS

We defined brain tumours as a mass of abnormal cells within the brain earlier. Any growth inside the skull can cause some symptoms regardless of the tumour is malignant or bening.

There are two categories in the classification of brain tumours. Primary brain tumours originate in the brain, and most of them are benign. A secondary brain tumour, also known

as a metastatic brain tumour, occurs when cancer cells spread to brain from another system.

Primary brain tumours can develop from brain cells, the membranes that surround the brain (meninges), nerve cells and glands. Although most primary brain tumours are bening, some malignant primary brain tumours also exist. Most common types of primary brain tumours are gliomas and meningiomas.

Other primary brain tumours are;

i. Pituitary tumours
ii. Pineal gland tumours
iii. Ependymomas
iv. Craniopharyngiomas
v. Primary central nervous system lymphomas
vi. Meningiomas
vii. Schwannomas
viii. Primary germ cell tumours of the brain

Secondary brain tumours, as mentioned, are the cancel cells coming from other systems of the body and they make up the majority of the brain cancers. The following cancers can metastasize to the brain;

i. Lung cancer
ii. Breast cancer
iii. Kidney cancer
iv. Skin cancer

All secondary brain tumours are malignant.

1.4 DIAGNOSIS OF BRAIN TUMOURS

People with a brain tumour may experience several different symptoms or signs. Some symptoms can be general, and some can be specific, which allows easier identification of brain tumours. Most of the symptoms starts with the increased pressure caused by the tumour on the brain (or the spinal cord). Depending on the localization of the tumour,

patients experience more specific symptoms but the most common symptom (which is a very common symptom through several diseases) is the headache caused by the increased intra-cranial pressure.

The most common symptoms of the brain tumours are;

1.4.1 Headaches

Worsening headaches are a common symptom through brain tumours, and more than 50 percent of people with brain tumours have a headache. A tumour in the brain increases the pressure on brain tissue, nerves, and blood vessels. Increased intracranial pressure most likely causes a headache or may change the headache pattern of the patient. Headache may be stronger in the morning. Vomiting or other neurological symptoms may accompany the headache. Headache may get worse during exercise, position change or cough. Standard (over-the-counter) painkillers may lose their effect on the headache.

Headache, even it is getting worse over time and/or activity, does not indicate a brain tumour alone and it is a prevalent symptom through various conditions from daily stress to stroke.

1.4.2 Seizures

Seizures can be defined as the changes in the brain's electrical activity. While some seizures can cause symptoms that affect daily life even lead injuries, some seizures may not be even noticeable by the patient.

As brain tumours grow, they have a high probability to create pressure on the nerve cells and interfere with the electrical activity of the brain which may result in a seizure.

Some seizures may appear just like a moment thoughtfulness which can be considered normal in most of the time; some seizures may appear with loss of motor control and violent shaking. Regardless of severity, all seizures must be considered as a serious, and the underlying medical condition must be researched.

50 percent of people with brain tumours experience at least one seizure and seizures can be seen at any stage of brain tumour development. With this level of incidence, seizures can be listed as one of the very common symptoms of brain tumours. But other neurological problems and brain diseases can also lead seizures so every seizure must be extensively researched.

1.4.3 Personality or Mood Changes

As mentioned, some anatomical regions of the brain are responsible for personality, mood, and behaviour and the regulatory glands for the hormones that affect personality and mood. Tumours that disrupt the functionality of these regions may affect the personality and behaviour of the patient. For example, while the patient is happy and relaxed, just after a minute, may start an argument for no apparent reason. The tumours that grow in the frontal lobe, the temporal lobe, and some specific parts of the cerebrum may lead to personality changes and mood swings.

While the patient may experience personality changes and mood swings because of a brain tumour, they can also get these symptoms from the brain tumour treatments like chemotherapy or other medications.

1.4.4 Memory and Consciousness Related Symptoms

Depending on the location of the brain tumour, memory or other cognitive functions of the patient may be affected. While a tumour in the temporal or frontal lobes affects the memory of the patient, a tumour in the parietal or frontal lobe affects the reasoning and decision-making capabilities of the patient. Most common symptoms are;

i. Patient has difficulty in concentrating and distracted easily.
ii. Short-term memory of the patient is impaired.
iii. Planning and multi-tasking capabilities of the patient are decreased.
iv. The patient is easily confused even about simple subjects or tasks.

These symptoms can be seen at any stage, but just like personality changes and mood swings, they can also occur in relation to brain tumour treatments like chemotherapy or other medications.

Apart from brain tumours, vitamin deficiencies, some medications or physiological disorders and several other medical conditions can also be the underlying reason of memory and consciousness related symptoms.

1.4.5 Nausea and Vomiting

Brain tumours affect the hormone balance of the body which may lead to nausea and vomiting in the early stages. Also, nausea and vomiting are pervasive side effects of chemotherapy and other brain tumour medications. Nausea and vomiting are very common symptoms among several medical conditions.

1.4.6 Fatigue

Fatigue is another common symptom of several medical conditions and brain tumours can also lead to fatigue as well. Patients lose the ability to focus, easily irritable, sometimes fall asleep during the day, feel weak and feel exhausted most or all of the time.

1.4.7 Depression

Beyond personality changes and mood swings, patients can also show signs of depression (major depressive disorder) where the patient feels sadness, tearfulness, emptiness and/or hopelessness. This condition affects how the patient feels, thinks and behave and even prevent the patient from performing daily activities.

Depression is a very complex medical condition and often observed in patients who diagnosed with a brain tumour. Depression is also very common among caregivers and loved ones of the brain tumour patients. Some patients may also develop thoughts of self-harm or suicide.

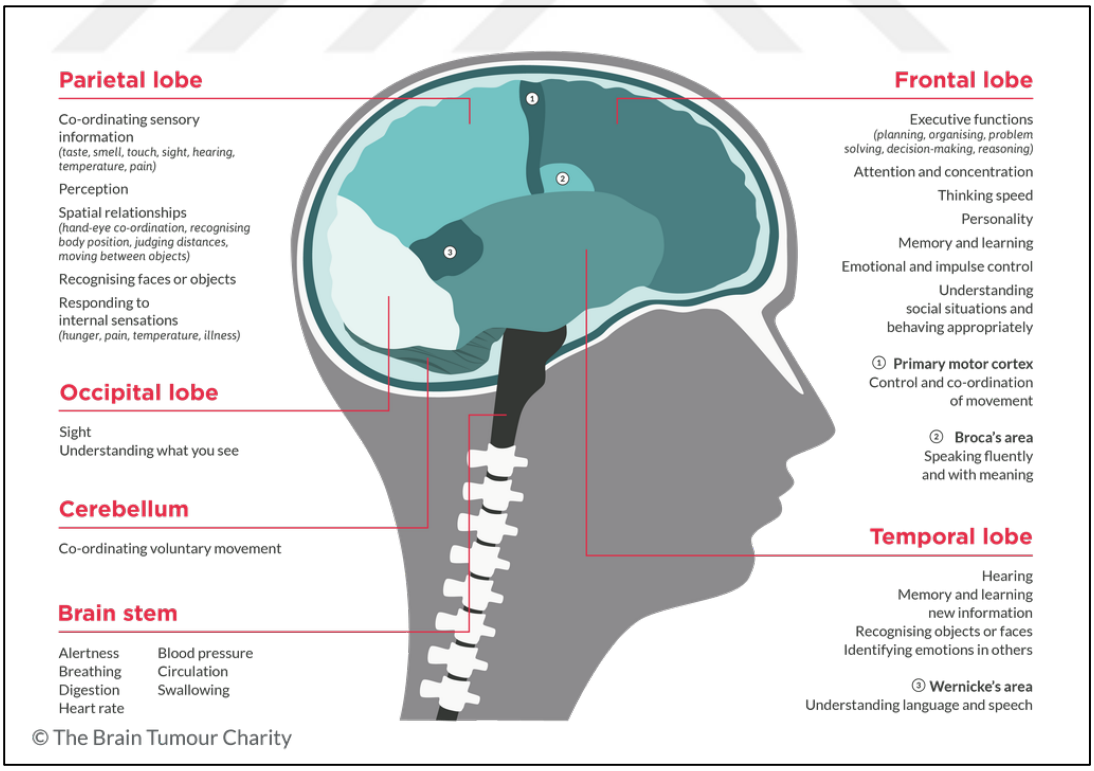
1.4.8 Decrease in Ability of Daily Activities

Patients may also experience a decrease in the ability to do some daily activities. While some brain tumours cause numbness of the hands and feet, weakness is also pervasive. Weakness and numbness usually happen in only one side of the body and help the neurologists to understand the location and size of the tumour.

As most of the symptoms of brain tumours, weakness and numbness are also shared with several other medical conditions such as diabetic neuropathy, Guillain-Barre syndrome, multiple sclerosis or can be caused by cancer treatment.

Patients develop different symptoms depending on the location of the brain tumour. The following list contains a summary of location-specific symptoms of brain tumour patients.

Image 1.8: High-Level Overview of Functions of Brain's Region



Source: The Brain Tumour Charity

A tumour located at the frontal lobe may cause difficulty / impairments with

i. Concentrating
ii. Speaking and communicating
iii. Controlling emotions and behaviour
iv. Learning new information
v. Lack of inhibition
vi. (making inappropriate comments during conversation or laughing in inappropriate situations)
vii. Weakness on the opposite side of the body from the tumour
viii. Loss of smell.

A tumour located at the temporal lobe may cause difficulty / impairments with

i. Hearing
ii. Speaking
iii. Identifying and categorizing objects
iv. Learning new information
v. Correctly identifying emotions in others
vi. Memory loss
vii. Seizures or blackouts
viii. Sensations of strange smells

A tumour located at the parietal lobe may cause difficulty / impairments with

i. Bringing together information from your different senses (touch, vision, hearing, smell, taste) and making sense of it
ii. Co-ordinating movements
iii. Spatial awareness e.g. judging distances, hand-eye co-ordination
iv. Speaking, understanding words, writing and reading
v. Numbness on the opposite side of the body from the tumour

A tumour located at the occipital lobe may cause difficulty / impairments with

i. Difficulty with vision e.g. identifying objects or colours
ii. Loss of vision on one side

A tumour located at the cerebellum may cause difficulty / impairments with

i. Difficulty with balance
ii. Loss of co-ordination
iii. Difficulty walking and speaking
iv. Flickering of the eyes
v. Vomiting
vi. Stiff neck
vii. Problems with dexterity (skills in using your hands)

A tumour located at the brainstem may cause difficulty / impairments with

i. Unsteadiness and difficulty walking
ii. Facial weakness
iii. Double vision
iv. Difficulty speaking and swallowing

Diagnosis process of a brain tumour usually starts with a neurological examination but sometimes, depending on the symptoms of patients, other fields may forward the patient to Neurology for further neurological examination after completing their examination without a finding or suspect from a Neurological symptom.

A Neurologist usually starts with a neurological examination and depending on the symptoms, request some imaging tests. In this section, we will describe the neurological examination and imaging tests which allows us to identify a brain tumour.

1.4.9 Neurological Examination

As mentioned, brain tumours have various symptoms depending on the size and location and neurological examination is usually the first step of identifying a brain tumour or any other intra-cranial lesion.

The neurological examination begins with the patient story, described by the patient. It is essential to ask the reason for the visit and symptoms to the patient which most likely

determine the course of the neurological examination. In some cases, listening to the patient's story from caregivers or family members might also be helpful.

Although most of the brain tumours can be identified visually from the MRI scans, complete diagnosis is only possible with a neurological examination.

The human nervous system consists of several specialized systems, and neurological examination helps us to understand the issues with those systems. During the neurological examination, the physical usually makes several assessments that can be grouped into seven categories.

1. Assessment and observation of mental status
2. Assessment of cranial nerves I to XII,
3. Assessment of motor system including muscle tone, bulk, and strength of deltoid, biceps, and triceps, knee extension and flexion, ankle dorsiflexion/plantarflexion, toe dorsiflexion, hip flexion/ extension/abduction and finger abduction,
4. Assessment of muscle stretch reflexes (biceps, triceps, knee, ankle) and plantar reflex,
5. Assessment of sensory system for light touch, vibration, pain, and position sense (including Romberg testing),
6. Assessment of coordination (fine finger moves, rapid alternating movements, finger-nose-finger, heel-knee-shin),
7. Assessment of gait and stance.

The neurological examination also includes the examination of other parameters of the patient like mental status, attention, language, memory, higher intellectual functions like general knowledge, abstraction, judgment, insight, reasoning, and mood.

It is usually possible to predict the existence and location of brain tumours with a neurological examination and observations, performed meticulously.

As mentioned, neurological observation is also curial, and a good neurological "observation" begins at the moment the patient enters the room and continues until the patient leaves the room.

1.4.10 Assessment of the Mental Status

Assessment of the consciousness is the first step of neurological examination, and we can define consciousness as the state of being aware of the individual and his / her environment. Two parameters evaluate Consciousness, consciousness level and content of the patient. The level of consciousness is evaluated by the state of alertness of the individual. The individual may be in a state of awake, or maybe in constant sleep or may be prone to sleep. The ability to be evoked by verbal stimulation or painful stimuli in patients with persistent sleep or sleep tendency indicates the level of consciousness. The ability to be aroused only with one stimulus indicates that consciousness is still open, but a problem related to consciousness.

The second parameter used in the definition and evaluation of consciousness is the content of consciousness. The content of consciousness is determined by the location, time and person orientation, which can be a measure of how events are correctly perceived and evaluated. Consciousness, place, person orientation may be complete, or one or more of these may be impaired. All determinations made about the level of consciousness should be noted in the patient's file with the date and time of detection, and changes in consciousness should be observed over time.

Depending on its location, size, and structure, brain tumours may cause changes in the patient's level of consciousness. However, other intracranial lesions (e.g., hematoma, ischemia) and infections of the central nervous system (e.g., meningitis, encephalitis), epilepsy, coma, metabolic disorders, and toxic substances may also cause changes in consciousness level or temporary or permanent loss of consciousness.

As part of the mental status assessment, attentiveness should also be considered as a critical parameter. The physician should observe if the patient is paying attention to the conversation or is, he distractible and requiring re-focusing.

Speech, language, and memory skills should also be observed as fluency, repetition, comprehension, reading, writing, and naming abilities might be affected by a brain tumour (or other CNS related issues).

1.4.10.1 Assessment of cranial nerves I to XII

The cranial nerves are the pair of nerves that exit through foramina in the skull and connect the brain to different parts of the body — the cranial nerves named with a Roman numeral as CN I to CN XII. The order based on the location of the cranial nerve and the nerve closest to frontal bone (olfactory nerve) designated as CN I and the nerve closest to occipital bone designated as CN XII. Cranial nerves are responsible for sensory or motor functions, but some cranial nerves are responsible for both sensory and motor functions. During the neurological examination, the physician may observe various sensory and motor functions for impairment, and any functional problem will give an idea regarding the type and location intra-cranial lesion.

We would like to emphasize that the examination summaries listed below are from an oncological perspective and it is not intended to define a comprehensive examination.

1.4.10.2 Cranial nerve I (olfactory nerve)

The primary function of the olfactory nerve is the smell. To test the CN I, the patient asked to smell a non-irritating material (e.g., soap, coffee, mint) while his/her eyes are closed and guess what it is. In the second phase, the same procedure repeated by closing both nostrils separately. Various neurological conditions like Alzheimer's disease, Parkinson's disease, Korsakoff's psychosis, and Huntington's chorea may cause dyssomnia or dysfunction of smell. Also, Anosmia might be a symptom of oncologic conditions like tumours of the floor of the anterior fossa, such as meningiomas of the sphenoid ridge or olfactory groove. Also, other intra-cranial tumours like frontal lobe glioma, neuroblastoma, suprasellar meningioma, sphenoidal ridge meningioma, and other meningiomas may cause olfactory dysfunction.

1.4.10.3 Cranial nerve II (optic nerve)

The primary function of the optic nerve is the vision. The optic nerve pair reaches the occipital lobe through a complex and long path in the skull. Brain tumours cause various vision-related symptoms because of the length and transverse route of the optic nerve pair.

In order to evaluate the vision, visual acuity should be determined, visual field test and fundoscopic examination should be performed. In a neurological examination, the evaluation of vision and visual pathways provides much information about brain function, so it is essential not only brain tumours and other lesions affecting the optic nerve, but also a detailed evaluation of the visual function in order to get an idea of different locations.

Tumours that create pressure over optic nerve can cause deterioration of the sight. In one eye, a complete visual loss is mostly associated with optic nerve pathology, and loss of visual field suggests intracranial pathologies.

During the assessment of CN II and CN III, pupil size is evaluated. In general, the differences between pupils expected to be of the same size as 1 mm can be considered normal. In unconscious patients, more than 1 mm difference between pupils (anisocoria) is a sign of brain herniation, and the patient should be treated with the assumption that life is at risk. In conscious patients, this situation does not suggest brain herniation, suggesting a local problem. Pathologies in the hypothalamic, brain stem or cervical sympathetic pathways may lead to Horner syndrome in which myosis, ptosis, and anhydrous findings are combined.

Examination of direct and indirect light reflexes in both eyes provides information about mesencephalon, and cranial nerves II. and III. Following the direction of the light source to the left eye, there is a constriction in the left eye, but if it is not in the right eye, the left optic nerve and mesencephalon are working normally but are considered to be a problem in the right oculomotor nerve.

There is no constriction in the left eye after the light source directed to the left eye, but in the right eye, the problem is in the left oculomotor nerve. If there were problems in the optic nerve or mesencephalon, there would be no constriction in the right eye.

There is no constriction in the eyes when the light source directed to the left eye, but when there is a constriction in both eyes when the light directed to the right eye, the problem is in the left optic nerve or the left pretectal area. If there was a problem in the brain stem, there should be no constriction in the right eye.

Finally, if there is a problem in the mesencephalon, no constriction will occur in the pupils, whether the light source directed to the right or left eye.

1.4.10.4 Cranial nerves III, IV and VI (oculomotor, trochlear, and abducens nerves)

The common feature of these three cranial nerves is that they innervate the muscles responsible for the movement of the eye. The coordinated movement of the two eyes under normal conditions is called the conjugate movement of the eye. In order to maintain this coordination, there should not be a pathology affecting the connection between the cranial nerves III. and VI., the medial longitudinal fascicle (MLF) and paramedian pontine reticular formation (PPRF). Because some brain tumours like brainstem tumours or a pituitary tumour that extends into one or both cavernous sinuses may affect movements of the pupils, an extensive examination of cranial nerves III, IV, and VI are essential in case of a suspicious condition of pupil movements.

1.4.10.5 Cranial nerve V (trigeminal nerve)

The trigeminal nerve has three divisions: the ophthalmic, maxillary, and mandibular nerves and it innervates various locations. First, it innervates the cornea and conjunctiva of the eye, mucosa of the sinuses, nasal and oral cavities, and dura of the middle, anterior, and part of the posterior cranial fossae.

Second, the mandibular division carries out the motor innervation of the muscles of mastication that are the muscles that maintain movements of the mandible. Motor

functions of the nerve also include the innervation of the tensor tympani and tensor palati muscles.

As the trigeminal nerve has both motor and sensory functions, examination of the nerve should both focus the motor and sensory functions. Brain tumours that create pressure on trigeminal nerve sections may affect the motor and sensory functions of the nerve but also several other medical conditions including craniofacial trauma, dental trauma, maxillary sinusitis, aneurysm of the internal carotid artery, cavernous sinus thrombosis and so on (Dyck et al, Peripheral neuropathy. 2nd ed. Philadelphia. p. 1224–65).

1.4.10.6 Cranial nerve VII (facial nerve)

The motor portion of the Cranial Nerve VII is responsible for movements of the face and supplies all the facial musculature. A partial to complete facial paralysis with symptoms like an open eye, dropping of the mouth ipsilateral to the lesion may be caused by nuclear or infranuclear lesions where a supranuclear lesion has different symptoms like dropping of the mouth contralateral to the lesion. Cranial Nerve VII also has a sensory portion which is responsible for the taste to the anterior two-thirds of the tongue, cutaneous sensory impulses from the external auditory meatus and region back of the ear, and secretory and vasomotor fibers to the lacrimal gland, the mucous membranes of the nose and mouth, and the submandibular and sublingual salivary glands.

Because tumours and other intracranial lesions that affect the Cranial Nerve VII may cause several symptoms, thoughtful examination of both the motor and peripheral components of Cranial Nerve VII is essential. Even tiny details like the delayed closure of an eyelid or a light drop of the corners of the mouth during speaking or smiling might be a sign.

1.4.10.7 Cranial nerve VIII (vestibulocochlear nerve)

Vestibulocochlear nerve is composed of two components: cochlear (hearing) and vestibular (equilibrium) and is also called as Auditory nerve. Its examination covers both auditory and vestibular functions. Tumours like a vestibular schwannoma (Acoustic Neuroma) and Neurofibromatosis affects the functions of the vestibulocochlear nerve so

any balance issues, or abnormal responses to Rinne test, or Weber test should be evaluated carefully.

1.4.10.8 Cranial nerve IX and X (glossopharyngeal and vagus Nerves)

Glossopharyngeal and Vagus nerves, which are responsible for swallowing, phonation, guttural and palatal articulation (the 7th cranial nerve also has a component for labial articulation) usually tested together.

Lesions of the glossopharyngeal nerve usually have symptoms like swallowing difficulty, taste and sensation impairments at the posterior one-third part of the tongue and palate, and dysfunction of the parotid gland. Vagus nerve lesions produce palatal and pharyngeal paralysis and some autonomic dysfunctions.

Any signs of damage to Cranial Nerves IX and X that accompanied with typical symptoms of brain tumours should be further examined for an intracranial lesion.

1.4.10.9 Cranial nerve XI (spinal accessory nerve)

The spinal accessory nerve supplies the trapezius and sternocleidomastoid muscles which provide head, neck, and shoulder movements. Any impairments or paralysis with the movements of head, neck, and shoulder movements, spinal accessory nerve damage should be suspected. Muscle atrophy and fasciculations accompany when the lesion is nuclear or infranuclear.

While isolated functions of the spinal accessory nerve might be affected alone but because the Cranial Nerve XI travel together with Cranial Nerves IX, and X in the jugular foramen, all three nerves might be compressed by tumours or aneurysms (Vernet's syndrome) and symptoms for all three nerve can be seen together.

1.4.10.10 Cranial nerve XII (hypoglossal nerve)

Cranial Nerve XII is responsible for all tongue movements. Lesions that affect this nerve will cause paralysis, atrophy, weakness, and fasciculations of the tongue. Tumours can compress this nerve in the hypoglossal canal and the jugular foramen. Also, intraspinal

tumours along with amyotrophic lateral sclerosis and polio may cause atrophy, weakness, or paralysis and fasciculations and should be examined carefully.

1.5 IMAGING TESTS

In neuro-oncology, various imaging methods are used in order to determine and follow the localization, expansion, type and malignancy of the tumours. Purpose of imaging methods in neuro-oncology can be grouped into three.

The first purpose of neurological imaging is the primary diagnosis. After a neurological examination, the physician may prefer to proceed with an advanced investigation of the patient is suspected of an intracranial lesion. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are usually used to review the anatomical structure of the tumour. Magnetic Resonance Spectroscopy and Positron Emission Tomography are used to investigate the molecular events within and metabolic state of the tumour. Functional MRI and functional PET, in combination with electrophysiological methods like transcranial magnetic stimulation, are being used to delineate functionally important neuronal tissue, which has to be preserved from treatment-induced damage, as well as to gather information on tumour-induced brain plasticity (Jacobs et al 2005).

Second, neurological imaging is an essential part of the treatment planning and the surgery itself. Imaging is used during placement of stereotaxic biopsy, validation of the resection status, radiation applications, and delineation of the tumour from healthy and functionally important neuronal tissue. Intraoperative MRI has an essential role in neuro-oncology. Over the past two decades, intraoperative magnetic resonance imaging (MRI) has emerged as an increasingly important modality to enhance surgical safety while providing the surgeon with updated information to guide their resection (Jacobs et al 2005).

The third area where neurological imaging used is post-treatment follow-up. Neurological imaging methods are used to measure the success of the surgical operation and other treatments and to measure the body reaction, to detect recurrent tumours and to monitor tissue changes such as necrosis due to applied treatment.

1.5.1 Anatomic Imaging

CT (Computed Tomography) and MRI (Magnetic Resonance Imaging) are the primary imaging modalities in cranial and spinal neoplastic diseases. CT imaging is preferred in patients with acute neurological symptoms, as it is the fastest method to eliminate medical conditions that require emergency neurological treatment, such as intracranial haemorrhage, cerebral hernia and acute hydrocephalus, in cases with suspected or known cranial tumour. CT is a widely available imaging method, and current CT devices make it possible to scan the entire brain in less than 30 seconds. Regardless of the CT result, results should be confirmed by contrast-enhanced MRI if there is a suspicion of a brain tumour. If the development of the symptoms is subacute and the MRI result can be taken within a day or two, it will be more appropriate to start with MRI.

In cases that patient has no known spinal cord trauma or cauda equina compression, MRI, which provides better contrast between the spinal cord, cerebrospinal fluid and other tissues in the spinal canal, should be preferred as the primary imaging modality. In cases that MRI results cannot be obtained within a reasonable time, CT myelography should be used.

CT is more cost-effective, more accessible, faster than MRI, and has a higher tolerance for patient movements during the procedure. The major disadvantage of CT is that the patient is exposed to ionising radiation and provides less contrast in the soft tissues.

The most significant advantage of MRI according to CT is the ability of the patient not to be exposed to radiation, the ability to create extremely high contrast between different tissue types and the ability to integrate with various advanced imaging techniques such as spectroscopy, perfusion, diffusion tensor.

Anatomical imaging methods allow us to get information about tumour characterisation and composition.

1.5.2 Metabolic Imaging

MRI and CT imaging modalities are used for diagnosis and management of structural lesions and brain tumours most of the time. Positron emission tomography (PET) provides a measurement of local tracer activity at a very high sensitivity. This is a unique feature to PET that no other imaging modalities can offer. MRI and CT are the standard imaging modalities for most of the time. However, PET allows us to improve patient management by providing critical information about metabolism, proliferation rate and invasiveness of the tumour. It is also possible to understand these parameters of the tumour with functionality which allows us to create a more personalised treatment plan for each. PET is also used to understand the metabolism's response to therapy.

For the future, combining the soft tissue contrast of MRI with the sensitivity of PET will be the goal for multimodality imaging in brain tumours. Integrating the indirect measure of cell density with apparent diffusion coefficient maps and an indirect measure of cell amino acid transport with dynamic FET-PET enables assessing different and complementary tumour characteristics reflecting tumoral aggressiveness potential (Bernstein and Berger 2014, p. 74). Such integrated MRI-PET assessing simultaneously morphological, dynamic, and various parameters might be the gold standard for diagnosis of gliomas in the future (Catana C et al, 2012).

1.5.3 Physiological Imaging

Neuroimaging has an important role in the diagnosis, preoperative planning, intra-operative evaluation, and prognosis. The development of technology has led to significant innovations and developments in imaging techniques. Today, we are at the verge of the technology that provides physiology-based information that is not provided by traditional imaging modalities. With a combination of physiological and anatomic MRI, characterisation of the tumours and getting extensive information about the tumour biology will be possible. Although we have access to this technology today, physiology-based MRI methods swill requires validation and correlation with clinical outcomes data.

Although CT is very sensitive in detecting some conditions like acute haemorrhage, hydrocephalus and herniation, it is still.

CT is not an appropriate imaging method for detecting subtle changes in brain parenchyma. CT also does not provide flexible multiplanar acquisition, which limits three-dimensional depiction of the tumour. CT also involves ionising radiation, and its iodinated contrast agent can cause a severe allergic reaction. CT also does not provide high-resolution information about soft tissue, even with the intravenous contrast agent.

The standard imaging modality for the diagnosis and management of brain tumours is contrast-enhanced MRI (specifically contrast-enhanced T1 weighted imaging and fluid-attenuated inversion recovery (FLAIR)) for it does not involve ionising radiation, provide exquisite anatomic detail and has the multiplanar capability. Although MRI provides extensive information about the morphological abnormality, it suffers from nonspecificity which can be explained as different disease processes can appear similar at MRI and the metabolic or functional processes cannot be evaluated based on anatomic MRI alone. Although several physiology-based MRI methods have become part of the armamentarium of imaging modalities, most of these advanced MRI methods are still considered investigational and require further outcomes data and clinical validation.

1.5.4 Functional Imaging

Surgery is a common method of treatment plans of patients with a brain tumour. The attempt to complete removal of tumour tissue brings the risk of functional loss due to removal of non-tumorous brain tissue surrounding the tumour tissue. In order to prevent any damage to healthy brain tissue, brain tumour surgeries require detailed functional mapping of cortical regions around a tumour. Electrical cortical stimulation (ECS) and Electrocorticography (ECoG) are the interoperative methods that are accepted as golden standards, but as they can be only applied during operation, these methods do not provide any support for presurgical planning which has a significant impact on the success of the surgery. Preoperative localisation of the tumour will allow surgery team to limit the area of resection which will help to protect neurologic functionality and minimise the risks of surgery. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalographic imaging (MEGI) are the tools that are used to map the functional brain organisation preoperatively and non-invasively.

2. OVERVIEW OF SPECIFIC TUMOURS OF THE CENTRAL NERVOUS SYSTEM

2.1 INTRODUCTION

We aim to provide an overview of the surgical pathology and the genetic and molecular changes of common tumours of the nervous system in children and adults. We used the current histological classification for nervous system tumours of World Health Organization (WHO) as framework. The framework defined by Bailey and Cushing at 1926 (6) is still used as the primary classification method today. Bailey and Cushing named the tumours after the recognized cell types in the developing embryo/fetus or adult that the tumour cells most resembled histologically. We still do not know the cell type of origin of most of the brain tumours. We also do not have any identified premalignant stages. Most of the brain tumours are morphologically heterogeneous, and many of them are known to become more malignant over time with their progression initially being focal.

WHO uses four grades for classifying the brain tumours. Grade I tumours are biologically least aggressive tumours and most of the time they can be cured with surgery alone where a Grade IV tumours are biologically most aggressive tumours and most of the time, they have a rapid proliferation and the tumour cells infiltrate locally and disseminate within the central nervous system. Grade IV tumours are rapidly fatal if they are not treated. WHO criteria's for tumour grading includes cellularity, degree of polymorphism and atypia, the incidence of mitoses, the presence of spontaneous necrosis and degree of microvascular proliferation (angiogenesis).

Tumour type and grade are important factors determining the choice of conventional therapy and histological diagnosis must be completed before starting any therapies for therapies like radiation and chemotherapy will alter the tumour morphology which will make classification and grading almost impossible.

In this section, we will list the tumours of the central nervous system, which will be based on the latest (2016) classification of World Health Organization. It is beyond scope of

this study to give extended information regarding tumour biology, we will just list the main categories and the tumours with some basic information.

2.2 WHO CLASSIFICATION AND GRADING OF TUMOURS OF THE CENTRAL NERVOUS SYSTEM

For a very long time, tumours are graded by using their microscopic features and classified according to their similarities under magnification, developmental differentiation states and putative cells of origin. Between 2000 to 2007, the WHO classified tumours using their histological features along with the genetic changes underlying the tumorigenesis of CNS tumours. In 2016, WHO published an updated version of its classification of the CNS tumours and this version changed the primary classification parameters first time in the history from histological assessment approach to a new approach that includes the diagnostic categories that depend on genotype. The 2016 version of the WHO classification does not only use the genetic parameters because there is still a considerable amount of research required to make this classification based on genetic data and also the genetic parameters that can be assessed with immunochemistry or FISH is not easily accessible by all centres. Because of this, the WHO included a NOS diagnostic designation to its 2016 classification. NOS designation in 2016 classification indicates that there is insufficient information to assign a more specific code. So, the NOS category includes both tumours that have not been tested for the genetic parameter(s) and tumours that have been tested but did not show the diagnostic genetic alterations.

The WHO grade is still based on histological features and is one component of a set of criteria used to predict response therapy and outcome. Clinical findings like patient age, gender, performance status, and tumour location, radiological assessment results, proliferation index values and genetic alterations are the other prediction parameters. The genetic profile has become increasingly important because some genetic changes like IDH mutation in diffuse gliomas have been found to have crucial prognostic implications (Louis et al 2016). For each tumour entity, the combination of these parameters contributes to an overall estimate of prognosis.

Following table contains the list of tumours of the central nervous system and WHO's classification and grading for each tumour.

Table 2.1: WHO classification and grading of tumours of the central nervous system.

Tumour Type	WHO Grade
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 gliant 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	

Tumour Type	WHO Grade
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	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medullablastoma (all subtypes)	IV
Embryonal tumour with multilayer rosettes, C19MC-altered	IV

Tumour Type	WHO Grade
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)	II, 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
Spindle cell oncocytoma	I

Source: WHO Classification of Tumours of the Central Nervous System, Revised 4th Edition, International Agency for Research on Cancer

2.3 DEFINITIONS OF THE TUMOURS OF THE CENTRAL NERVOUS SYSTEM

In this section, we will give brief definitions of selected tumours that listed at Table 2.1. Information like clinical features, macroscopy, microscopy, and genetic profile is beyond the scope of our study. Not otherwise specified, all definitions are from the WHO 2016 classification.

2.3.1 Diffuse Astrocytoma, IDH-Mutant

A diffusely infiltrating astrocytoma with a mutation in either the IDH1 or IDH2 gene. IDH-mutant diffuse astrocytoma typically features moderately pleomorphic cells and is characterized by a high degree of cellular differentiation and slow growth. The diagnosis is supported by the presence of ATRX and TP53 mutation. The presence of a component morphologically resembling oligodendroglioma is compatible with this diagnosis in the absence of 1p/19q codeletion. This tumour most commonly affects young adults and occurs throughout the CNS but is preferentially located in the frontal lobes (Qin et al 2010). Diffuse astrocytomas have an intrinsic capacity for malignant progression to IDH-mutant anaplastic astrocytoma and eventually to IDH-mutant glioblastoma. Diffuse astrocytoma corresponds histologically to WHO grade II.

IDH-mutant diffuse astrocytomas can be located in any region of the CNS, but most commonly develop supratentorially in the frontal lobes (Stockhammer et al 2012). This is similar to the preferential localization of IDH-mutant and 1p/19q codeleted oligodendroglioma (Laigle-Donadey et al 2004, Zlatescu et al 2001) and supports the hypothesis that these gliomas develop from a distinct population of precursor cells (Ohgaki and Kleihues 2013).

The results of neuroimaging studies can be extremely variable. On CT, diffuse astrocytomas most often present as poorly defined, homogenous masses of low density, without contrast enhancement. However, calcification and cystic change may be present early in evolution of the tumour. MRI studies usually show T1-hypodensity and T2-hyperintensity, with enlargement of the areas involved early in the evolution of the

tumour. Gadolinium enhancement is not common in low-grade diffuse astrocytomas but tends to appear during tumour progression.

2.3.2 Anaplastic Astrocytoma, IDH-Mutant

A diffusely infiltrating astrocytoma with local or dispersed anaplasia, significant proliferative activity, and a mutation in either the IDH1 or IDH2 gene. Anaplastic astrocytomas can arise from lower-grade diffuse astrocytomas but are more commonly diagnosed without indication of a less-malignant precursor lesion. The presence of a component morphologically resembling oligodendroglioma is compatible with this diagnosis in the absence of 1p/19q codeletion. Anaplastic astrocytomas have an intrinsic tendency for malignant progression to IDH-mutant glioblastoma. IDH-mutant anaplastic astrocytoma corresponds histologically to WHO grade III.

IDH-mutant anaplastic astrocytomas can develop in any region of the CNS but most frequently occur in the cerebrum. These tumours, like other IDH-mutant diffuse gliomas (including oligodendrogliomas, diffuse astrocytomas, and IDH-mutant glioblastomas), are preferentially located in the frontal lobe.

IDH-mutant anaplastic astrocytoma presents as a poorly defined mass of low density. Unlike in WHO grade II diffuse astrocytomas, partial contrast enhancement is usually observed, but the central necrosis with ring enhancement typical of glioblastomas is absent. More rapid tumour growth with development of peritumoral oedema can lead to mass shifts and increased intracranial pressure.

2.3.3 Glioblastoma, IDH-Wildtype

A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism (in most cases), mitotic activity, and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis; and which lacks mutations in the IDH genes. IDH-wildtype glioblastoma is the most common and most malignant astrocytic glioma, accounting for about 90 percent of all glioblastomas and typically affecting adults, with a mean patient age at diagnosis of 62 years and a male-to-female ration of about 1.35:1. As the synonymous designation “IDH-wildtype primary

glioblastoma" indicates, this glioblastoma typically arises de novo, with no recognizable lower-grade precursor lesion. A preferentially supratentorial location is characteristic. The tumour diffusely infiltrates adjacent and distant brain structures. Glioblastoma and its variants correspond histologically to WHO grade IV. However, in the setting of current therapy, IDH-mutant glioblastomas may follow a clinical course that is less aggressive than is typical of WHO grade IV tumours.

Glioblastoma is often centred in the subcortical white matter and deeper grey matter of the cerebral hemispheres. In a series of 987 glioblastomas from the University of Zurich, the most frequently affected sites were the temporal lobe (31 percent of cases), the parietal lobe (in 24 percent), the frontal lobe (in 23 percent), and the occipital lobe (in 16 percent). Similar location trends are seen in the USA (Becker et al 1989). Whereas primary, IDH-wildtype glioblastomas have a wide-spread anatomical distribution, secondary, IDH-mutant glioblastomas have a striking predilection for the frontal lobe, particularly in the region surrounding the rostral lateral ventricles (Lai et al, 2011). In general, tumour infiltration extends into the adjacent cortex and through the corpus callosum into the contralateral hemisphere. Glioblastoma of the basal ganglia and thalamus is common, especially in children. Glioblastoma of the brainstem is uncommon and most often affects children (Dorhmann et al 1976). The cerebellum and spinal cord are rare sites.

Glioblastomas are irregularly shaped and have a ring-shaped zone of contrast enhancement around a dark, central area of necrosis. They may extend widely into adjacent lobes, the opposite hemisphere, and the brain stem. In the setting of a ring-enhancing mass, biopsies showing high-grade astrocytoma but not demonstrating frank histological features of glioblastoma should be suspected to have been inadequately sampled.

2.3.4 Glioblastoma, IDH-Mutant

A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism (in most cases), mitotic activity, and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis; with a mutation either the IDH1 or IDH2 gene. IDH-mutant glioblastomas account for approximately 10

percent of all glioblastomas. Glioblastomas that develop through malignant progression from diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III) are always associated with IDH mutation and therefore carry the synonym “secondary glioblastoma, IDH-mutant”. IDH-mutant glioblastoma is morphologically indistinguishable from IDH-wildtype glioblastoma, except for a lesser extent of necrosis. IDH-mutant glioblastomas manifest in younger patients (with a mean patient age at diagnosis of 45 years), are preferentially located in the frontal lobe, and carry a significantly better prognosis than IDH-wildtype glioblastomas (Nobusawa et al 2009, Yan et al 2009). IDH-mutant glioblastoma corresponds histologically to WHO grade IV. The prognosis of IDH-mutant glioblastoma is considerably better than that of IDH-wildtype glioblastoma; however, WHO grading reflects that the natural course of the disease rather than response to therapy. Therefore, because most patients eventually succumb to high-grade disease, IDH-mutant glioblastomas are designated as WHO grade IV.

Whereas IDH-wildtype glioblastomas show a widespread anatomical distribution, IDH-mutant glioblastomas have a striking predominance of frontal lobe involvement, in particular in the region surrounding the rostral extension of the lateral ventricles (Lai et al 2011). This is similar to the preferential localization of WHO grade II IDH-mutant diffuse astrocytoma (Stockhammer et al 2012) and IDH-mutant and 1p/19q codeleted oligodendroglioma (Laigle-Donadey et al 2004, Zlatescu et al 2001), supporting the hypothesis that these gliomas develop from a distinct population of common precursor cells (Ohgaki and Kleihues 2013, Beier et al 2007).

Unlike in IDH-wildtype glioblastoma, large areas of central necrosis are usually absent. Compared with IDH-wildtype glioblastoma, IDH-mutant glioblastoma presents more frequently with non-enhancing tumour components on MRI, with larger size at diagnosis, with lesser extent of oedema, and with increased prevalence of cystic and diffuse components (Lai et al 2011, Eoli et al 2007).

2.3.5 Diffuse Midline Glioma, H3 K27M-Mutant

An infiltrative midline high-grade glioma with predominantly astrocytic differentiation and a K27M mutation in either H3F3A or HIST1H3B/C. H3 K27M-mutant diffuse midline glioma predominates in children but can also be seen in adults, with the most common locations being brain stem, thalamus, and spinal cord. Brain stem and pontine examples were previously known as brain stem glioma and diffuse intrinsic pontine glioma (DIPG), respectively. Mitotic activity is present in most cases, but it is not necessary for diagnosis; microvascular proliferation and necrosis may be seen. Tumour cells diffusively infiltrate adjacent and distant brain structures. The prognosis is poor, despite current therapies, with a 2-year survival rate of <10 percent. H3 K27M-mutant diffuse midline glioma corresponds to WHO grade IV.

Diffuse midline gliomas typically arise in the pons, thalamus, or spinal cord, with occasional examples involving the cerebellum.

On MRI, diffuse midline gliomas are usually T1-hypointense and T2-hyperintense. Contrast enhancement, necrosis, and7or haemorrhage may be present. DIPG typically presents as a large, expansile, and often asymmetrical brain stem mass occupying more than two thirds of the pons (Warren 2012). There may be an exophytic component encasing the basilar artery or protruding into the fourth ventricle. Infiltration into the cerebellar peduncles, the cerebellar hemispheres, the midbrain, and the medulla is frequent. Contrast enhancement rarely involves >25 percent of the tumour volume (Bartels et al 2011).

2.3.6 Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted

A diffusely infiltrating, slow-growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q. Histologically, IDH-mutant and 1p/19q-codeleted oligodendroglioma is composed of tumour cells morphologically resembling oligodendrocytes, with isomorphic rounded nuclei and an artefactually swollen clear cytoplasm on routinely processed paraffin sections. Microcalcifications and a delicate branching capillary network are typical. The presence of an astrocytic tumour component is compatible with the diagnosis when molecular testing reveals the entity-defining

combination of IDH mutation and 1p/19q codeletion. The vast majority of IDH-mutant and 1p/19q-codeleted oligodendrogliomas occur in adult patients, with preferential location in the cerebral hemispheres (most frequently in the frontal lobe). IDH-mutant and 1p/19q-codeleted oligodendroglioma corresponds histologically to WHO grade II.

IDH-mutant and 1p/19q-codeleted oligodendrogliomas arise preferentially in the white matter and cortex of the cerebral hemispheres. The frontal lobe is the most common location (involved in >50 percent of all patients) followed in order of decreasing frequency by the temporal, parietal, and occipital lobes.

Involvement of more than one cerebral lobe or bilateral tumour spread is not uncommon. Rare locations include the posterior fossa, basal ganglia, and brain stem. Leptomeningeal spread is seen only a minority of patients (Roldan et al 2011). There have been rare cases of primary leptomeningeal oligodendrogliomas (Ng and Poon 1999) or oligodendroglial gliomatosis cerebri (Taillibert et al 2006). Primary oligodendrogliomas of the spinal cord are rare, accounting only for 1.5 percent of all oligodendrogliomas and 2 percent of all spinal cord tumours (Fountas et al 2005). Rare cases of primary spinal intramedullary oligodendroglioma and secondary meningeal dissemination have been reported, including a 1p/19q-codeleted tumour (Fountas et al 2005). Isolated cases of oligodendroglioma arising in ovarian teratomas have been reported, although there was no assessment of IDH mutation and 1p/19q-codeletion status (Ud Din et al 2012).

On CT, IDH-mutant and 1p/19q-codeleted oligodendrogliomas usually present as hypodense or isodense well-demarcated mass lesions, typically located in the cortex and subcortical white matter. Calcification is common but not diagnostic. MRI shows a lesion that is T1-hypointense and T2-hyperintense. The lesion is usually well demarcated and shows little perifocal oedema (Walker et al 2011). Some tumours show heterogeneous and7or areas of cystic degeneration. Gadolinium enhancement has been detected in <20 percent of WHO grade II oligodendrogliomas but in >70 percent of WHO grade III anaplastic oligodendrogliomas (Khalid et al 2012). Contrast enhancement in low-grade oligodendrogliomas has been associated with less favourable prognosis (von Deimling et al 1990). Demonstration of elevated 2-hydroxglutarate levels by MR spectroscopy is a

promising new means of non-invasive detection of IDH-mutant gliomas (including oligodendrogliomas) (Choi et al 2012). Differences in certain features between 1p/19q-codeleted and 1p/19q-intact low-grade gliomas have been reported on MR spectroscopy (van den Bent and Bromberg 2012, Fellah et al 2013, Brown et al 2008), but reliable discrimination by neuroimaging is not yet possible.

2.3.7 Anaplastic Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted

An IDH-mutant and 1p/19q-codeleted oligodendroglioma with focal or diffuse histological features of anaplasia (in particular, pathological microvascular proliferation and/or brisk mitotic activity). In IDH-mutant and 1p/19q-codeleted anaplastic oligodendroglioma, necrosis (with or without palisading) may be present but does not indicate progression to glioblastoma. The presence of an astrocytic tumour component is compatible with the diagnosis when molecular testing reveals combined IDH mutation and 1p/19q-codeletion. The vast majority of IDH-mutant and 1p/19q-codeleted anaplastic oligodendrogliomas manifest in adult patients. The tumours are preferentially located in the cerebral hemispheres, with the frontal lobe being the most common location. IDH-mutant and 1p/19q-codeleted anaplastic oligodendroglioma corresponds histologically to WHO grade III.

Anaplastic oligodendrogliomas and WHO grade II oligodendrogliomas share a preference for the frontal lobe, followed by the temporal lobe. However, the tumours can also originate at other sites within the CNS, and there have been rare cases of spinal intramedullary anaplastic oligodendroglioma.

Anaplastic oligodendrogliomas can show heterogeneous patterns, due to the variable presence of necrosis, cystic degeneration, intratumoural haemorrhages, and calcification. On CT and MRI, contrast enhancement is seen in most patients and can be either patchy or homogeneous (van den Bent and Bromberg 2012). However, lack of contrast enhancement does not exclude anaplastic oligodendroglioma. Ring enhancement is less common in IDH-mutant and 1p/19q-codeleted anaplastic oligodendrogliomas than in malignant gliomas, in particular glioblastomas without these molecular markers (van den Bent and Bromberg 2012, Cairncross et al 1998).

2.3.8 Pilocytic Astrocytoma

An astrocytoma classically characterized by a biphasic pattern with variable proportions of compacted bipolar cells with Rosenthal fibres and loose, textured multipolar cells with microcysts and occasional granular bodies. Genetically, pilocytic astrocytomas are characterized by the presence of mutations in genes coding for proteins involved in the MAPK pathway (Zhang et al. 2013, Akyurek et al. 2006). The most frequent genetic change is tandem duplication of 7q34 involving the BRAF gene resulting in oncogenic BRAF fusion proteins. Pilocytic astrocytomas are the most common glioma in children and adolescents and affect males slightly more often than females. They are preferentially located in the cerebellum and cerebral midline structures (i.e. the optic pathways, hypothalamus and brain stem) but can be encountered anywhere along neuroaxis (Louis et al. 2016). They are generally circumscribed and slow-growing and may be cystic. Pilocytic astrocytoma largely behaves as is typical of a WHO grade I tumour (Louis et al. 2016), and patients can be cured by surgical resection. However, complete resection may not be possible in some locations, such as the optic pathways and the hypothalamus. Pilocytic astrocytomas, particularly those involving the optic pathways, are a hallmark of neurofibromatosis type 1 (NF1). Pilomyxoid astrocytoma is considered to be a variant of pilocytic astrocytoma. Pilocytic astrocytoma corresponds histologically to WHO grade I.

Pilocytic astrocytomas arise throughout the neuroaxis; however, in the paediatric population, more tumours arise in the infratentorial region.

2.3.9 Subependymal Giant Cell Astrocytoma

A benign, slow-growing tumour composed of large ganglionic astrocytes, typically arising in the wall of the lateral ventricles. Subependymal giant cell astrocytoma (SEGA) has a strong association with the tuberous sclerosis syndrome. SEGA corresponds histologically to WHO grade I.

SEGAs arise from the lateral walls of the lateral ventricles adjacent to the foramen of Monro.

On CT, SEGAs present as solid, partially calcified masses located in the walls of the lateral ventricles, mostly near the foramen of Monro. Ipsilateral or bilateral ventricular enlargement may be apparent. On MRI, the tumours are usually heterogeneous, isointense, or slightly hypointense on T1-weighted images, and hyperintense on T2-weighted images, with marked contrast enhancement (Inoue et al. 1998). Prominent signal voids that represent dilated vessels are occasionally seen within the tumours. Like other brain neoplasms, SEGAs may show a high ratio of N-acetylaspartate to creatinine on proton MR spectroscopy, which seems to be a valuable tool for the early detection of neoplastic transformation of subependymal nodules (Ichimura et al. 1998). Leptomenengial dissemination with drop metastases has been described (Telfeian et al. 2004).

2.3.10 Pleomorphic Xanthoastrocytoma

An astrocytic glioma with large pleomorphic and frequently multinucleated cells, spindle and lipidized cells, a dense peri-cellular reticulin network, and numerous eosinophilic granular bodies. Pleomorphic xanthoastrocytoma tumour cells are neoplastic astrocytes, but there is often neuronal differentiation (Gianni et al. 2002, Hirose et al. 2001, Kepes et al. 1979). Mitotic activity is low (< 5 mitoses per 10 high-power fields). BRAF V600E mutation is common in pleomorphic xanthoastrocytoma, and its presence in the absence of an IDH mutation strongly supports the diagnosis. Pleo-morphic xanthoastrocytoma is rare (constituting < 1 percent of all astrocytic neoplasms) and most commonly affects children and young adults, with a median patient age at diagnosis of 22 years (Giannini et al. 1999). The tumour has a typical superficial location in the cerebral hemispheres, most frequently in the temporal lobe, with involvement of the adjacent leptomeninges and with cyst formation. Despite its alarming histological appearance, pleomorphic xanthoastrocytoma has a relatively favour-able prognosis compared with diffusely infiltrative astrocytoma, with 70.9 percent recurrence-free and 90.4 percent overall survival rates at 5 years (Ida et al. 2015). Pleomorphic xanthoastrocytoma corresponds histologically to WHO grade II.

A superficial location, involving the leptomeninges and cerebrum (meningocerebral) is characteristic of this neoplasm. Approximately 98 percent of cases occur supratentorially,

most commonly in the temporal lobe (Giannini et al. 1999, Kepes et al. 1979). Cases involving the cerebellum and spinal cord have also be reported (Nakamura et al. 2006, Gil-Gouveia et al. 2004), and two cases of primary pleomorphic xanthoastrocytoma of the retina in children have been reported (Zarate and Sampaolesi 1999).

Pleomorphic xanthoastrocytoma is usually a supratentorial mass, peripherally located and frequently cystic, involving cortex and overlying leptomeninges. CT and MRI scans outline the tumour mass and/ or its cyst. On CT, tumour appearance is variable (hypodense, hyperdense, or mixed), with strong, sometimes heterogeneous contrast enhancement (Osborn AG, et al. 2004). Tumour cysts are hypodense. On MRI, the solid portion of the tumour is either hypointense or isointense to grey matter on T1-weighted images and shows a hyper-intense or mixed signal on T2-weighted and FLAIR images, whereas the cystic component is isointense to cerebrospinal fluid. Postcontrast enhancement is moderate or strong (Osborn AG, et al. 2004). Perifocal oedema is usually not pronounced, due to the slow growth of the tumour.

2.3.11 Anaplastic Pleomorphic Xanthoastrocytoma

Definition A pleomorphic xanthoastrocytoma with 5 mitoses per 10 high-power fields. Patients with anaplastic pleomorphic xanthoastrocytoma have significantly worse survival than those whose tumours show < 5 mitoses per 10 high-power fields (Ida et al. 2015, Giannini et al. 1999). Necrosis may be present, but its significance in the absence of increased mitotic activity is unknown (Ida et al. 2015). The frequency of BRAF V600E mutation is lower among anaplastic pleomorphic xanthoastrocytomas than among WHO grade II pleomorphic xanthoastrocytomas, and the prognostic significance of the mutation is unknown (Ida et al. 2015, Schmidt et al. 2013). Grading Anaplastic pleomorphic xanthoastrocytoma corresponds histologically to WHO grade III.

Like WHO grade II pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma is typically a supratentorial tumour, with the temporal lobe being the most commonly involved lobe.

2.3.12 Subependymoma

A slow-growing, exophytic, intraventricular glial neoplasm characterized by clusters of bland to mildly pleomorphic, mitotically inactive cells embedded in an abundant fibrillary matrix with frequent microcystic change. Subependymomas are often detected incidentally, by neuroimaging or at autopsy, and have a very favourable prognosis (Louis et al. 2016, Hoffman et al. 2014, Wu et al. 2014, Kandenwein et al. 2011). Some tumours have the admixed histological features of both subependymoma and ependymoma. Grading Subependymoma Corresponds histologically to WHO grade I.

Subependymomas are distinguished by their intraventricular location, sharp demarcation, slow growth, and usually non-invasive behaviour. The most frequent site is the fourth ventricle (accounting for 50-60 percent of cases), followed by the lateral ventricles (accounting for 30-40 percent). Less common sites include the third ventricle and septum pellucidum. In rare cases, tumours occur intraparenchymally in the cerebrum (Kim et al 2014). In the spinal cord, sub-ependymomas manifest as cervical and cervicothoracic intramedullary or (rarely) extramedullary masses (Rushing et al. 2007, Jallo et al. 1996).

Subependymomas present as sharply demarcated nodular masses that are usually non-enhancing. Calcification and foci of haemorrhage may be apparent. Intramedullary cases are typically eccentric in location, rather than centrally positioned as is typical of intraspinal ependymomas. The lesions are hypointense to hyperintense on both and T2-weighted MRI, with minimal to moderate enhancement (Scheie et al. 2011, Rushing et al. 2007).

2.3.13 Myxopapillary ependymoma

A glial tumour arising almost exclusively in the region of the conus medullaris, cauda equina, and filum terminate, and histologically characterized by elongated, fibrillary processes arranged in radial patterns around vascularized, mucoid, fibrovascular cores. Myxopapillary ependymoma is a slow-growing variant of ependymoma. It typically occurs in young adults. The tumour generally has a favourable prognosis but can be difficult to resect completely. When this is the case, residual tumour may recur repeatedly, as the tumour be-comes entangled with spinal nerves. Grading Histologically,

myxopapillary ependymoma corresponds to WHO grade I. How-ever, this variant may have a more aggressive biological behaviour in children and a poor outcome after incomplete resection.

Myxopapillary ependymomas occur almost exclusively in the region of the callus medullaris, cauda equina, and filum terminate. They may originate from ependymal glia of the filum terminate to involve the cauda equina, and only rarely invade nerve roots or erode sacral bone. Multifocal tumours have been described (Nakama et al. 2005). Myxopapillary ependymomas can occasionally be observed at other locations, such as the cervicothoracic spinal cord (Sonneland et al. 1985), the fourth ventricle (Lim and Jang 2006), the lateral ventricles (Sato et al. 1983), and the brain parenchyma (Warnick et al. 1993). Subcutaneous sacrococcygeal or presacral myxopapillary ependymomas constitute a distinct sub-group. They are thought to originate from ectopic ependymal remnants (Ilhan et al. 1998). Intrasacral variants can clinically mimic chordoma.

Myxopapillary ependymomas are typically sharply circumscribed and contrast-enhancing. Extensive cystic change and haemorrhage may be seen.

2.3.14 Ependymoma

A circumscribed glioma composed of uniform small cells with round nuclei in a fibrillary matrix and characterized by a fibrillary matrix and characterized by perivascular anucleate zones (pseudorosettes) with ependymal rosettes also found in about one quarter of cases. Classic ependymoma generally has a low cell density and a low mitotic count. It very rarely invades adjacent CNS parenchyma to any significant extent. Cilia and microvilli are seen on ultrastructural examination. Classic ependymomas are mainly intracranial tumours; they do occur in the spinal cord, but the myxopapillary variant is more common at this site. Classic ependymomas occur in both adults and children, although most posterior fossa tumours present in childhood. Ependymomas have a variable clinical outcome, which is primarily dependent on extent of surgical resection, the use of irradiation as an adjuvant therapy, and molecular group (Pajtler et al. 2015, Godfraind et al. 2012). Three distinct histopathological phenotypes, which are classified as ependymoma variants (although without particular clinicopathological significance)

can be a prominent component of both classic and anaplastic ependymoma: papillary ependymoma, clear cell ependymoma, and tanycytic ependymoma.

Traditionally, classic ependymoma and anaplastic ependymoma are considered to correspond histologically to WHO grades II and III, respectively. However, no association between grade and biological behaviour or survival has been definitively established (Ellison et al. 2011, Figarella-Branger et al. 2000 , Kepes JJ 1993). Of the various studies of prognostic variables and outcome in ependymoma, those that have not found an association between grade (II vs III) and progression-free or overall survival outnumber those that have. The published ratios of grade II to grade III tumours in series of ependymomas vary widely, from 17:1 to 1:7, and the explanation for such inconsistent data is multifactorial (Ellison et al. 2011, Godfraind C 2009, Tomura et al 1997). The interpretation of most histopathological variables used in this classification for grading purposes is subjective, and ependymomas are morphologically heterogeneous. For example, the significance of grading on the basis of focal microvascular proliferation or focally increased mitotic counts within large areas of bland architectural and cytological features is difficult to determine. There have been few studies of the prognostic significance of WHO grade or individual pathological features across large trial cohorts in which proper multivariate analyses of prognostic variables can be performed, and there have been only three studies in which evaluation of histological variables was defined stringently and undertaken by several observers (Ellison et al. 2011, Godfraind C 2009, Tomura et al 1997). Due to these limiting factors, grading is almost never used for therapeutic stratification of patients with ependymoma. Given that specific genetic alterations and molecular groups have recently been proposed as prognostic or predictive factors for these tumours (Pajtler et al. 2015, Mack et al. 2014, Witt et al. 2011), the practice of histologically grading ependymoma may soon become obsolete together.

Ependymomas may occur along the ventricular system or spinal canal, in the cerebral hemispheres, or at extra-CNS sites. Overall, 60 percent of the tumours develop in the posterior fossa, 30 percent in the supratentorial compartment, and 10 percent in the spinal canal [http://seer.cancer.gov/archive/csr/19752004]. In adult patients, infratentorial and spinal ependymomas Occur with almost equal frequency, whereas infratentorial

ependymomas predominate in Children (Kudo et al. 1990). In children aged < 3 years at presentation, 80 percent of ependymomas are in the posterior fossa (Purdy et al. 2014). Posterior fossa ependymomas are located in the fourth ventricle and sometimes involve the cerebellopontine angle; in the fourth ventricle, 60 percent, 30 percent, and 10 percent of the tumours originate in the floor, lateral aspect, and roof, respectively (Sanford and Gajjar 1997, Ikezaki et al. 1993). Supratentorial ependymomas arise from the lateral or third ventricles (in 60 percent of cases) or from the cerebral hemispheres, without obvious connection to a ventricle (in 40 percent of cases). In the spinal cord, cervical or cervicothoracic localization is common among classic ependymomas. In contrast, the myxopapillary variant predominantly affects the conus and cauda equina. Rare extra-CNS ependymomas have been observed in the ovaries (Komuro et al. 2001), broad ligaments (Bell et al. 1984), pelvic and abdominal cavities, mediastinum, and lung. Myxopapillary ependymomas occur in the subcutaneous tissue of the sacrococcygeal area.

Gadolinium-enhanced MRI shows well-circumscribed masses with various degrees of contrast enhancement. Ventricular obstruction or brain stem displacement and hydrocephalus are common accompanying features. Supratentorial tumours often exhibit cystic components. Intra-tumoural haemorrhage and calcification are occasionally observed. Gross infiltration of adjacent brain structures and oedema are very rare. MRI is particularly useful for determining the relationship with surrounding structures, invasion along the cerebro-spinal fluid pathway, and syrinx formation. Cerebrospinal fluid spread is a key factor for staging, prognostication, and treatment.

2.3.15 Anaplastic Ependymoma

A circumscribed glioma composed of uniform small cells with round nuclei in a fibrillary matrix and characterized by perivascular anucleate zones (pseudorosettes), ependymal rosettes in about one quarter of cases, a high nuclear-to-cytoplasmic ratio, and a high mitotic count. A diagnosis of anaplastic ependymoma can be confidently made when an ependymal tumour shows a high cell density and elevated mitotic count along-side widespread microvascular proliferation and necrosis. Like the classic tumour, anaplastic ependymoma rarely invades adjacent CNS parenchyma to any significant extent. Cilia and microvilli are seen on ultrastructural examination. Anaplastic ependymomas are

mainly intracranial tumours; they are rare in the spinal cord. Anaplastic ependymomas occur in both adults and children, al-though most posterior fossa tumours present in childhood. Clear cell, papillary, or tanycytic morphology can be a feature of both classic and anaplastic ependymomas. Anaplastic ependymomas have a variable clinical outcome, which is primarily dependent on extent of surgical resection and molecular group (Pajtler et al. 2015, Godfraind et al. 2012). In defining molecular groups of ependymoma, transcriptome or methylome profiling has established the relevance of anatomical site to ependymoma biology.

In a recent study that will likely serve as the basis for the future molecular classification of the disease (Pajtler et al. 2015), nine groups of ependymoma were described (three for each of the three major CNS anatomical compartments: the supratentorial compartment, posterior fossa, and spinal compartment). The modal patient age at presentation, clinical outcome, and frequencies of histopathological variants and genetic alterations vary across these groups.

Traditionally, classic ependymoma and anaplastic ependymoma are considered to correspond histologically to WHO grades II and III, respectively. However, no association between grade and biological behaviour or survival has been definitively established (Purdy et al. 2014, Ellison et al. 2011, Figarella-Branger et al. 2000). Of the various studies of prognostic variables and outcome in ependymoma, those that did not find an association be-tween grade (II vs III) and progression-free or overall survival outnumber those that did. The published ratios of grade II to grade III tumours in series of ependymomas vary widely, from 17:1 to 1:7, and the explanation for such inconsistent data is multifactorial (Ellison et al. 2011, Figarella-Branger et al. 2000, Tomura et al 1997). The interpretation of most histopathological variables used in this classification for grading purposes is subjective, and ependymomas are morphologically heterogeneous. There have been few studies of the prognostic significance of WHO grade or individual pathological features in large trial cohorts in which proper multivariate analyses of prognostic variables can be performed, and there have been only three studies in which evaluation of histological variables was defined stringently and undertaken by several observers (Ellison et al. 2011, Figarella-Branger et al. 2000, Tomura et al 1997).

Due to these limiting factors, grading is hardly ever used for therapeutic stratification of patients with ependymoma. Given that specific genetic alterations and molecular groups have recently been proposed as prognostic or predictive factors for these tumours (Mack et al. 2014, Pajtler et al. 2015, Witt et al. 2011), the practice of histologically grading ependymoma may soon become obsolete altogether.

2.3.16 Chordoid Glioma of Third Ventricle

A slow-growing, non-invasive glial tumour located in the third ventricle, histologically characterized by clusters and cords of epithelioid tumour cells expressing GFAP, within a variably mucinous stroma typically containing a lymphoplasmacytic infiltrate. Chordoid gliomas of the third ventricle occur in adults and have a favourable prognosis, particularly in the setting of gross total resection. Chordoid glioma of the third ventricle corresponds histologically to WHO grade II.

Chordoid gliomas occupy the anterior portion of the third ventricle, with larger tumours also filling the middle and posterior aspects (Pomper et al. 2001). They generally arise in the midline and displace normal structures in all directions as they enlarge. Neuroimaging findings, including reports of small, localized tumours, suggest that chordoid gliomas arise in the region of the lamina terminalis in the ventral wall of the third ventricle (Leeds et al. 2006, Pasquier et al. 2002). In at least some cases, radiological studies have demonstrated an intraparenchymal hypothalamic component (Pomper et al. 2001).

On neuroimaging, chordoid gliomas present as well-circumscribed ovoid masses within the anterior third ventricle. On MRI, they are T1-isointense to brain and show strong, homogeneous contrast enhancement (Pomper et al. 2001). Mass effect is generally distributed symmetrically and causes vasogenic oedema in compressed adjacent CNS structures, including the optic tracts, basal ganglia, and internal capsules. Most tumours are continuous with the hypothalamus and some appear to have an intrinsic anterior hypothalamic component, suggesting a potential site of origin (Leeds et al. 2006).

2.3.17 Angiocentric glioma

An epilepsy-associated, stable or Show-growing cerebral tumour Primarily affecting children and young adults; histologically characterized by an angiocentric pattern of growth, monomorphous bipolar cells, and features of ependymal differentiation. Angiocentric glioma (also called monomorphous angiocentric glioma (Wang et al. 2005) and angiocentric neuroepithelial tumour (Lellouch-Tubiana et al. 2005)) has an uncertain relationship to other neoplasms exhibiting ependymal differentiation. Examples with this pattern have been reported as cortical ependymoma (Lehman et al. 2003). Tumours harbouring both angiocentric glioma and ependymoma patterns have also been reported (Van Gompel et al. 2011). The relationship between angiocentric glioma and classic ependymoma thus remains to be defined. Angiocentric glioma corresponds histologically to WHO grade I. Angiocentric glioma corresponds histologically to WHO grade I.

On MRI, the superficial, if not cortically based, lesion is well circumscribed, bright on FLAIR images, and non—contrast-enhancing. A cortical band of T1-hyperinten-sity is present in some cases. A stalk-like extension to the subjacent lateral ventricle is another variable feature (Koral et al. 2012).

2.3.18 Astroblastoma

A rare glial neoplasm composed of cells that are positive for GFAP and have broad, non- or slightly tapering process-es radiating towards central blood vessels (astroblastic pseudorosettes) that often demonstrate sclerosis. Astroblastoma mainly affects children, adolescents, and young adults, and occurs nearly exclusively in the cerebral hemispheres. Neoplasms exhibiting foci of astroblastoma-type perivascular structuring but having components of otherwise conventional astrocytoma or ependymoma should not be given this designation.

The biological behaviour of astroblastoma varies. In the absence of sufficient clinicopathological data, it would be pre-mature to establish WHO grade(s) at this time. However, the literature has categorized these tumours as either well differentiated or malignant (anaplastic). In one series, well-differentiated tumours had low mitotic activity (1 mitosis per 10 high-power fields) and an average Ki-67 proliferation index of 3 percent

(Brat et al. 2000). Regional (infarct-like) necrosis has been noted in 30 percent of these tumours. Neither vascular proliferation nor spontaneous necrosis with palisading has been seen. Malignant astroblastomas are characterized by the presence of focal or multi-focal regions of high cellularity, anaplastic nuclear features, increased mitotic activity (> 5 mitoses per 10 high-power fields), microvascular proliferation, and necrosis with palisading. In most cases, these high-grade features are found focally in the setting of a classic, better-differentiated astroblastoma. The Ki-67 proliferation index in these malignant astroblastomas is typically > 10 percent.

Astroblastomas typically involve the cerebral hemispheres (Sughrue et al 2011, Ahmed et al 2014, Russel and Rubinstein 1989, Husain and Leestma 1986). Among 177 intracranial cases in the SEER data for which the site was known, the supratentorial compartment was involved in 144 cases (81 percent) and the infratentorial in 33 cases (19 percent). The spinal cord is only rarely involved.

On CT and MRI, astroblastomas present as well-demarcated, non-calcified, nodular or lobulated masses with frequent cystic change and conspicuous contrast enhancement (Sener 2002).

2.3.19 Choroid Plexus Papilloma

A benign ventricular papillary neoplasm derived from choroid plexus epithelium, with very low or absent mitotic activity. Histologically, choroid plexus papilloma Histologically, choroid plexus papilloma closely resembles the non-neoplastic choroid plexus, and most tumour cells are positive for the potassium channel KIR7.1. Patients are usually cured by complete surgical resection. Choroid plexus papilloma corresponds histologically to WHO grade I.

Choroid plexus papillomas are located within the ventricular system where the normal choroid plexus can be found. They are seen most often in the lateral ventricles, followed by the fourth and third ventricles. They are rarely found within the spinal cord or in ectopic locations (Paulus and Janisch 1990). Multifocal occurrence is exceptional (Peyre M et al. 2012). A meta-analysis found that the median patient age was 1.5 years for

tumours in the lateral and third ventricles, 22.5 years for those in the fourth ventricle, and 35.5 years for those in the cerebellopontine angle (Wolff et al. 2002).

2.3.20 Atypical Choroid Plexus Papilloma

A choroid plexus papilloma that has increased mitotic activity but does not fulfil the criteria for choroid plexus carcinoma. Atypical choroid plexus papillomas in children aged > 3 years and in adults are more likely to recur than their classic counterparts. Atypical choroid plexus papilloma corresponds histologically to WHO grade II.

Atypical choroid plexus papillomas arise in locations where normal choroid plexus can be found. Whereas typical choroid plexus papillomas occur in the supratentorial and infratentorial regions with nearly equal frequency, atypical choroid plexus equal frequency, atypical choroid plexus papillomas are more common within the lateral ventricles (Jeibmann et al. 2006). In a large series of patients with atypical choroid plexus papillomas, 83 percent of the tumours were located in the lateral ventricles, 13 percent in the third ventricle, and 3 percent in the fourth ventricle (Wrede et al. 2009).

No differences in MRI characteristics have been reported between choroid plexus papilloma and atypical choroid plexus papilloma (Wrede et al. 2009).

2.3.21 Choroid Plexus Carcinoma

A frankly malignant epithelial neoplasm most commonly occurring in the lateral ventricles of children, showing at least four of the following five histological features: frequent mitoses, increased cellular density, nuclear pleomorphism, blurring of the papillary pattern with poorly structures sheets of tumour cells, and necrotic areas. Choroid plexus carcinoma frequently invades neighbouring brain structures and metastasizes via cerebrospinal fluid. Preserved nuclear expression of SMARCB1 and SMARCA4 (i.e. no inactivation of the SMARCB1 or SMARCA4 gene) in virtually all tumours helps in the differential diagnosis with atypical teratoid/rhabdoid tumour. Choroid plexus carcinoma corresponds histologically to WHO grade III.

The great majority of choroid plexus carcinomas are located within and around the lateral ventricles (Lafay-Cousin et al. 2011).

On MRI, choroid plexus carcinomas typically present as large intraventricular lesions with irregular enhancing margins, a heterogeneous signal on T2-weighted and 11-weighted images, oedema in adjacent brain, hydrocephalus, and disseminated tumour (Meyers et al. 2004).

2.3.22 Dysembryoplastic Neuroepithelial Tumour

A benign glioneuronal neoplasm typically located in the temporal lobe of children or young adults with early-onset epilepsy; predominantly with a cortical location and a multinodular architecture; and with a histological hallmark of a specific glioneuronal element characterized by columns made up of bundles of axons oriented perpendicularly to the cortical surface. These columns are lined by oligodendrocyte-like cells embedded in a mu-cold matrix and interspersed with floating neurons. If only the specific glioneuronal element is observed, the simple form of dysembryoplastic neuroepithelial tumour (DNT) is diagnosed. Complex variants of DNT additionally contain glial tumour components, often with a nodular appearance. The presence of 1DH mutation or 1p/19q codeletion excludes the diagnosis of DNT. Long-term follow-up after epilepsy surgery shows an excellent outcome; recurrence or progression is exceptional. DNT corresponds histologically to WHO grade I.

DNTs can be located in any part of the supratentorial cortex but show a predilection for the temporal lobe (Campos et al 2009), preferentially involving the mesial structures (Ingold et al. 2008, Chan et al. 2006, Janson et al 2006, Daumas 1995, Daumas-Duport 1995, Daumas-Duport 1993, Prayson and Estes 1992, Daumas-Duport et al 1989, Daumas-Duport et al 1988). The second most frequent location is the frontal lobe (Campos et al 2009). In a meta-analysis of 624 reported DNTs, 67.3 percent were located in the temporal lobe, 16.3 percent in the frontal lobe, and 16.4 percent in other locations (Thom et al. 2011), such as the caudate nucleus (Kurian et al. 2005, Guesmi et al. 1999) or lateral ventricles (Ongürü et al. 2003), the septum pellucidum (Harter et al. 2006, Jackson 2001), the trigonoseptal region (Guesmi et al. 1999), the midbrain and tectum

(Kurtkaya-Yapıcıer et al. 2002), and the cerebellum (Yasha et al. 1998, Kuchelmeister et al. 1995, Daumas-Duport et al 1988) or brain stem (Nakamura et al. 2006). Multifocal DNTs have also been reported, indicating that these tumours can also be found in the region of the third ventricle, the basal ganglia, and the pons (Schittenhelm et al. 2007, Krossnes et al. 2005, Whittle et al. 1999, Lellouch-Tubiana et al. 1995).

Cortical topography and the absence of mass effect and of significant tumoural oedema are important criteria for differentiating between DNTs and diffuse gliomas. DNTs usually encompass the thick-ness of the normal cortex. In a minority of cases, the area of signal abnormality also extends into the subcortical white matter (Louis et al. 2016,Campos et al 2009, Fernandez et al. 2003, Daumas 1995, Kuroiwa et al. 1995, Daumas-Duport 1993, Daumas-Duport et al 1989). On MRI, most DNTs present as T2-hyperintense multiple or single pseudocysts. Non-cystic tissue is hypointense or nearly isointense to grey matter on T1- weighted images and hyperintense on T2-weighted and FLAIR images (Louis et al. 2016). In tumours that are located at the convexity, deformation of the overlying calvaria is often seen on imaging, and this finding further supports the diagnosis of DNT (Louis et al. 2016, Kuroiwa et al. 1995, Daumas 1995, Daumas-Duport 1993, Daumas-Duport et al 1989). Calcifications are often seen on CT. When present, they occur within more deeply located tumour portions, usually in the vicinity of contrast-enhancing regions and haemorrhages (Louis et al. 2016). On CT and MR1, about 20 percent to one third of DNTs show contrast enhancement, often in multiple rings rather than homogeneously (Louis et al. 2016). Nodular or ring-shaped contrast enhancement may occur in a previously non-enhancing tumour (Louis et al. 2016, Campos et al 2009), and increased lesion size, with or without perk tumoral oedema, may also be observed on imaging follow-up. However, in DNTs, these changes are not signs of malignant transformation but are usually due to ischaemic and/or haemorrhagic changes (Louis et al. 2016, Jensen et al. 2006, Daumas-Duport and Varlet 2003).

2.3.23 Gangliocytoma

A rare, well-differentiated, slow-growing neuroepithelial neoplasm composed of irregular clusters of mostly mature neoplastic ganglion cells, often with dysplastic

features. The stroma consists of non-neo-plastic glial elements. Transitional forms between gangliocytoma and ganglioglioma exist, and the distinction of these two entities is not always possible. Gangliocytoma corresponds histologically to WHO grade I.

Like gangliogliomas, these tumours can occur throughout the CNS.

Radiological data specifically addressing gangliocytoma have not been reported.

2.3.24 Ganglioglioma

A well-differentiated, slow-growing glioneuronal neoplasm composed of dysplastic ganglion cells (i.e. large cells with dysmorphic neuronal features, without the architectural arrangement or cytological characteristics of cortical neurons) in combination with neoplastic glial cells. Gangliogliomas preferentially present in the temporal lobe of children or young adults with early-onset focal epilepsy. Intracortical cystic structures and a circumscribed area of cortical (and sub-cortical) signal enhancement are characteristic on FLAIR and T2-weighted MRI. BRAFV600E mutation occurs in approximately 25 percent of gangliogliomas, whereas IDH mutation or combined loss of chromosomal arms 1p and 19q exclude a diagnosis of a ganglioglioma. The prognosis is favourable, with a recurrence-free survival rate as high as 97 percent at 7.5 years. Most gangliogliomas correspond histologically to WHO grade I. Some gangliogliomas with anaplastic features in their glial component (i.e. anaplastic gangliogliomas) are considered to correspond histologically to WHO grade III (Jenkins et al. 2012, Majores et al. 2008). Criteria for WHO grade II have been discussed but not established (Majores et al. 2008, Luyken et al. 2004).

These tumours can occur throughout the CNS, including in the cerebrum, brain stem, cerebellum, spinal cord, optic nerves, pituitary, and pineal gland. The majority (> 70 percent) of gangliogliomas occur in the temporal lobe (Louis et al. 2016, Blümcke and Wiestler 2002).

Classic imaging features include intra-cortical cyst(s) and a circumscribed area of cortical (and subcortical) signal increase on FLAIR and T2-weighted images (Louis et al. 2016).

Contrast enhancement varies in intensity from none to marked, and may be solid, rim, or nodular. Tumour calcification can be detected in 30 percent of tumours. Scalloping of the calvaria may be seen adjacent to superficially located cerebral tumours.

2.3.25 Anaplastic Ganglioglioma

A glioneuronal tumour composed of dysplastic ganglion cells and an anaplastic glial component with elevated mitotic activity. Anaplastic gangliogliomas correspond histologically to WHO grade III.

2.3.26 Dysplastic Gangliocytoma of Cerebellum (Lhermitte-Duclos)

A rare, benign cerebellar mass composed of dysplastic ganglion cells that conform to the existing cortical architecture. In dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), the enlarged ganglion cells are predominantly located within the internal granule layer and thicken the cerebellar folia. The mass is a major CNS manifestation of Cowden syndrome, an autosomal dominant condition that causes a variety of hamartomas and neoplasms. It is not yet clear whether dysplastic cerebellar gangliocytoma is neoplastic or hamartomatous. If neoplastic, it corresponds histologically to WHO grade I.

Dysplastic cerebellar gangliocytoma lesions are found in the cerebellar hemispheres.

Neuroradiological studies demonstrate distorted architecture in the affected cerebellar hemisphere, with enlarged cerebellar folia and cystic changes in some cases. MRI is particularly sensitive in depicting the enlarged folia, with alternating T1-hypointense and T2-hyperintense tiger-striped striations (Louis et al. 2016, Giorgianni et al. 2013). The lesions typically do not enhance. Advanced techniques (including FDG-PET972, MR spectroscopy (Fauria-Robinson et al. 2014), and diffusion-weighted imaging (Louis et al. 2016) have also been used to characterize Lhermitte-Duclos disease. Infiltrating medulloblastomas have been reported to mimic dysplastic cerebellar gangliocytoma on imaging (Louis et al. 2016, Douglas-Akinwande et al. 2009).

2.3.27 Desmoplastic Infantile Astrocytoma and Ganglioglioma

A rare, benign cerebellar mass composed of dysplastic ganglion cells that conform to the existing cortical architecture. In dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), the enlarged ganglion cells are predominantly located within the internal granule layer and thicken the cerebellar folia. The mass is a major CNS manifestation of Cowden syndrome, an autosomal dominant condition that causes a variety of hamartomas and neoplasms. It is not yet clear whether dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) is neoplastic or hamartomatous. If neoplastic, it corresponds histologically to WHO grade I.

Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) lesions are found in the cerebellar hemispheres. Advanced techniques (including FDG-PET (Louis et al. 2016), MR spectroscopy (Fauria-Robinson et al. 2014), and diffusion-weighted imaging148) have also been used to characterize Lhermitte-Duclos disease. Infiltrating medulloblastomas have been reported to mimic dysplastic cerebellar gangliocytoma on imaging (Louis et al. 2016, Douglas-Akinwande et al. 2009). Imaging Neuroradiological studies demonstrate distorted architecture in the affected cerebellar hemisphere, with enlarged cerebellar folia and cystic changes in some cases. IVRI is particularly sensitive in depicting the enlarged folia, with alternating T1-hypointense and T2-hyperintense tiger-striped striations (Louis et al. 2016). The lesions typically do not enhance.

2.3.28 Papillary Glioneuronal Tumour

A low-grade biphasic neoplasm with astrocytic and neuronal differentiation and histopathological features including a pseudopapillary structure composed of flat to cuboidal astrocytes that are positive for GFAP lining hyalinized vessels, interpapillary collections of synaptophysin positive neurocytes, and occasional ganglion cells; with low mitotic activity and infrequent necrosis or microvascular proliferation. Papillary glioneuronal tumour (PGNT) is a rare glioneuronal tumour that preferentially occurs in the supratentorial compartment in young adults, with no sex preference. A circumscribed cystic or solid mass with contrast enhancement is characteristic on MRI. A novel translocation t(9;17) (q31;q24), which results in an SLC44A1-PRKCA fusion oncogene, is present in a high proportion of cases. The prognosis is good. Most PGNTs correspond

histologically to WHO grade I and behave in a manner consistent with this grade (Jenkinson et al. 2003), but a minority of cases show atypical histological features or late biological progression (Louis et al. 2016, Javahery et al. 2009, Ishizawa et al. 2006).

PGNTs are typically located in the cerebral hemispheres, often in proximity to the ventricles, and with a predilection for the temporal lobe (Louis et al. 2016, Rushing et al. 2005, Komori et al. 1998). Occasionally, they grow intraventricularly (Louis et al. 2016). On MRI and CT, the tumours present as demarcated, solid to cystic, contrast-enhancing masses with little mass effect. A cystic or mural nodule architecture may be seen.

Radiologically, a cystic component is typical, but the tumours can be broadly classified into four groups; cysts with mural nodules, masses that are cystic only, mixed cystic and solid masses, and masses that are solid only (Schlamann et al. 2014). The tumours are usually located in the white matter, frequently near the ventricle (Louis et al. 2016, Schlamann et al. 2014). On MRI, the solid portion is isointense or hypointense on T1-weighted images and diffusion-weighted images, and hyperintense on T2-weighted images and FLAIR images (Louis et al. 2016). Most of the tumours (85 percent) have no (or only minimal) peritumoural oedema, even when they are large in volume (Louis et al. 2016, Schlamann et al. 2014). About 10 percent of the reported cases showed overt or occult signs of intratumoral haemorrhage (Louis et al. 2016). Calcification has also been reported in some cases (Louis et al. 2016).

2.3.29 Central Neurocytoma

Definition An uncommon intraventricular neoplasm composed of uniform round cells with a neuronal immunophenotype and low proliferation index. Central neurocytoma is usually located in the region of the foramen of Monro, pre-dominantly affects young adults, and has a favourable prognosis.

Central neurocytoma corresponds histologically to WHO grade II. The tumours are usually benign, but some recur, even after total surgical removal. Because the prognostic values of anaplastic features and the Ki-67 proliferation index are still uncertain, it is not

yet possible to attribute two distinct histological grades (I and II) to central neurocytoma variants.

Localization Central neurocytomas are typically located supratentorially in the lateral ventricle(s) and/or the third ventricle. The most common site is the anterior portion of one of the lateral ventricles, followed by combined extension into the lateral and third ventricles, and by a bilateral intraventricular location. Attachment to the septum pellucidum seems to be a feature of the tumour (Louis et al. 2016). Isolated third and fourth ventricular occurrence is rare (Louis et al. 2016).

On CT, the masses are usually isodense or slightly hyperdense. Calcifications and cystic changes may be seen. On IVRI, central neurocytomas are 71- isointense to brain and have a so-called soap-bubble multicystic appearance on T2-weighted images. They often exhibit FLAIR hyperintensity, with a well-defined margin. In all cases, heterogeneous enhancement after gadolinium injection is observed, and the tumour may show vascular flow voids. Haemorrhage may be seen (Louis et al. 2016). An inverted alanine peak and a notable glycine peak on proton MR spectroscopy are useful in the differential diagnosis of intraventricular neoplasms (Louis et al. 2016, Majos et al. 2009).

2.3.30 Extraventricular Neurocytoma

A tumour composed of small uniform cells that demonstrate neuronal differentiation but are not 1DH-mutant, and that presents throughout the CNS, without apparent association with the ventricular system. Extraventricular neurocytoma is usually well circumscribed and slow-growing and shares most histological features with central neurocytoma. Because some tumours (including pilocytic astrocytomas, dysembryoplastic neuroepithelial tumours, gangliogliomas, papillary glioneuronal tumours [PGNTs], oligodendrogliomas with neurocytic features, and diffuse leptomeningeal glioneuronal mourn) show synaptophysin expression, synaptophysin expression is not sufficient to establish a diagnosis of extraventricular neurocytoma. Strong and diffuse OLIG2 expression is not compatible with a diagnosis of extraventricular neurocytoma. Some entities that are genetically well defined (e.g. IDH-mutant and 1 p/19q-codeleted oligodendroglioma and PGNTs) should be excluded by appropriate genetic testing.

However, the genetic characteristics of extraventricular neurocytoma are not yet well defined.

Extraventricular neurocytomas correspond histologically to WHO grade II. There have been suggestions for further grading on the basis of mitotic rate, Ki-67 Proliferation index, and the presence or absence of vascular proliferation and/or -necrosis (Louis et al. 2016). The term "atypical" has been used for lesions with an elevated mitotic rate and Ki-67 proliferation index (Louis et al. 2016). There is some evidence that each of these factors is associated with risk of recurrence, but definitive grading criteria have not yet been established.

The cerebral hemispheres are the most common site for extraventricular neurocytoma (affected in 71 percent of cases). The tumours most often affect the frontal lobes (in 30 percent of cases), followed by the spinal cord (in 14 percent). These tumours can occur in the thalamus, hypothalamic region, cerebellum, and pons, with isolated cases reported in cranial nerves, the cauda equina, the sellar region, and even outside the craniospinal compartment (Louis et al. 2016).

On MRI, extraventricular neurocytoma presents as a solitary, well-demarcated mass of non-specific signal intensity and variable contrast enhancement, with a cystic component in 58 percent of cases, mild perilesional oedema in 51.5 percent, and calcification in 34 percent (Louis et al. 2016, Liu et al. 2013, Yi et al. 2012). The solid component is predominantly isointense on T1-weighted images but may be hypointense. On T2-weighted and FLAIR images, the signal is predominantly hyperintense.

2.3.31 Cerebellar Liponeurocytoma

A rare cerebellar neoplasm with advanced neuronal/neurocytic differentiation and focal lipoma-like changes. Cerebellar liponeurocytoma affects adults, has low proliferative activity, and usually has a favourable prognosis. How-ever, recurrence can occur, and malignant progression has been reported. Cerebellar liponeurocytoma corresponds histologically to WHO grade II. Recurrences have been reported in almost 50 percent of cases. Recurrent tumours may display increased mitotic activity, an in-creased Ki-67

proliferation index, vascular proliferation, and necrosis (Louis et al. 2016). The time to clinical progression is often long (mean: 6.5 years), but in some cases relapse occurs within a few months (Jenkinson et al. 2003).

Cerebellar liponeurocytoma most commonly involves the cerebellar hemispheres but can also be located in the paramedian region or vermis and extend to the cerebellopontine angle or fourth ventricle (Louis et al. 2016).

On CT, the tumour is variably isodense or hypodense, with focal areas of marked hypoattenuation corresponding to fat density (Louis et al. 2016). On T1-weighted MRI, the tumour is isointense to hypointense, with patchy areas of hyperintensity corresponding to regions of high lipid content. Enhancement with gadolinium is usually heterogeneous, with areas of tumour showing variable degrees of enhancement. On T2-weighted MRI, the tumour slightly hyperintense to the adjacent rain, with focal areas of marked hyperintensity. Associated oedema is minimal absent (Louis et al. 2016). Fat-suppressed images may be helpful in supporting a preoperative diagnosis (Louis et al. 2016).

2.3.32 Pineocytoma

A well-differentiated pineal parenchymal neoplasm composed of uniform cells forming large pineocytomatous rosettes and/or of pleomorphic cells showing gangliocytic differentiation. Pineocytoma is a rare neoplasm. It ac-counts for about 20 percent of all pineal parenchymal tumours and typically affects adults, with a mean patient age at diagnosis of 43 years. There is a female pre-dominance, with a male-to-female ratio of 0.6:1. Other characteristics are exclusive localization in the pineal region and a well-demarcated solid mass without infiltrative or disseminating growth. Specific genetic alterations have not yet been identified. The prognosis is good after total surgical removal. Pineocytoma corresponds histologically to WHO grade I.

Pineocytomas typically remain localized in the pineal area, where they compress adjacent structures, including the cerebral aqueduct, brain stem, and cerebellum. Protrusion into the posterior third ventricle is common.

On CT, pineocytomas usually present as globular, well-delineated masses < 3 cm in diameter. They appear hypodense and homogeneous, some harbouring either peripheral or central calcification (Louis et al. 2016). Occasional cystic changes may be seen and are usually not easily confused with typical pineal cysts (Louis et al. 2016). Most tumours exhibit heterogeneous contrast enhancement. Isodense to slightly hyperdense appearance and homogeneous contrast enhancement on CT have also been reported (Louis et al. 2016). Accompanying hydrocephalus is a common feature (Schild et al. 1993). On MRI, the tumours tend to be hypointense or isointense on T1-weighted images and hyperintense on T2-weighted images, with strong, homogeneous contrast enhancement (Louis et al. 2016). The margins with sur-rounding structures are usually well defined and are best analysed by MRI.

2.3.33 Pineal Parenchymal Tumour of Intermediate Differentiation

A tumour of the pineal gland that is intermediate in malignancy between pineocytoma and pineoblastoma and is com-posed of diffuse sheets or large lobules of monomorphic round cells that appear more differentiated than those observed in pineoblastomas. Pleomorphic cytology may be present. Pineal parenchymal tumours of intermediate differentiation (PPTIDs) occur mainly in adults (mean patient age: 41 years), and show variable biological and clinical behaviour, from low-grade tumours with frequent local and delayed recurrences to high-grade tumours with risk of craniospinal dissemination. Accordingly, mitotic activity, Ki-67 proliferation index, and neuronal and neuroendocrine differentiation are also variable, and reported 5-year overall survival rates range from 39 percent to 74 percent (Louis et al. 2016, Jouvet et al. 2000). The biological behaviour of pineal parenchymal tumour of intermediate differentiation is variable and may correspond to WHO grades II or III, but definite histological grading criteria remain to be defined.

PPTIDs are localized in the pineal region.

On imaging, PPTIDs usually present as bulky masses with local invasion. They are more rarely circumscribed. On CT, the tumours may show occasional peripheral so-

called exploded calcifications (Komakula et al. 2011). On MRI, PPTIDs are heterogeneous and mostly hypointense on T1-weighted images and hyperintense on T2-weighted images. On both CT and MRI, postcontrast enhancement is usually marked and heterogeneous (Ito et al. 2014, Komakula et al. 2011).

2.3.34 Pineoblastoma

A poorly differentiated, highly cellular, malignant embryonal neoplasm arising in the pineal gland. Pineoblastoma usually occurs within the first two decades of life (mean patient age: 17.8 years), with a predilection for children. It is histologically characterized by the presence of patternless sheets of small immature neuroepithelial cells with a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei, and scant cytoplasm. Proliferation activity is high, with frequent mitoses and a Ki-67 proliferation index of > 20 percent. SMARCB1 nuclear ex-pression is retained, enabling distinction from atypical teratoid/rhabdoid tumour. Isochromosome 17q or amplification of 19q13.42 are usually not seen. Pineoblastomas tend to spread via cerebro-spinal fluid pathways and often follow aggressive clinical courses.

Pineoblastoma corresponds histologically to WHO grade IV.

Pineoblastomas are localized in the pineal region.

On neuroimaging, pineoblastomas present as large, multilobulated masses in the pineal region and show frequent invasion of surrounding structures, including the tectum, thalamus, and splenium of the corpus callosum (Louis et al. 2016). Small cystic/necrotic areas and oedema may be observed (Louis et al. 2016). On CT, pineoblastomas are usually slightly hyperdense, with postcontrast enhancement (Louis et al. 2016). Calcifications are infrequent (Louis et al. 2016). Nearly all patients show obstructive hydrocephalus (Louis et al. 2016). On 11-weighted VRI, the tumours are often hypointense to isointense, with heterogeneous contrast enhancement. They are isointense to mildly hyperintense on T2-weighted images (Louis et al. 2016).

2.3.35 Papillary Tumour of The Pineal Region

A neuroepithelial tumour localized in the pineal region and characterized by a combination of papillary and solid areas, with epithelial-like cells and immunoreactivity for cytokeratins (especially CK18). Papillary tumour of the pineal region affects children and adults (mean patient age: 35 years) and presents as a large, well-circumscribed mass, often with T1-hyperintensity. The tumours are associated with frequent recurrence (occurring in 58 percent of cases by 5 years), but spinal dissemination is rare. Overall survival is 73 percent at 5 years and 71.6 percent at 10 years. The biological behaviour of papillary tumour of the pineal region is variable and may correspond to WHO grades II or III, but definite histological grading criteria remain to be defined.

By definition, papillary tumours of the pineal region arise in the pineal region.

On neuroimaging, papillary tumours of the pineal region present as well-circumscribed heterogeneous masses composed of cystic and solid portions and centred by the posterior commissure or the pineal region. Aqueductal obstruction with hydrocephalus is a frequent associated finding (Louis et al. 2016, Sato et al. 2009). The tumours may demonstrate intrinsic T1-hyperintensity (Louis et al. 2016, Sato et al. 2009). In the absence of calcification, haemorrhage, melanin, or fat on imaging, this T1-hyperintensity may be related to secretory material with high-protein and glycoprotein content (Louis et al. 2016). However, others have found this feature to be absent (Louis et al. 2016). Postcontrast enhancement is usually heterogeneous.

2.3.36 Medullablastoma (all subtypes)

The diagnosis of medulloblastoma, NOS, is appropriate when an embryonal neural tumour is located in the fourth ventricle or cerebellum and the nature of biopsied tissue prevents classification of the tumour into one of the genetically or histologically defined categories of medulloblastoma. This situation usually arises when there is uncertainty about a tumour's architectural and cytological features as a result of insufficient tissue sampling or the presence of tissue artefacts. For the diagnosis of medulloblastoma, NOS, it is important to exclude histopathologically similar entities, such as high-grade small

cell gliomas, embryonal tumour with multi-layered rosettes, and atypical teratoid/rhabdoid tumours.

Medulloblastoma is the most common CNS embryonal tumour of childhood. Of all paediatric brain tumours, medulloblastoma is second in frequency only to pilocytic astrocytoma, and accounts for 25 percent of all intracranial neoplasms. The annual overall incidence of medulloblastoma is 1.8 cases per 1 million population, whereas the annual childhood incidence is 6 cases per 1 million children; these incidence rates have not changed over time (Partap et al. 2009). As is the case with other high-grade brain tumours, the incidence of medulloblastoma differs across ethnicities. In the USA, overall annual incidence is highest among White non-Hispanics (2.2 cases per 1 million population), followed by Hispanics (2.1 per 1 million) and African Americans (1.5 per 1 million) [http://www.cbtrus.org/2011-NPCRSEER/WEB-0407-Report-3-3-2011 .pdf]. As many as a quarter of all medulloblastomas occur in adults, but < 1 percent of adult intracranial tumours are medulloblastomas (Louis et al. 2016).

2.3.36.1 Age and sex distribution

The median patient age at diagnosis of medulloblastoma is 9 years, with peaks in incidence at 3 and 7 years of age (Louis et al. 2016). Of all patients with medulloblastoma, 77 percent are aged < 19 years (Farwel et al. 1984). The tumour has an overall male-to-female ratio of 1.7:1. Among patients aged > 3 years, the male-to-female ratio is but the incidence rates among boys and girls aged 3 years are equal (Louis et al. 2016). The various molecular groups and histopathological variants of medulloblastoma have different age distributions (Louis et al. 2016).

2.3.36.2 Localization

Medulloblastomas grow into the fourth ventricle or are located in the cerebellar parenchyma (Louis et al. 2016). Some cerebellar tumours can be laterally located in a hemisphere.

2.3.36.3 Clinical features

Medulloblastomas growing in the fourth ventricle cause increased intracranial pressure by exerting mass effect and blocking cerebrospinal fluid pathways. Therefore, most patients present with a short history of raised intracranial pressure: headaches that have increased in frequency and severity, frequent nausea upon waking, and bouts of vomiting. Cerebellar ataxia is common. Symptoms and signs relating to compression of cranial nerves or long tracts passing through the brain stem are uncommon.

2.3.36.4 Spread

Like other embryonal tumours, medulloblastoma has a propensity to spread through cerebrospinal fluid pathways to seed the neuraxis with metastatic tumour deposits. Rarely, it spreads to organ systems outside the CNS, particularly to bones and the lymphatic system. Reports of metastasis to the peritoneum implicate ventriculoperitoneal shunts.

2.3.36.5 Macroscopy

Most medulloblastomas arise in the region of the cerebellar vermis, as pink or grey often friable masses that fill the fourth ventricle. Medulloblastomas located in the cerebellar hemispheres tend to be firm and more circumscribed, and generally correspond to the desmoplastic/nodular variant with SHH pathway activation. Small foci of necrosis can be grossly evident, but extensive necrosis is rare. In disseminated medulloblastoma, discrete tumour nodules are often found in the craniospinal leptomeninges or cerebrospinal fluid pathways.

2.3.36.6 Microscopy

Several morphological variants of medulloblastoma are recognized, alongside the classic tumour: desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, and large cell / anaplastic medulloblastoma. Their specific microscopic architectural and cytological features are described in the corresponding sections of this volume. A dominant population of undifferentiated cells with a high nuclear-to-cytoplasmic ratio and mitotic figures is a common feature, justifying the designation "embryonal", but it is important to consider other entities in the differential diagnosis.

High-grade small cell gliomas and some ependymomas have an embryonal-like cytology, and elements of the embryonal tumour with multi-layered rosettes or atypical teratoid/ rhabdoid tumour can be identical to medulloblastoma. Any of these entities can be confused with medulloblastoma, especially in small biopsies, so determining a tumour's immunophenotype or genetic profile is an important part of working through the differential diagnosis.

Two distinctive morphological variants of medulloblastoma are described in this section, because they may occur in the setting of a classic or large cell / anaplastic tumour and are no longer considered distinct histopathological variants. These are the rare (accounting for < 1 percent of cases) medulloblastoma with myogenic differentiation (previously called medullomyoblastoma) and medulloblastoma with melanotic differentiation (previously called melanocytic medulloblastoma). Although these tumours are very rare, it is not uncommon for their phenotypes to occur together.

In addition to a conventional embryonal element, medulloblastoma with myogenic differentiation contains a variable number and distribution of spindle-shaped rhabdomyoblastic cells and sometimes large cells with abundant eosinophilic cytoplasm (Louis et al. 2016, Sacdeva et al. 2008). Occasionally, elongated differentiated strap cells, with the cross-striations of skeletal muscle, are evident.
Medulloblastoma with melanotic differentiation contains a small number of melanin-producing cells, which sometimes form clumps (Louis et al. 2016). These may appear entirely undifferentiated (like other embryonal cells) or have an epithelioid phenotype. Epithelioid melanin-producing cells may form tubules, papillae, or cell clusters.

2.3.37 Embryonal Tumour with Multilayer Rosettes, C19MC-altered

An aggressive CNS embryonal tumour with multi-layered rosettes and alterations (including amplification and fusions) in the C19MC locus at 19q13.42.

C19MC-altered embryonal tumours with multi-layered rosettes (ETMRs) can develop in the cerebrum, brain stem, or cerebellum and span a broad histological spectrum. As well as multi-layered rosettes, many tumours also contain both primitive embryonal regions

and differentiated areas with broad swaths of neoplastic neuropil. Most paediatric CNS embryonal tumours previously classified as embryonal tumour with abundant neuropil and true rosettes, ependymoblastoma, and medulloepithelioma are included in this group (Korshunov et al. 2014). However, any CNS embryonal tumour with C19MC amplification or fusion qualifies for this designation, including those without distinctive histopathological features. Like other CNS embryonal tumours, C19MC-altered ETMR corresponds histologically to WHO grade IV.

ETMRs develop in both the supratentorial and infratentorial compartments. The most common site is the cerebral hemisphere (affected in 70 percent of cases), with frequent involvement of the frontal and parietotemporal regions (Korshunov et al. 2014). Occasionally, these tumours can be very large, involving multiple lobes and even both cerebral hemispheres. An infratentorial location is less frequent, with either cerebellum or brain stem affected in 30 percent of cases. Tumour protrusion into the cerebellopontine cistern may be observed. Some extracranial tumours (e.g. intraocular medulloepithelioma and sacrococcygeal ependymoblastoma) share some histopathological features with intracranial ETMR but disclose striking molecular diversity and consequently deserve a separate nosological designation (Jakobiec et al. 2015, Korshunov et al. 2015).

CT and MRI usually show contrast enhancing large tumour masses, abundant neuropil and true rosettes. Biphasic histological pattern: areas of small embryonal cells with multi-layered rosettes and neuropil-like areas with neoplastic neurocytic cells.

2.3.38 Atypical Teratoid/Rhabdoid Tumour

A malignant CNS embryonal tumour composed predominantly of poorly differentiated elements and frequently including rhabdoid cells, with inactivation of SMARCBI (INII) or (extremely rarely) SMARCA4 (BRGI). Atypical teratoid/rhabdoid tumours (AT/RTs) occur most frequently in young children. Neoplastic cells demonstrate histological and immunohistochemical evidence of polyphenotypic differentiation along neuroectodermal, epithelial, and mesenchymal lines. Diagnosis of AT/RT requires demonstration of inactivation of SMARCBI or, if intact, SMARCA4 genes, either by routine immunohistochemical staining for their proteins or by other appropriate means.

Tumours with this morphology but lacking this molecular genetic confirmation should be classified as CNS embryonal tumours with rhabdoid features. AT/RT corresponds histologically to WHO grade IV.

In two large series of paediatric cases, the ratio of supratentorial to infratentorial tumours was 4:3 (Louis et al. 2016). Supratentorial tumours are often located in the cerebral hemispheres and less frequently in the ventricular system, suprasellar region, or pineal gland. Infratentorial tumours can be located in the cerebellar hemispheres, cerebellopontine angle, and brain stem, and are relatively prevalent in the first 2 years of life. Infrequently, AT/RT arises in the spinal cord. Seeding of AT/RT via the cerebrospinal fluid pathways is common and is found in as many as one quarter of all patients at presentation (Louis et al. 2016). Infratentorial localization is very rare in adult patients diagnosed with AT/RT (Louis et al. 2016).

CT and MRI findings are similar to those in patients with other embryonal tumours. AT/RTs are isodense to hyperintense on FLAIR images and show restricted diffusion. Cystic and/or necrotic regions are apparent as zones of heterogeneous signal intensity. Almost all tumours are variably contrast-enhancing, and leptomeningeal dissemination can be seen in as many as a quarter of cases at presentation (Louis et al. 2016).

2.3.39 Schwannoma

A benign, typically encapsulated nerve sheath tumour composed entirely of well-differentiated Schwann cells with loss of merlin (the NF2 gene product) expression in conventional forms. Schwannomas are solitary and sporadic in the vast majority of cases, can affect patients of any age, and follow a benign clinical course. Multiple schwannomas are associated with neurofibromatosis type 2 (NF2) and schwannomatosis. Conventional, non-melanotic schwannomas and their variants correspond histologically to WHO grade I.

The vast majority of schwannomas occur outside the CNS. Peripheral nerves in the skin and subcutaneous tissue are most often affected. Intracranial schwannomas show a strong predilection for the eighth cranial nerve in the cerebellopontine angle, particularly in NF2

(Louis et al. 2016). They arise at the transition zone between central and peripheral myelination and affect the vestibular division. The adjacent cochlear division is almost never the site of origin. This characteristic location, which is not shared by neurofibromas or malignant peripheral nerve sheath tumours, results in diagnostically helpful enlargement of the internal auditory meatus on neuroimaging. Intralabyrinthine schwannomas are uncommon (Louis et al. 2016). Intraspinal schwannomas show a strong predilection for sensory nerve roots; motor and autonomic nerves are affected far less often. Occasional CNS schwannomas are not associated with a recognizable nerve; these include approximately 70 reported cases of spinal intramedullary schwannomas and 40 cases of cerebral parenchymal or intraventricular schwannomas Dural examples are rare (Louis et al. 2016). Peripheral nerve schwannomas, unlike neurofibromas, tend to be attached to nerve trunks, most often involving the head and neck region or flexor surfaces of the extremities. Visceral schwannomas are rare, as are osseous examples (Louis et al. 2016).

MRI shows a well-circumscribed, sometimes cystic and often heterogeneously enhancing mass (Louis et al. 2016). Vestibular schwannomas often display a classic ice-cream-cone sign, with the tapered intraosseous cone exiting the internal auditory canal and expanding out to a rounded cerebellopontine angle mass. Masses in paraspinal and head and neck sites may be associated with bone erosion, which is sometimes evident on plain X-ray. Paraspinal examples may also show a dumbbell shape, with a point of constriction at the neural exit foramen.

2.3.40 Neurofibroma

A benign, well-demarcated, intraneural or diffusely infiltrative extraneural nerve sheath tumour consisting of neoplastic, well-differentiated Schwann cells intermixed with non-neoplastic elements including perineurial-like cells, fibroblasts, mast cells, a variably myxoid to collagenous matrix, and residual axons or ganglion cells.

Multiple and plexiform neurofibromas are typically associated with neurofibromatosis type 1 (NFI), whereas sporadic neurofibromas are common, mostly cutaneous tumours

that can affect patients of any age and any area of the body. Neurofibroma corresponds histologically to WHO grade l.

Neurofibroma presents most commonly as a cutaneous nodule (localized cutaneous neurofibroma), less often as a circumscribed mass in a peripheral nerve (localized intraneural neurofibroma), or as a plexiform mass within a major nerve trunk or plexus. Least frequent is diffuse but localized involvement of skin and subcutaneous tissue (diffuse cutaneous neurofibroma) or extensive to massive involvement of soft tissue of a body area (localized gigantism and elephantiasis neuromatosa). Neurofibromas rarely involve spinal roots sporadically, but commonly do so in patients with NFI, in which multiple bilateral tumours are often associated with scoliosis and risks of malignant transformation; in contrast, they almost never involve cranial nerves.

Rarely painful, neurofibroma presents as a mass. Deeper tumours, including paraspinal forms, present with motor and sensory deficits attributable to the nerve of origin. The presence of multiple neurofibromas is the hallmark of NFI, in association with many other characteristic manifestations.

Cutaneous neurofibromas are nodular to polypoid and circumscribed, or are diffuse, and involve skin and subcutaneous tissue. Neurofibromas confined to nerves are fusiform and (in all but their proximal and distal margins) well circumscribed. Plexiform neurofibromas consist either of multinodular tangles (resembling a bag of worms), when involving multiple trunks of a neural plexus, or of rope-like lesions, when multiple fascicles of a large, non-branching nerve such as the sciatic nerve are affected. On cut surface, they are firm, glistening, and greyish tan.

Neurofibromas are composed in large part of neoplastic Schwann cells with thin, curved to elongated nuclei and scant cytoplasm, as well as fibroblasts in a matrix of collagen fibres and Alcian blue-positive myxoid material. These cells have considerably smaller nuclei than those of schwannomas. The cell processes are thin and often not visible on routine light microscopy. Residual axons are often present within neurofibromas and can be highlighted with neurofilament immunohistochemistry or Bodian silver

impregnations. Large diffuse neurofibromas often contain highly characteristic tactile-like structures (specifically pseudo-Meissner corpuscles) and may also contain melanotic cells. Stromal collagen formation varies greatly in abundance and sometimes takes the form of dense, refractile bundles with a so-called shredded-carrot appearance. Intraneural neurofibromas often remain confined to the nerve, encompassed by its thickened epineurium. In contrast, tumours arising in small cutaneous nerves commonly spread diffusely into surrounding dermis and soft tissues. Unlike in schwannomas, blood vessels in neurofibromas generally lack hyalinization, and although neurofibromas sometimes resemble the Antoni B regions of a schwannoma, they generally lack Antoni A-like regions and Verocay bodies.

2.3.41 Perineurioma

A tumour composed entirely of neoplastic perineurial cells. Intraneural perineuriomas are benign and consist of proliferating perineurial cells within the endoneurium, forming characteristic pseudo-onion bulbs. Soft tissue perineuriomas are typically not associated with nerve, are variably whorled, and are usually benign. Malignant soft tissue perineurioma is a rare variant of malignant peripheral nerve sheath tumour displaying perineurial differentiation. Intraneural perineuriomas long mistakenly considered a form of hypertrophic neuropathy, is now recognized as a neoplasm. Intraneural perineuriomas correspond histologically to WHO grade l. Soft tissue perineuriomas range from benign (corresponding histologically to WHO grade l) to variably malignant (corresponding histologically to WHO grades II-III).

Intraneural perineuriomas primarily affect peripheral nerves of the extremities; cranial nerve lesions are rare (Louis et al. 2016), One example was reportedly associated with Beckwith-Wiedemann syndrome (Louis et al. 2016). Soft tissue perineuriomas are located in the deep soft tissue and are grossly unassociated with nerve. Visceral involvement is rare (Louis et al. 2016). One example involving the CNS arose within a lateral ventricle (Louis et al. 2016).

2.3.42 Meningioma

A group of mostly benign, slow-growing neoplasms that most likely derive from the meningothelial cells of the arachnoid layer. There are three major groups of meningiomas, which differ in grade and biological behaviour (Table 2.2).

Most meningiomas correspond histologically to WHO grade I (benign). Certain histological subtypes or meningiomas, with specific combinations of morphological parameters, are associated with less favourable clinical outcomes and correspond histologically to WHO grades II and III (Table II).

Table 2.2: Meningioma variables grouped by WHO grade and biological behaviour.

Tumour	WHO Grade	ICD-O Code
Meningothelial meningioma*	WHO Grade I	9531/0
Fibrous (fibroblastic) meningioma*	WHO Grade I	9532/0
Transitional (mixed) meningioma*	WHO Grade I	9537/0
Psammomatous meningioma*	WHO Grade I	9533/0
Angiomatous meningioma*	WHO Grade I	9534/0
Microcystic meningioma*	WHO Grade I	9530/0
Secretory meningioma*	WHO Grade I	9530/0
Lymphoplasmacyte-rich meningioma*	WHO Grade I	9530/0
Metaplastic meningioma*	WHO Grade I	9530/0
Chordoid meningioma**	WHO Grade II	9538/1
Clear cell meningioma**	WHO Grade II	9538/1
Atypical meningioma**	WHO Grade II	9539/1
Papillary meningioma**	WHO Grade III	9538/3
Rhabdoid meningioma**	WHO Grade III	9538/3
Anaplastic meningioma**	WHO Grade III	9530/3

* Meningiomas with low risk of recurrence and aggressive behaviour:

** Meningiomas with greater likelihood of recurrence and aggressive behaviour.

The vast majority of meningiomas arise in intracranial, intraspinal, or orbital locations. Intraventricular and epidural examples are uncommon. Rare examples have been reported outside the neural axis (e.g. in the lung). Within the cranial cavity, common sites include the cerebral convexities (with tumours often located parasagittally, in association with the falx and venous sinus), olfactory grooves, sphenoid ridges, para-/suprasellar regions, optic nerve sheath, petrous ridges, tentorium, and posterior fossa. Most spinal meningiomas occur in the thoracic region. Atypical and anaplastic meningiomas most commonly affect the convexities and other non-skull base sites (Louis et al. 2016). Metastases of malignant meningiomas most often involve lung, pleura, bone, or liver.

Meningiomas are generally slow-growing and produce neurological signs and symptoms due to compression of adjacent structures; the specific deficits depend on tumour location. Headache and seizures are common (but non-specific) presentations.

On MRI, meningiomas typically present as isodense, uniformly contrast-enhancing dural masses. Calcification is common and is best seen on CT A characteristic feature is the so-called dural tail surrounding the dural perimeter of the mass. This familiar imaging sign corresponds to reactive fibrovascular tissue and does not necessarily predict foci of dural involvement by tumour. Peritumoural cerebral oedema is occasionally prominent, in particular with certain histological variants and high-grade examples (Louis et al. 2016). Cyst formation may occur within or at the periphery of a meningioma. Neuroimaging features are not entirely specific for identifying meningiomas, predicting tumour behaviour, or excluding other diagnoses.

Even benign meningiomas commonly invade adjacent anatomical structures (especially dura), although the rate and extent of local spread are often greater in the more aggressive subtypes. Thus, depending on location and grade, some meningiomas produce considerable patient morbidity and mortality. Extracranial metastases are extremely rare, occurring in about 1 in 1000 meningiomas and most often in association with WHO grade III tumours. The rare metastases of histologically benign meningiomas typically occur after surgery but can arise de novo as well.

2.3.43 Mesenchymal, Non-Meningothelial Tumours

Benign and malignant mesenchymal tumours originating in the CNS, with terminology and histological features corresponding to their soft tissue and bone counterparts.

Mesenchymal tumours arise more commonly in the meninges than in the CNS parenchyma or choroid plexus. In principle, any mesenchymal tumour may arise within or secondarily impact on the nervous system, but the primary mesenchymal CNS tumours are very rare. They can occur in patients of any age and arise more commonly in

supratentorial than in infratentorial or spinal locations. The clinical symptoms and neuroradiological appearance of most tumours are non-specific.
The histological features of mesenchymal tumours affecting the CNS are similar to those of the corresponding extracranial soft tissue and bone tumours (Louis et al. 2016). Solitary fibrous tumour / haemangiopericytoma (by far the most common mesenchymal, non-meningothelial neoplasm) and peripheral nerve sheath tumours (the most common neoplasms of cranial and paraspinal nerves) are described separately. Antiquated nosological terms, such as "spindle cell sarcoma", "pleomorphic sarcoma," and "myxosarcoma" have been replaced by designations indicating more specific differentiation or updated terminology (Louis et al. 2016). The nonspecific diagnostic term "meningeal sarcoma" is also to be avoided, because it has been used in the past to denote both sarcomatoid anaplastic meningiomas and various types of sarcomas.

Mesenchymal, non-meningothelial tumours range from benign neoplasms (corresponding histologically to WHO grade l) to highly malignant sarcomas (corresponding histologically to WHO grade IV).

Tumours arising in meninges are more common than those originating within CNS parenchyma or in choroid plexus. Most mesenchymal tumours are supratentorial, but rhabdomyosarcomas are more often infratentorial. Chondrosarcormas involving the CNS arise most often in the skull base. Among benign mesenchymal lesions, intracranial lipomas have a characteristic location and typically occur at midline sites, such as the anterior corpus callosum, quadrigeminal plate, suprasellar and hypothalamic regions, and auditory canal. Spinal cord examples involve the conus medullaris-filum terminale and also occur at the thoracic level. Intraventricular and tuber cinereum lipomas are rare (Louis et al. 2016). Occasional CNS lipomas have a fibrous connection with surrounding soft or subcutaneous tissue. Osteolipomas have predilection for the suprasellar/interpeduncular regions (Louis et al. 2016). Most spinal lipomas (in particular angiolipomas) arise in the epidural space.

Primary meningeal sarcomatosis is a diffuse leptomeningeal sarcoma lacking circumscribed masses (Louis et al. 2016). Although this entity is strictly defined as a

nonmeningothelial mesenchymal tumour, most published cases have not been diagnosed according to modern nomenclature. Re-examination of published cases using immunohistochemistry has revealed that most cases actually constitute carcinoma, lymphoma, glioma, or embryonal tumour.

2.3.44 Diffuse Large B-cell Lymphoma of the CNS

A diffuse large B-cell lymphoma (DLBCL) confined to the CNS at presentation.
Excluded from this entity are lymphomas arising in the dura, intravascular large B-cell lymphoma, and lymphomas of T-cell or NK-cell lineage (which may also present in the CNS), as well as lymphomas with systemic involvement or with secondary involvement of the CNS. Immunodeficiency-associated primary CNS lymphomas are not covered in this title.

About 60 percent of all PCNSLs involve the supratentorial space, including the frontal lobe (in 15 percent of cases), temporal lobe (in 8 percent), parietal lobe (in 7 percent), and occipital lobe (in 3 percent), basal ganglia and periventricular brain parenchyma (in 10 percent), and corpus callosum (in 5 percent). The posterior fossa and spinal cord are less frequently affected (in 13 percent and 1 percent of cases, respectively) (Louis et al. 2016). A single tumour is encountered in 60-70 percent of patients, with the remainder presenting with multiple tumours (Louis et al. 2016). The leptomeninges may be involved, but exclusive meningeal manifestation is unusual. Ocular manifestation (i.e. in the vitreous, retina, or optic nerve) occurs in 20 percent of patients and may antedate intracranial disease (Jahnke et al. 2006). Extraneural dissemination is very rare. In cases with systemic spread, PCNSL has a propensity to home to the testis, another immunoprivileged organ (Louis et al. 2016, Jahnke et al. 2006).

Patients present with cognitive dysfunction, psychomotor slowing, and focal neurological symptoms more frequently than with headache, seizures, and cranial nerve palsies. Blurred vision and eye floaters are symptoms of ocular involvement (Louis et al. 2016).

MRI is the most sensitive technique to detect PCNSL, which is hypointense on T1-weighted images, isointense to hyperintense on T2-weighted images, and densely

enhancing on postcontrast images. Peritumoural oedema is relatively limited and is less severe than in malignant gliomas and metastases (Louis et al. 2016). Meningeal involvement may present as hyperintense enhancement (Louis et al. 2016). With steroid therapy, lesions may vanish within hours (Louis et al. 2016).

2.3.45 Langerhans Cell Histiocytosis

A clonal proliferation of Langerhans-type cells that express CD1a, langerin (CD207), and S100 protein. Langerhans cell histiocytosis most frequently affects children. The CNS can be affected via direct invasion from craniofacial bone and skull base or from meninges, via extra-axial masses of the hypothalamic-pituitary region, or in a leukoencephalopathy-like pattern, and primary intraparenchymal CNS masses may also occur. This entity was previously referred to as eosinophilic granuloma and/or histiocytosis X.

Imaging studies of Langerhans cell histiocytosis have shown that the most common presentation of CNS involvement is as lesions of the craniofacial bone and skull base (seen in 56 percent of cases), with or without soft-tissue extension. Intracranial, extra-axial masses are also common, particularly in the hypothalamic—pituitary region (seen in 50 percent of all cases), meninges (in 29 percent), and choroid plexus (in 6 percent). A leukoencephalopathy-like pattern, with or without dentate nucleus or basal ganglia neurodegeneration, is seen in 36 percent of all Langerhans cell histiocytosis cases, and cerebral atrophy occurs in 8 percent (Louis et al. 2016). Rare intraparenchymal CNS masses have also been described.

The most common neurological sign of Langerhans cell histiocytosis is diabetes insipidus (occurring in 25 percent of cases overall and 50 percent of cases of multisystemic disease), with about 60 percent of patients also showing signs of hypothalamic dysfunction (e.g. obesity, hypopituitarism, and growth retardation). The clinical features of Langerhans cell histiocytosis-associated neurodegenerative lesions range from asymptomatic imaging abnormalities to tremors, gait disturbances, dysarthria, dysphagia, motor spasticity, ataxia, behavioural disturbances, learning difficulties, global cognitive deficits, and/or psychiatric disease (Louis et al. 2016).

Histiocytic lesions of the skull present as patchy T2-hyperintense lesions, eventually resulting in a punched-out or geographical appearance of the bone (Zaveri et al. 2014).

Within the CNS parenchyma, Langerhans cell histiocytosis presents as hyperintense lesions with non-specific enhancement on T2-weighted images. Involvement of the pituitary region may be associated with loss of the posterior pituitary bright spot in TI-weighted images and thickening of the pituitary stalk in contrast-enhanced images (Zaveri et al. 2014).

3. BRAIN TUMOUR TREATMENT

3.1 THE CLINICAL CHALLENGE OF PATIENT-SPECIFIC PROGNOSIS AND TREATMENT RESPONSE

Most midbrain tumours, especially glioma, have a wide variety of phenotypes, even if they are of the same histological degree. These tumours are characterized by rapid cell proliferation and invasion of neighbouring healthy brain tissues, which presents a clinically challenging case and results in high morbidity and mortality. Despite advances in medical imaging techniques, advances in surgery, radiation therapy, and chemotherapy, standard treatment options for brain tumours, especially gliomas, do not differ significantly on a patient basis. Despite cancer studies that have been going on for the last 50 years, prognosis has not changed significantly, especially in glioma patients. We believe that the inclusion of patient-specific data in the process enables personalized oncologic treatment and that a more effective oncological treatment planning can be done by predicting what prognosis can be expected on which treatment parameters are preferred.

Regardless of the degree of glioma, the most prominent feature is that the brain cells in which they spread are healthy in gross pathology and histological samples. Non-invasive imaging methods such as magnetic resonance imaging (MRI) and Computed Tomography (CT) are used for primary assessment and staging of gliomas to reduce morbidity caused by extensive biopsies. However, these non-invasive techniques often do not provide detailed results covering the whole tumour spread.

As in treatment planning, post-treatment follow-up for recurrence and progression is performed using the same imaging techniques. The ability to identify the entire cell population of gliomas and their ability to infiltrate normal-appearing brain tissue makes personalized treatment approaches difficult but essential for patients.

In this section, we will discuss treatment modalities and complications related to brain tumours.

3.2 SURGERY AND COMPICATIONS OF SURGERY

The first step of the surgery is the perioperative stage which have a critical role on the surgical outcome. Evaluating a patient with brain tumour have three important steps: obtaining a comprehensive history of the patient, a careful examination of the patient, and assessment of the tumour using relevant imaging methods. After considering all patient information, medical team needs to decide on the best suitable surgical method for the patient.

3.2.1 Stereotactic Brain Lesion Biopsy

Despite advances in imaging methods, tissue biopsy is of great importance in the treatment of brain tumours. Stereotactic biopsies usually are suitable for the lesions that are small, deep, or where craniotomy is risky.

Although it is easier for brain surgeons than a craniotomy, a comprehensive anatomy knowledge is needed in stereotactic biopsy to maximize patient comfort during surgery and to minimize postoperative complications. After the operation, the patient should be closely monitored, and any complications should be detected at the earliest possible stage, and the highest surgical success should be targeted, which requires comprehensive information on possible complications.

In a stereotactic biopsy, bleeding in the biopsy area is one of the most feared complications that adversely affect the general condition of the patient and cause neurological symptoms. These haemorrhages are the primary source of neurological morbidity and mortality.

Clinically silent haemorrhage often observed in the stereotactic biopsy.

In order to prevent haemorrhage or prevent haemorrhage caused complications, all necessary steps should be taken at the preoperative planning.

3.2.2 Image Guided Craniotomy

Recently, operational imaging devices, which have become almost a standard component of neurosurgery operating rooms, generally provide images of the two or three-dimensional pathological anatomy of the brain and aim to provide a more precise, efficient and technically complete operation during the surgery. Although surgical navigation systems are a significant support for the surgeon, it is not necessary to use it for all patients (trauma cases of foreshadowing).

It is essential to choose the most suitable imaging methods to achieve the highest level of efficiency. The choice of imaging method depends on the type, stage and anatomical location of the tumour.

The risks of craniotomy are similar to those of other brain surgeries. Bleeding, infection, inflammation and accumulation of fluid in the head are the most common risks.

3.2.3 Endoscopic Approaches

In recent years, endoscopy is one of the most frequently used methods to reach the skull base and intra-ventricular tumours. Increasing the field of view provided by the microscope and providing light support for the visualization of the operating field and smaller areas and corners is the main reason why the use of the endoscope is increasingly preferred. The endoscopic approach requires a strong knowledge of anatomy and allows the targeting of many tumour types and access to the anatomical location with different approaches. The anatomic corridors used, approaches and targeted anatomic locations are given in Table 3.1.

Table 3.1: Endonasal Skull Base Approaches

Corridor	Approach	Target
Transsphenoidal	Transellar Transplanum, transtuberculum Transclival Transcavernous Transcanalicular	Pituitary gland Suprasellar cistern Upper one third of clivus Medial cavernous sinus Medial optic canal
Transnasal	Transcibriform Transclival Transodontoid	Olfactory groove Lower two thirds of clivus and petrous apex Craniovertebral junction
Transethmoidal	Transfovea ethmoidalis Transorbital Transsphenoidal	Anterior fossa Medial orbit Lateral cavernous sinus
Transmaxillary	Transpterygoidal	Pterygopalatine fossa Infratemporal fossa Lateral sphenoid sinus Lateral cavernous sinus Meckel's cave

The endoscopic approach may not be a very efficient method for solid tumours due to its limitations and some limitations. Because the anatomic corridors used are extremely small, the endoscopic approach is generally not preferred for calcified tumours larger than 2 cm.

Endoscopic skull base surgery requires extremely high anatomical knowledge and surgical skills and is a high-risk operation due to the relatively small working area and the necessity to work close to critical neurovascular systems. Although the most common risk is CSF leakage, there are other common risks associated with endoscopic approach including infection, bleeding, septal perforation, atrophic rhinitis, iatrogenic sinusitis, cranial nerve palsies, anosmia, pituitary dysfunction, diabetes insipidus, vision loss, stroke, and death (Bernstein and Berger 2014).

3.2.4 Complications of Surgery

Craniotomy has many risks. To keep these risks to a minimum, the surgical team must be highly knowledgeable and experienced. However, of course, not only the surgical team, but also all pre-operative and post-operative team members should take these risk factors into account and take the necessary measures to maximize patient health and comfort and be prepared for all scenarios. In this section, we will briefly explain the risk factors listed in Table 3.2, which may be encountered in all craniotomy operations, no matter how much precautions we take.

Although there is a disagreement regarding what constitutes a complication, that discussion is beyond the scope of our study so we will use a widely accepted list of complications associated with craniotomy.

Table 3.2: Complications Associated with Craniotomy

Neurologic	**Regional**	**Systemic**
Motor or sensory	Seizure	Deep vein thrombosis
Deficit	Hydrocephalus	Pulmonary embolus
Aphasia/dysphasia	Pneumocephalus	Pneumonia
Visual field deficit	Wound infection	Urinary infection
Caused by:	Meningitis	Sepsis
Direct brain injury	Brain abscess	Myocardial infarction
Brain edema	Cerebrospinal fistula	Gastrointestinal bleed
Vascular injury		Electrolyte disturbance
Hematoma		

Source: Wolters Kluwer Health. Sawaya R, Hammoud M, Schoppa D, et al.

Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 1998;42:1044– 1056.

3.3 NEUROLOGIC COMPLICATIONS

3.3.1 Brain Edema

Brain edema is the underlying cause of most neurological morbidity and mortality and may result in herniation and even death in its extreme form.

3.3.2 Injury of Neuro-vascular Structures

Although damage to the vascular structures is encountered at a lower rate for other neurological complications, if the necessary precautions are not taken in a timely manner, it may affect the course of the case very quickly. In some cases (eg major venous obstruction), the neurological complication may occur later and therefore the chance of timely action is greatly reduced. Damage of the arteries during the operation may cause neurological damage that the patient will have to live with throughout his life. In order to minimize the risk of these complications, the surgical team should understand the connection of the tumour to the surrounding tissue and vessel structure, determine the optimal operation strategy for the patient using all necessary imaging methods and determine the strategies to be followed in case of possible complications.

3.3.3 Hematomas

Postoperative hematoma cases usually present with an altered level of consciousness, focal neurologic deficits, and seizures. Pre-operative preparation processes have great importance in the prevention of post-operative hematomas, together with operation technique and post-operative care. For example, monitoring pre-operative drug use, prothrombin and partial thromboplastin times are some of the pre-operative measures that can be taken to minimize risk.

3.3.4 Regional Complications

Regional complications may be localized at the site of operation or occur at a different location in the brain, but usually, do not cause permanent neurological damage.

3.3.5 Seizures

Postoperatively, seizures that usually encountered when the patient is in the recovery room may progress to epilepsy if not timely intervention. Various factors, such as the known preoperative epilepsy and the proximity of the intervention site to the motor cortex, increase the risk of postoperative seizures.

Careful analysis of all patient information prior to the operation has a significant contribution to predicting seizure risk and taking necessary measures. In patients with a known history of epilepsy or tumours in or near the motor cortex, seizures are expected to be supported postoperatively with Keppra and Atrivan in the perioperative period.

In case of seizures after the operation, regardless of history, neurological imaging should be performed, and detailed examination should be performed in terms of oedema, haemorrhage or infarction that may cause seizures and all options that trigger seizures should be eliminated in order of risk.

3.4 INFECTIONS

Many degrees of infection can be seen after craniotomy. These infections may be caused by contamination of the operation site with skin pathogens during the operation, as well as stitch-induced superficial wound infection, which may evolve into a more severe infection if not treated.

Operative time, intensive corticosteroid use, the proximity of the operation site to the paranasal sinuses and CSF fistula are among the factors that increase the risk of infection (Narotam et al 1994).

3.5 SYSTEMIC COMPLICATIONS

There is a wide range of medical complications that can be seen after a craniotomy including but not limited to pulmonary embolism, infection (pneumonia, sepsis, urinary tract infection), MI, gastrointestinal haemorrhage, and DVT.

The most frequent systemic complication after a craniotomy is DVT, and the risk of DVT increases at cases with GBM or systemic cancer. The other risk factors for DVT are age, prolonged bed rest, lower extremity paresis, and operation duration.

Mobilizing the patient as soon as possible after the craniotomy is essential to minimize the risk of thromboembolic events.

It is essential to take other medical measures to take in patient-specific precautions in order to minimize the risk of systemic complications.

3.6 RADIATION

Radiation produces highly reactive free radicals in tissues. These free radicals damage nuclear DNA, resulting in reproductive cell death during cellular division or apoptotic cell death in response to the DNA injury (Hall 2000). The discovery of cell radio-responsiveness and ability to manage dose (amount of energy deposited per unit mass at a point in tissue, commonly referred as Gy) and direction of radiation, it became possible to use radiation for killing or damaging the tumour cells and the radiation, which is harmful to the human body became a powerful tool for cancer therapy.

An extensive assessment of the patient by a radiation oncologist is essential. Also, any past and coexisting diseases that may increase the risk factors of late radiation effects must be evaluated carefully. Patient age, functional/neurologic performance status (Karnofsky Performance Scale), and tumour histology are strong prognostic factors for outcome and require consideration when counselling patients about treatment options and the expected benefits of radiation (Velten 2009).

Radiosurgery designed for the destruction of brain circuits for functional disorders, but the first radiosurgery developed before imaging with computed tomography, making it difficult to use and utilize. The second generation, Gamma Knife, was introduced in 1975, allowing much more effective dose adjustment and targeting of neoplastic and vascular mass lesions, resulting in much faster progress in acceptance and utilization. In the third generation, the beam sources and diameter significantly improved, significant progress

was made in dose adjustment and targeting, and integrated with computed tomography (CT) and magnetic resonance imaging (MRI) devices. Modern examples of the third generation have also integrated robotic equipment, enabling a more extensive range of interventions and maximizing operational efficiency.

Radiosurgery generally used in small lesions, and products developed in previous technological stages had an intervention scope limited to 3 cm in diameter. The use of radiosurgery in large tumours is still limited, beyond technical limitations, as part of safe dose planning.

Radiosurgery completely changed neuro-oncology. It enabled precise and efficient management of brain tumours regardless of location, size, type and stage. Especially in multiple metastases, it has gained an essential place in anatomically risky locations or patients at high risk for interventional interventions. Technological advances in this area have expanded and will continue to expand the scope of radiosurgery to include spine and internal organs outside the brain.

Like all other oncologic treatments, radiotherapy and radiosurgery also has some expected side-effects, including but not limited to headache, nausea, and vomiting, and dose adjustments must be made if necessary. Some radiotherapy techniques like craniospinal irradiation for germinoma or medulloblastoma has a higher risk for fatigue, nausea, hearing dysfunction, cough, and diarrhoea due to the volume of radiation and the exit path (oropharynx, mediastinum, and abdomen) of the radiation. Most of the acute side-effects of the radiotherapy usually subside 4 to 6 weeks. At 12 to 16 weeks post radiation, transient demyelination secondary to damage to oligodendroglial cells may occasionally result in the return of fatigue sometimes accompanied by worsening clinical symptoms and imaging findings suggestive of early tumour progression (Bernstein and Berger 2014).

Necrosis can be confused with recurrence of the tumour, which, if not diagnosed correctly, may alter the course of treatment. Although PET and other metabolic imaging

methods can be used to differentiate necrosis from the recurrent tumour. But gold standard is still pathological confirmation of the tissue.

As a result, advancing technology allows the safe use of radiation in imaging and treatment. These methods, which are developed day by day in terms of patient comfort and treatment effectiveness, can be used in combination with craniotomy, thus providing a more effective and safe treatment option in cases that cannot be treated with radiotherapy alone.

3.7 SYSTEMIC THERAPY

Although a multimodality approach using surgical, radiotherapy and chemotherapy is the most common strategy in the treatment of malignant tumours, the conditions in which chemotherapy will be applied should be carefully selected. Chemotherapy may not have any effect on tumour cells, but it may create a toxic effect for the patient on radiographically stable patients. Its effect may not be adequately measured in cases undergoing maximal surgical resection, or it may not be possible to measure tumour response to chemotherapy in some tumour types with low proliferation rates such as low-grade gliomas.

Various cytotoxic chemotherapy agents are used to treat patients with brain tumours including alkylating and methlating agents, antimetabolites, topoisomerase inhibitors, and taxanes. Medical teams may use drugs as single agents or may use a combination of drugs depending on the case but there are only a few number of drug combinations thus far approved to be effective on the tumours of the CNS.

Table 3.3: Chemotherapy Agents Approved by the U.S. Food and Drug Administration for Central Nervous System Tumours

Drug	Class	Indication
Lomustine	Nitrosoureas	1970s: newly diagnosed GBM and recurrent glioma

Drug	Class	Indication
Polifeprosan 20 with carmustine implant	Nitrosoureas	1997: newly diagnosed GBM and recurrent glioma
Temozolomide	Methylating agent	1999: recurrent grade 3 astrocytoma 2005: newly diagnosed GBM
Bevacizumab	Monoclonal Ab to VEGF	2008: recurrent GBM
Everolimus	mTOR inhibator	2010: subependymal giant cell astrocytoma

Source: Neuro-oncology: The Essentials. ISBN: 978-1-60406-883-2 P: 222

3.7.1 Nitrosoureas

The nitrosoureas are bifunctional alkylating agents that were previously the most widely used drugs for patients with brain tumours. In recent years, a methylating agent temozolomide has become more frequently used as initial treatment (de- scribed later). The nitrosoureas alkylate DNA in multiple loca- tions, primarily on guanine but also on adenine and cytosine, as well as carbamylate amino groups through isocyanate products. The resultant DNA crosslinks produce single- or double-strand breaks, as well as depletion of glutathione, causing inhibition of DNA repair and RNA synthesis. The most commonly used nitrosoureas are lomustine (CCNU), an oral agent, and carmustine (bischloroethylnitrosourea [BCNU]), an intravenous agent (Bernstein and Berger 2014).

3.7.2 Temozolomide, Procarbazine, and Dacarbazine

Temozolomide, procarbazine, and dacarbazine [(dimethyltri- azeno)imidazole carboxamide (DTIC)] are methylating agents. They are also sometimes considered alkylating agents. They produce cytotoxicity by causing single-strand breaks in tumor cell DNA.

3.7.3 Platinum Compounds

Carboplatin and cisplatin produce DNA toxicity via chelation and the formation of intrastrand DNA crosslinks. These are water-soluble alkylating agents that are given via

intravenous or intra-arterial routes. Penetration into the brain is signifi- cantly limited by an intact blood–brain barrier; however, in the setting of a malignant glioma, the blood–brain barrier is at least partially disrupted, accounting for the modest objec- tive responses seen with this group of drugs. Cisplatin is usu- ally given in combination with other chemotherapy drugs, often with BCNU and other alkylating agents, particularly in childhood tumors (Bernstein and Berger 2014).

3.7.4 Vinca Alkaloids and Epipodophyllotoxins

The vinca alkaloids, vincristine and vinblastine, act on tubu- lin, the basic subunit of microtubules. They inhibit microtu- bule assembly by depolymerization, ultimately producing mitotic arrest (Bernstein and Berger 2014).

3.7.5 Taxanes

The taxanes affect microtubule assembly by stabilization of microtubule dynamics. Two taxanes are commercially avail- able: paclitaxel (Taxol, Bristol-Meyers Squibb, New York, NY) and docetaxel (Taxotere, Sanofi-Aventis, Bridgewater, NJ). They bind to the b-subunit on the microtubule and produce polym- erization. Inhibition of depolymerization ultimately causes a mitotic block and, most likely, apoptotic cell death. The tax- anes are given by intravenous injection, and various schedules have been evaluated. Myelosuppression, alopecia, neurotox- icity, cardiac arrhythmia, and hypersensitivity reactions are reported toxicities (Bernstein and Berger 2014).

3.7.6 Topoisomerase I Inhibitors

Topoisomerase is a critical enzyme in cellular growth regulation. Inhibition of this enzyme system can lead to DNA strand breaks. Etoposide inhibits topoisom- erase II; the camptothecins inhibit topoisomerase I. Campto- thecin, the first topoisomerase I inhibitor, was found to be highly toxic (Bernstein and Berger 2014).

Not only the effectiveness of chemotherapy varies from person to person, but there are also widespread side effects of chemotherapy as well. Most common side effects of chemotherapy are fatigue, feeling sick and vomiting, hair loss, infections, anaemia, bruising and bleeding, sore mouth, loss of appetite, changes in skin and nails,

concentration problems, memory problems, sleep problems, sexual function problems, fertility issues, diarrhoea, constipation, and emotional imbalances.

3.8 INTRA-TUMOURAL CHEMOTHERAPY

The amount of tissue that can be removed with surgery is limited since excessive tissue intake can trigger different neurological problems. Similarly, the use of radiation to target the tumour in doses that appropriate to the destruction of the tumour can also cause damage to healthy tissues adjacent to the tumour. As a result, in chemotherapy and radiotherapy, the doses required to achieve the desired results in central nervous system tumours can reach toxic levels. In addition to the fact that the required doses cannot be administered due to toxic effects, the restriction of access to drugs to the brain due to the blood-brain barrier is one of the factors that make treatment difficult.

In order to minimize the toxic effect, to maximize the yield and to minimize the damage to adjacent healthy tissues, alternative approaches to chemotherapy have been studied, and three clinical approaches have been accepted today. These approaches are direct injection, convection-enhanced delivery (CED), and implantation of a drug-loaded polymeric matrix within the tumour.

3.9 DIRECT INJECTION

The first method developed for direct administration of chemotherapy is the injection of the drug directly into the tissue or ventricle. Direct injection makes it possible to inject the drug to be injected within a few millimetres of space, thus introducing a necessity such as high dose drug injection to a single point, which may cause toxicity at the target point of the dose used.

Convection-enhanced delivery is a drug delivery method in which macromolecules are distributed into brain parenchyma using a positive pressure gradient. Whereas diffusion uses a concentration gradient to distribute molecules, the use of a pressure gradient facilitates the distribution of a homogeneous concentration of small and large molecules over large distances by bulk displacement of the extracellular fluid with the infusate. The

therapeutic agent is delivered into the parenchyma via a microcatheter inserted into the tissue with infusion rates of 0.5 to 10 μL/min (Bernstein and Berger 2014).

3.10 COMPLICATIONS OF MEDICAL THERAPY

As with all other tumours, the treatment of brain tumours is a very challenging process. The combination of different treatment modalities, especially in high grade tumours, increases the likelihood of many side effects. It is vital for neuro-oncology specialists to distinguish the effects of the tumour on the central nervous system and treatment-induced symptoms, especially in treatments which multiple modalities are combined.

Despite the numerous side effects of the tumour and the current treatment modalities, the level of post-treatment success is very low, especially in high-grade tumours. Therefore, early-stage diagnosis is of great importance for the success of treatment and post-treatment process. Secondary lesions, which can often be overlooked, are still a significant problem in today's clinical processes, especially in the presence of multiple lesions. Therefore, early and accurate diagnosis is as important as planning the right and effective treatment. Todays developing technology has made possible applications that cannot be imagined in the past and has led many types of research about diagnosis and treatment. In this part of our study, we will briefly talk about the side effects of different methods used in the treatment of tumours of the central nervous system, and proceed to the presentation of our non-invasive method for the detection of brain lesions and other lesions using cranial magnetic resonance images, which include the diagnosis, treatment planning and post-treatment follow-up processes.

One of the most critical difficulties in the use of drugs used in chemotherapy is the development of immunity to drugs and the difficulties in using the right dose of the drug. Table 3.4 shows the chemotherapeutic agents used against malignant brain tumours and their potential risks.

Table 3.4: Chemotherapeutic Agents Commonly Used for the Treatment of Malignant Brain Tumours and Their Potential Risks

Class	Agent	Side Effect
Alkylating Agents		
Imidazotetrazine derivative of dacarbazine	Temozolomide Cyclophosphamide	Fatigue and hypersomnolence, myelosuppression (particularly lymphopenia and thrombocytopenia), nausea, vomiting, constipation, acneiform rash Hemorrhagic cystitis, myelosuppression, nausea, vomiting, cardiac toxicity, secondary malignancies
Atypical alkylating agents— platinum agents	Cisplatin Carboplatin	Nausea, vomiting, peripheral neuropathy, ototoxicity, nephrotoxicity, dysgeusia, hypokalemia, hypomagnesemia, visual losses Nausea and vomiting Myelosuppression, peripheral neuropathy, hypokalemia, hypomagnesemia
Nitrosoureas	Carmustine (BCNU) Lomustine (CCNU)	Myelosuppression, nausea, vomiting, pulmonary toxicity, secondary acute leukemia Myelosuppression, nausea, vomiting, delayed renal and pulmonary toxicity
Antimetabolites		
Folic acid analogues	Methotrexate	Neutropenia, mucositis, renal toxicity, hepatotoxicity, pulmonary toxicity, pleural effusion

Class	Agent	Side Effect
Pyrimidine analogues	5-Fluorouracil Cytarabine	Myelosuppression, stomatitis/mucositis, diarrhea, rash, hand–foot syndrome, cardiac toxicity (e.g., acute arterial spasm) Leukopenia, thrombocytopenia, gastrointestinal toxicity, conjunctivitis, keratitis, neurologic toxicity
Purine analogues	Thioguanine	Myelosuppression, gastrointestinal toxicity, hepatotoxicity
Natural Products		
Vinca alkaloids	Vincristine	Neurologic toxicity, constipation, hyponatremia, rash
Podophyllotoxins	Etoposide (VP-16)	Myelosuppression, allergic reaction, dermatologic effects, hepatotoxicity
Antitumor antibiotics	Bleomycin Mitomycin C	Anaphylaxis, mucositis, nausea, vomiting, pulmonary fibrosis, hyperpigmentation Myelosuppression, mucositis, alopecia, aplastic anemia, hepatotoxicity, radiation recall effects
Taxanes	Paclitaxel	Hypersensitivity reaction, myelosuppression, neurotoxicity, cardiac toxicity, alopecia, radiation recall effects
Miscellaneous		
Methylhydrazines	Procarbazine	Myelosuppression, nausea, vomiting, neurologic toxicity, allergic reaction, azoospermia, infertility, monoamine oxidase drug reaction

Class	Agent	Side Effect
Novel Agents		
Protein kinase C modulators	Tamoxifen (high dose)	Hot flashes, nausea, vomiting, dizziness, thromboembolic disease, neurotoxicity, ocular toxicity
Antiangiogenic agents	Bevacizumab	Nosebleeds, hypertension, proteinuria, venous thromboembolic complications, weakness, pain, diarrhea, gastrointestinal bleeding, gastrointestinal perforation, impaired wound healing, striae, wound dehiscence (including prior craniotomy scars), intracranial bleeding (< 3 percent life threatening; rare and possibly not related), fatigue, skin toxicity (rare), reversible posterior leukoencephalopathy (< 2 percent)
Epidermal growth factor receptor tyrosine kinase inhibitors	Erlotinib	Rash on face, neck, chest, back, and arms; diarrhea; loss of appetite; inflammation of the cornea
Cell growth and migration inhibitor	Isotretinoin	Birth defects, mood disorder, muscle pain, visual changes, hyperlipidemia

Source: Neuro-oncology: The Essentials. ISBN: 978-1-60406-883-2 P.519

Brain tumours cause various neurological symptoms. However, chemotherapy itself may trigger some neurological symptoms. Often these neurological symptoms are difficult to distinguish from the symptoms caused by the tumour, and in some cases, tumour and chemotherapy may lead to stronger neurological symptoms. Table 3.5 lists neurological symptoms caused by chemotherapeutic agents.

Table 3.5: Potential Neurologic Complications of Chemotherapeutic Agents Used in Patients with Malignant Brain Tumours

Agent	Type of Neurotoxicity	Clinical Manifestations
Vinca alkaloids	Peripheral Autonomic	Paresthesias, hyporeflexia, motor dysfunction, gait disorder, bone pain, cranial nerve abnormalities with facial palsy and ophthalmoplegia Parasympathetic nervous system dysfunction, constipation, orthostatic hypotension
Cisplatin	Peripheral Central Autonomic	Paresthesias, hyporeflexia, loss of vibratory sense, sensory ataxia Seizures, encephalopathy, cortical blindness Parasympathetic nervous system dysfunction, constipation, orthostatic hypotension
Cytarabine	Central	Encephalopathy, seizures, cerebellar dysfunction
Ifosfamide	Central	Hallucinations, seizures, cerebellar dysfunction
5-Fluorouracil	Central	Confusion, cognitive deficits, cerebellar dysfunction

Agent	Type of Neurotoxicity	Clinical Manifestations
Methotrexate	Optic neuropathy Central	Visual changes With IV administration: encephalopathy (worse with cranial irradiation)
Paclitaxel	Peripheral	Stocking glove paresthesias, loss of vibration sense, hyporeflexia, orthostatic hypotension
Procarbazine	Peripheral central Central	Seizures, encephalopathy Paresthesia, hyporeflexia Lethargy, depression, confusion, agitation, altered mental status
Tamoxifen (high dose)	Central	Unsteady gait, dysmetria, hyperreflexia, seizures

Source: Neuro-oncology: The Essentials. ISBN: 978-1-60406-883-2 P.520

Although radiotherapy is still the most effective treatment against malignant tumours, sufficient doses to kill tumour cells cause necrosis, limiting the dose that can be safely used. Table 3.6 lists the dose-related, idiosyncratic side effects, and drug-drug interactions for the most commonly used anticonvulsant medications.

Table 3.6: Dose-Related, Idiosyncratic Side Effects, and Drug–Drug Interactions for the Most Commonly Used Anticonvulsant Medications

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
Carbamazepine (CBZ)	Diplopia, ataxia, drowsiness, hyponatremia, choreo-athetosis, dystonia	Myelosuppression, hepatitis, rash (and allergic skin reactions),bradycardia, endocrine side effects	Drugs that increase plasma drug levels: cimetidine, diltiazem, macrolide antibiotics, e.g., erythromycin and clarithromycin, metronidazole, verapamil Drugs that decrease plasma drug levels: cisplatin, Adriamycin, vincristine, felbamate, rifampin, phenytoin, primidone, theophylline CBZ acts as a hepatic cytochrome P-450 inducer and can enhance the metabolism of many drugs, e.g., corticosteroids, warfarin, digoxin, vitamin D, quini- dine, theophylline and oral contraceptives; meaning that the dose of these drugs may need increasing

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
			Can also accelerate metabolism of various cytotoxic agents including nitrosoureas, paclitaxel, 9-amino-camptothecin, thiotepa, topotecan, and irinotecan, and newer targeted agents, e.g., imatinib, gefitinib, temsirolimus, erlotinib, and tipifarnib; this potentially reducing their effectiveness
Phenytoin (DPH)	Nystagmus, ataxia, lethargy, movement disorders	Gingival hypertrophy, megaloblastic anemia, rash (and allergic skin reactions), hepatotoxicity, endocrine side effects	Drugs that increase plasma drug levels: alcohol, diaze- pam, warfarin, estrogen, phenothiazines, isoniazid, salicylates Drugs that decrease plasma drug levels: carbamazepine, sucralfate, antacids, cisplatin, vincristine, and Adriamycin Drugs whose efficacy may be impaired by DPH:

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
			DPH acts as a hepatic cytochrome P-450 inducer and can enhance the metabolism of many drugs (see above) Can also accelerate metabolism of various cytotoxic agents including nitrosoureas, paclitaxel, 9-amino-camptothecin, thiotepa, topotecan, and irinote-can, and newer targeted agents, e.g., imatinib, gefitinib, temsirolimus, erlotinib, and tipifarnib; this potentially reducing their effectiveness Combinations of DPH with fluoropyrimidines (e.g., 5-fluorouracil increases DPH's toxic side effects)
Phenobarbital	Hypnotic properties, cognitive decline, hyperactivity, irritability, reparatory	Megaloblastic anemia, allergic reaction, hepatotoxicity	Anticoagulants, corticosteroids, estrogens, doxycholine acts as a hepatic cytochrome P-450 inducer and can enhance the metabolism of many drugs

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
	depression, nausea, vomiting		
Valproic acid	Sedative effects, tremor, ataxia	Skin rash, thrombocytopenia	Acetylsalicylic acid, carbamazepine, phenytoin It inhibits the glucuronidation of SN-38, active metabolite of irinotecan Drugs that decrease the plasma concentration: metho-trexate, Adriamycin, cisplatin Toxic effects of valproic acid can be increased when combined with cisplatin or nitrosoureas
Levetiracetam	Somnolence, asthenia, dizziness Routine therapeutic drug monitoring	Depression, nervousness, anxiety, emotional lability, and hostility (and rarely bizarre behavior such as suicidal ideation)	No interactions with other seizure medications or with warfarin, estrogens, or antibiotics

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
	not currently indicated		
Lamotrigine	Mild ataxia, dizziness, headache, insomnia and sleep disturbance uncommon (6 percent) Routine therapeutic drug monitoring not currently indicated Skin rash	Skin rash including Stevens-Johnson syndrome Aseptic meningitis (rare) Tourette syndrome (exceedingly rare) Leukopenia	Valproate may delay elimination of lamotrigine Carbamazepine, phenytoin, and other hepatic enzyme inducing medications may shorten half-life
Gabapentin	Somnolence, dizziness, ataxia, headache, fatigue Ocular side effects Anorexia, flatulence, Gingivitis	Isolated ataxia (rare) Aggression—very uncommon (e.g., in children with learning disabilities or cognitively delayed adults)	Using propoxyphene or acetaminophen together with gabapentin may increase side effects such as dizziness, drowsiness, confusion, difficulty concen- trating, and other nervous system or mental effects Elderly patients in particular may experience

Agent	Dose-Related Side Effects	Idiosyncratic Side Effects	Drug–Drug Interactions
			impair- ment in thinking, judgment, and coordination The concurrent use of levomethadyl acetate and gabapentin may result in additive CNS and respiratory depression, hypotension, sedation, or coma Avoid gabapentin if on sodium oxybate therapy

Source: Neuro-oncology: The Essentials. ISBN: 978-1-60406-883-2 P.524

3.11 EARLY IDENTIFICATION AND MIS-DIAGNISOS OF BRAIN TUMOURS

In this study, we tried to summarize all examination methods for the diagnosis of brain tumours. Despite the advanced imaging techniques used, the neurological examination may not be possible for a timely diagnosis of brain tumours. Diagnosis, treatment planning and implementation of the earliest possible stage, as in all cancers, primary and metastatic brain tumours is vital. We believe that clinical processes should be supported with the opportunities provided by the technology in order to minimize the patient's life expectancy, quality of life, side effects and permanent problems caused by the treatments to be applied. In this context, we think that information technologies can benefit from the ability to perform much faster, high capacity and sensitive analyzes in the diagnosis, treatment planning, treatment process and post-treatment of patients with brain tumours and to evaluate how the patient reacts to the applied treatment and to provide proactive treatment management.

There are many studies on this subject, but these studies have not been able to find clinical use for different reasons. These systems have not yet reached the required competence for use in clinical processes, as well as the slow adaptation of clinicians to these systems are among the obstacles ahead. We think that the main reason why many of the projects that are being tried to be implemented is not achieving clinical competence or finding a field of use is that these studies are not carried out in cooperation with the required branches. For a project to be implemented in the field of medicine, it is necessary for the relevant branch physicians, academic researchers, mathematics and software experts to work together, but unfortunately, it is challenging to bring these experts together, even for global companies. Even if a company can bring these experts together, the difficulties that they will have in accessing the clinical data required for the studies will be another problem.

As Bahçeşehir University Faculty of Medicine, we aimed to implement one of the oncological processes mentioned above by combining the data of our patients in the neurosurgery department of our university hospital with databases open to academic use, anonymizing all the data, and obtaining the approval of the ethics committee. We aimed to realize a project that will contribute to the solution of the targeted problem.

In MRI scans with multiple (even singular) lesions, one or more of the lesions are overlooked, which is frequently encountered. This is one of the most critical obstacles to early diagnosis and treatment. Because the lesions identified as idiopathic develops as a result of other examinations as a result of delayed diagnosis of these lesions, patients and relatives of the more difficult treatment process, as a result of the treatment may cause some permanent neurological, or systemic damage may even result in death.

3.12 WHY DO WE NEED AN AUTOMATED BRAIN TUMOUR IDENTIFICATION AND SEGMENTATION TOOL?

In cases where symptoms suggest a brain tumour, we try to confirm the presence of tumour by imaging following neurological examination. MRI and CT are the most commonly used imaging techniques, although they vary according to the condition of the

case. However, the vast number of cases in clinics, especially in radiology, and the lack of specialist physicians and health professionals, constitute an obstacle to the rapid and efficient interpretation of these images. However, there may be incomplete and erroneous interpretations from the clinician, and this leads to the disruptions mentioned earlier.

In order to avoid problems caused by these delays or errors, we think that it is necessary to benefit from image processing, machine learning and other technologies. Advances in image processing and machine learning have yet to reach a physician's ability to interpret. Therefore, we believe that using these systems alone for the diagnosis will not be accurate at this stage regardless of the consistency of the sample. However, we think that these technologies will be useful as a decision support system before or after the physician's evaluation.

We believe that the evaluation of a large number of pending examinations by a decision support system and marking the suspected lesions for faster and easier decision making by the physician will contribute to reducing the rate of errors in clinical processes.

3.13 COMBINING MATHEMATICS, MEDICINE and OTHER FIELDS

Developing such a decision support system as part of clinical processes requires expertise in different disciplines. In order to determine the application architecture and solution approach, experienced software engineers, mathematicians to develop the necessary algorithm and machine learning model, and of course clinicians for the provision of clinical information, and in our example, neuro-radiologists and neurosurgeons should work together with this team. However, in order to develop a solution that covers oncological processes, experts from more extensive and different disciplines need to work together. In the next section, we will discuss the use of machine learning in these processes and present our solution.

4. USING MACHINE LEARNING FOR DIAGNOSIS, TREATMENT PLANNING, AND PROGNOSIS IN THE TREATMENT OF BRAIN TUMOURS

In this section, we will first explain the components and the study model of the neuro-oncology decision support system that we propose, and then give details about our study aimed to provide the detection of brain lesions with image processing and machine learning techniques that we have identified for our study.

4.1 INTRODUCTION TO COMPUTATIONAL NEURO-ONCOLOGY

Neuro-oncology is a new field that evaluates and treats people with primary and secondary tumours of the brain, spinal cord, and the membranes that surround the brain and spinal cord. In the beginning, Neuro-oncology was considered as a subspecialty which arose from the evolution of neurosurgery. Today it is widely accepted as a distinct interdisciplinary field which requires coordinated work between medical oncologists, radiation oncologists, nervous system surgeons and, neurologists. Apart from diagnosis and treatment, neuro-oncology is also an academic field which pursues the development of new treatments, methods, and technologies that improves treatment quality and efficiency, patient safety, and rate of survival.

Cooperation of medicine with other disciplines is increasing faster than ever. Naturally, Mathematics is one of the most important fields that can work aside with medicine. Beyond statistics, Mathematics can be used for creating models and working on model-based studies which allows us to run simulations by using different parameters and getting results for different parameter sets faster than ever. Eventually, our models can learn from previous simulations and real-life case outputs to increase its accuracy. Apart from simulations, getting the advantage of increasing computational power and artificial intelligence applications, we can also integrate Mathematics into clinical processes. For example, we can create an algorithm for assessing the MRI or CT images for potential lesions within the brain and create warnings for the physicians or to validate the diagnosis of the physician and minimize the risk of misdiagnosis of any primary or secondary lesion.

4.1.1 The Main Objective: End-to-End Personalized Medicine

Our approach to computational neuro-oncology is based on one single goal: End-to-end personalized medicine. Tailoring the therapy with the best response and highest safety margin to ensure better patient care is what we understand from personalized medicine today. With the advantage of mathematical models, cost-effective and more accessible tools for each step of the "end-to-end personalized medicine" can be created.

4.1.2 Model Based Approach

A private data modal for each individual is created and that data modal is fed continuously with the test results, imaging data, genetic analysis, lab results, wearable devices, personal measurements (blood pressure, blood glucose level, saturation, pulse, weight, e.g.) and other data sources to identify and monitor the risks. Every entity will be defined as an object within the data model of the individual. So, the patient will be an object with properties but in order to run a simulation, researcher or physician must supply values of the properties of the object. For instance, the date of birth, gender, weight. All objects will constitute the private data model of the institute. Researchers and physicians may create different rule sets for the data model to simulate different scenarios.

In order to run a simulation, researcher or physician must also create rules based on the properties of the objects of data modal. A rule can simply be an if-then rule. (IF Patient.BloodPressure.Systolic >= val THEN …) Built-in functions also can be used. (IF Foundation.Vitals.IsBloodPressureWithinNormalRange(diastolic, systolic) THEN … ELSE …) Researchers may also implement their own functions for their private data modals so they can extend the features of the system per their requirements.

Two different engines will process the rules at different stages. First, the inference engine will process all the rules and input data to deduce new information. Then, the probabilistic logic network will process the provided information, rules and the output of the inference engine. Because there are several unknowns (symptoms, symptom properties, incorrect or missing information caused by the patient, allergies, drug reactions & side-effects, ...) we need a second engine to manage the uncertainty, to handle and reason about imprecise,

uncertain, incomplete, and inconsistent data, and reasoning involving uncertain conclusions.

Every event within the private data modal of the patient will be validated with the data from other private data modals (of other individuals) anonymously and every positively validated information will increase the accuracy and performance of the modal itself and will also be propagated to other private modals in order to maintain the same performance throughout all private modals which will optimise the overall system so the upcoming private modals will be generated by using all the information and experiences from existing private modals for optimum accuracy and performance.

Researchers may develop their own rulesets to simulate different scenarios by using one patient data or may use the consolidated patient data for further analysis and / or comparisons.

4.1.3 End-to-End Personalized Medicine and Computational Neuro-Oncology

The concept of end-to-end personalized medicine consists of five steps. Instead of focusing the post diagnosis period, it focuses to the entire life of the individual.

4.1.3.1 Step 1: Assessment of the risk factors, prevention, prognosis

All patient data is consolidated and assessed continuously for an increase in the likelihood of one of the risk elements. In case of an increased risk, the system will automatically generate an alert (via email, SMS, mobile application) to the patient, physician, or relatives. The alert data structure will contain the reason of the alert and also details of the prediction.

By using the knowledge base gathered from all private data models, system will be able to predict potential risks for the individual so preservative procedures can be applied to minimize the risk.

In case of a disease, system can also use the existing knowledge base to predict the prognosis, based on preferred treatment strategy for the individual.

4.1.3.2 Step 2: Diagnosis and validation

As I mentioned at the introduction, diagnostic errors contribute to 10 percent of patient deaths. That means diagnostic mistakes kill more people than Alzheimer's disease, diabetes, suicide, and car accidents combined. One of our goals is to improve the diagnosis procedures by giving physicians the tools that will support them during diagnosis sessions.

In order to achieve this, system will provide an artificial intelligence robot that will help physician to ask the correct questions, in correct order, at the correct time. This system will help increasing the diagnosis accuracy while minimizing the duration of a diagnosis session.

Once the diagnosis is confirmed, related physician will manually confirm the predicted diagnosis of the patient. This manual feedback will be used to train the model for the succeeded and failed predictions of the deep learning algorithms for upcoming predictions. System will also follow the upcoming test and imaging data of the patient to validate its predictions which means no manual feedback is necessary.

4.1.3.3 Example flow for diagnosis support

Patient Name: Patient X
Sex: Male
Date of Birth: 1 January 1985
Smoker: Yes
High Blood Pressure: No
Diabetes: No

Table 4.1: User-Interaction Workflow for symptom: Headache

Question	Option 1	Option 2	Option 3	Option 4	Option 5
How long has this been troubling him?	**Less than one day**	One day to one week	One week to one month	One month to one year	More than one year
Is his headache mainly located on one or both sides of the head?	Both sides	**One side**	I don't know		
Is it a throbbing headache?	**Yes**	No	I don't know		
How does bending forward affect his headache?	**Worsens**	No effect	I don't know		
How would he describe the intensity of the headache?	Mild	Moderate	**Severe**	I don't know	
Does he have any other symptoms?	**Yes**	No			

Table 4.2: User-Interaction Workflow for symptom: Blurred/Reduced Vision

Question	Option 1	Option 2	Option 3	Option 4	Option 5
How long has this been troubling him?	**Less than one day**	One day to one week	One week to one month	One month to one year	More than one year
Does the change in his vision affect one or both eyes?	One eye	**Both eyes**	I don't know		
Did the change in his vision happen suddenly?	**Yes**	No	I don't know		
Does he have any other symptoms?	Yes	**No**			

Table 4.3: Auto-generated User-Interaction Workflow based on given user responses

Question	Option 1	Option 2	Option 3	Option 4	Option 5
Did he suffer a head or neck injury before his first symptom occurred?	**Yes**	No	I don't know		
Is he confused about where he is, what time of day it is, or who he is?	Yes	**No**	I don't know		
Is his scalp sore when touched or pressed?	**Yes**	No	I don't know		
Is there any liquid coming from his ear?	Yes	**No**	I don't know		
Is there an area of swelling on his scalp or head?	Yes	**No**	I don't know		
Have his pupils recently become different in size from one another?	Yes	No	**I don't know**		

Does he seem emotionally distressed	**Yes**	No	I don't know		
Question	**Option 1**	**Option 2**	**Option 3**	**Option 4**	**Option 5**
Does he have pain in the bones or skin around his eye socket?	**Yes**	No	I don't know		
Does he have pain behind the eye?	Yes	**No**	I don't know		
Does he have any eye pain?	Yes	**No**	I don't know		
Does he appear agitated and physically restless?	**Yes**	No	I don't know		
Does he have watering eyes?	Yes	**No**	I don't know		
Is the white of his eye redder than usual?	Yes	No	**I don't know**		
Does he have any bruises on his scalp?	Yes	**No**	I don't know		
Does he have a runny nose?	Yes	**No**	I don't know		

Has he been vomiting?	**Yes**	No	I don't know		
Question	**Option 1**	**Option 2**	**Option 3**	**Option 4**	**Option 5**
Does he have to throw up when drinking even small amounts of fluid?	Yes	**No**	I don't know		
Has he been vomiting extremely forcefully?	Yes	**No**	I don't know		
Does he have to avoid looking at bright light because it causes eye pain?	Yes	**No**	I don't know		
Has he lost his appetite?	Yes	**No**	I don't know		
Is he extremely sensitive to sound?	Yes	**No**	I don't know		
Does he have severe difficulty concentrating?	Yes	**No**	I don't know		

Is his temple sore to the touch?	Yes	**No**	I don't know		
How are his symptoms changing over time?	They're getting worse	They're not as bad as they were	**They're staying about the same**		

AI Generated Results

1. Cluster headache (50 percent)
2. Skull fracture (10 percent)
3. Migraine (< 10 percent)
4. Whiplash (< 10 percent)
5. Acute subdural haematoma (< 10 percent)

Entire procedure takes approximately 1 to 5 minutes and AI generates predictions based on given answers. The system will show all necessary questions that should be asked to the patient and the questions will be determined by the AI algorithm depending on the given answers by the patient. At the end of the procedure, the AI algorithm will produce predictions based on given answers.

4.1.3.4 Step 3: Treatment planning

One of the most important features of computational neuro-oncology is treatment planning. There are several options for a neuro-oncology patient including surgery, different radio-oncology tools and strategies, and obviously several drug combinations.

The unknown in this equation is the reaction of the patient to each treatment tools individually and also the combination of therapies. At this step, we can use the modals we have to simulate the potential reaction of the patient to each therapy.

Also, we can use our models for risk assessment for the patient. For example, cardiovascular assessment of the patient is critical for a surgery decision. Depending on the cardiovascular status of the patient, surgery decision may be postponed for a supplementary treatment or completely cancelled which is a critical decision for the entire treatment plan. All parameters must be examined consistently and extremely carefully. An AI tool will be extremely helpful for the physicians during this process.

4.1.3.5 Step 4: Disease management, end-of-life care

Disease management can be defined as the concept of minimizing health care costs and improving the life for individuals by preventing the effects of the disease throughout

treatment. It is also important to identify any change at patient's conditions to update the treatment strategy effectively. With the “patient change tracker AI algorithm”, system monitors every test result of patient and run the simulations which has been defined (and automatically generated for the patient by using the knowledge base of the platform) for the patient automatically and generate a status change report to the physician.

Tracking the changes and comparing the progress of the disease against knowledge base will also support physicians to make a prediction for the timing of the terminal phase to better plan and organize end-of-life care. Because end-of-life care requires several decisions by the patient or their families, preparing the family of the patient as well with the patient to the terminal phase is extremely critical for better decisions.

End-of-life care process may be one of the most expensive processes because it requires rationing and several resources to be allocated. So, better planning and management of the end-of-life care is important to the hospitals and the staff of the hospitals as well. The adaptation of the family to the situation before the death and psychological support after the death of the patient can also considered as a part of end-of-life care because their own fear of death may affect their decisions and behaviour or they may feel guilty about past events in their relationship with the dying person. Family members may also be coping with unrelated problems, such as physical or mental illness, emotional and relationship issues, or legal difficulties. These problems can limit their ability to be involved, civil, helpful, or present. These problems will affect the decisions of the family members which may cause worse decisions about the treatment and during terminal phase.

Finally, we can create rules to assess if the patient’s organs are suitable for transplantation or not with a greater accuracy. Also, candidates at the transplantation queue for each organ can be analysed to identify the best match for the patient’s organs.

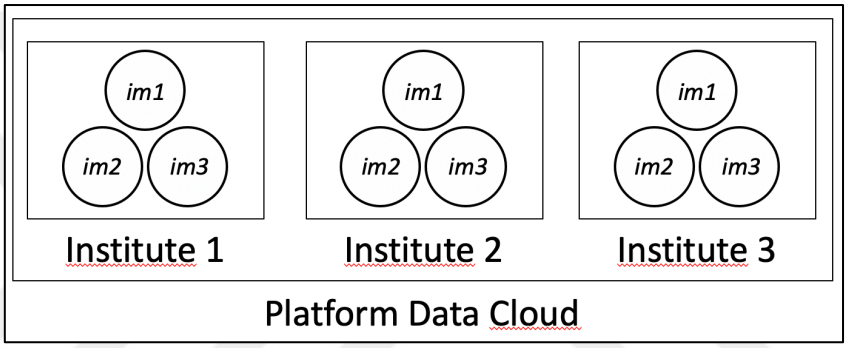
4.1.3.6 Step 5: Every disease improves the computational universe

Every model running as a stand-alone data model instance in order to protect the other instances from possible errors and allowing model owners to create their own entities and rules without affecting other instances. Institutes can create different entity models,

different rule-sets, different rule-scopes and create different simulations based on the entities, rule-sets and scopes they created easily.

System monitors the other instances in real-time and identifies successful rule-sets (which has higher accuracy, performing faster than existing rule-sets or completing a missing part of the master rule-sets) and optimizes the master rule-sets and entity models. These updates are propagated to other institute-models silently and institute model managers can synchronize their data models and rule-sets with the optimized information easily.

Image 4.1: Proposed Platform Cloud



As the system is fed with more data, the overall accuracy of diagnosis, treatment planning and other steps will be increased.

4.1.3.7 Step 6: Connection neuro-oncology patients and their physicians

Creating virtual clouds which groups the patients from same segment, or their physicians could be a secondary benefit of the system. By allowing physicians who has patients with similar diagnosis, progress, and genetic and vital signature communicate, system may provide a platform for physicians for developing treatment plans or running researches jointly.

4.2 MATHEMATICAL MODELING

“Model building is the art of selecting those aspects of a process that are relevant to the question being asked.” (Holland 1995)

A mathematical model is an abstract, simplified, mathematical construct related to a part of reality and created for a particular purpose (Bender 1978). While using mathematical models, we simply have a list of inputs, and an algorithm that tells us what the outputs will be with given inputs. By changing the input values, one can observe the difference between different parameters.

We can also define mathematical models as a triplet (S, Q, M) where S is a system, Q is a question relating to S, and M is a set of mathematical statements M={∑_1,∑_2,…,∑_n} which can be used to answer Q.

There are several mathematical models and there are also several approaches for grouping them. I will group mathematical models into four main categories in order to keep subject aligned with the scope of the research. If I was writing this research in the field of mathematics instead of medicine, my personal preference for categorizing mathematical models would be the SQM Space approach (Velten 2009) which categorizes the models by their respective S, Q, and M values.

A Simplified Categorization of Mathematical Models

First type of mathematical models is the qualitative models which describes the structure and metamorphoses among things or events or among properties of things or events. Example: Being exposed to HIV can lead to HIV infection.

Second type is Quantitative models. Example: A person exposed to N HIV virions has an X percent probability of getting infected. Most scientific researches prefer this approach.

Third type is Quantitative Mechanistic Models which actually works for very specific basic problems. Example: Heterosexual intercourse with a person with N HIV virions/mL leads to an HIV infection with probability X percent.

The final type is the Quantitative Mechanistic, Dynamical Models. Example: Modelling HIV and CD4 T-cells during infection. This model type is called dynamical because they

track how things change in time and mechanistic because they have equations or computer rules that explicitly describe how things happen.

The use of mathematical models avoids intuition alone and, in some cases, the risk, time and cost associated with primary research.

By definition, models involve assumption, abstraction and simplification. However, assumptions can be made explicit and the impact of uncertain assumptions upon the model results can be formally assessed.

Mathematical models are developed with the explicit function of informing decision-making. Decision models generate information on the expected costs and consequences of alternative courses of action and the probability that a given decision alternative is optimal, given current information.

Mathematical modelling rests within a Bayesian framework involving the synthesis of all relevant, often disparate, information in the development, implementation and interpretation of the model and its results (Spiegelhalter et al. 1999).

Finally, no mathematical model can be defined without extensive knowledge about the research field. Regardless of the field, in order to create a health decision model, a collaborative work of different specialities is a must. In the field of neuro-oncology, in order to create an efficient decision model for simulating different scenarios, a group of neurologists, neurosurgeons, medical oncologists, radiation oncologists, and experts from the genetics and molecular biology.

4.3 AUTOMATED BRAIN TUMOUR IDENTIFICATION AND SEGMENTATION

Numerous studies have been conducted on the analysis of brain tumours using image processing techniques, and there are techniques in the literature that adopt different methods. In this part of our study, we will briefly talk about the methods in the literature and then present our study.

4.4 COMMON BRAIN TUMOUR SEGMENTATION METHODS

1. Fast marching method is a method that can be used as a fast initialization algorithm for image segmentation. Its computational cost is minimal but automatic detection of the crossing of the interesting edges can be difficult to implement.

2. GA with deformable contour method is a genetic algorithm that a searching method applied with deformable contour to segment brain MR images. It is optimized in order to accelerate anatomic region identification at coarse scales and localizing brain contours at finer scales more accurately.

3. The maximum likelihood approach is used to segment the pathological tissue from normal tissues. Threshold values is the main problem of this approach because of the requirement of adjustment for most of the cases.

4. Hidden Markov random field-expectation maximization method is a stochastic process generated by an MRF whose state sequence cannot be observed directly but can be indirectly estimated through observations.

5. Modified expectation maximization This approach differentiates the health and the tumorous tissues. It performs with a high computational performance with appropriate MRI images and cases.

6. Thresholding method is simple and effective segmentation approach working by differentiating the intensities. Approach simply finds a threshold value which enables the classification of pixels into different categories.

7. Radial basis function neural network and contour model a combined radial basis function neural network and contour model-based MR image segmentation technique. The contour model is used as a pre-segmentation step by developing the clear boundaries between the different tissues. RBF neural network is then used to segment the various brain tissues into different groups.

8. Atlas-based segmentation is able to segment several structures simultaneously while preserving the anatomy topology. The method provides a good trade-off between accuracy and robustness and leads to reproducible segmentation and labelling.

9. Modified suppressed fuzzy c-means segmentation MS-FCM performs clustering and parameter section for the suppressed fuzzy c-means algorithm simultaneously. It can easily select the parameter in Suppressed-FCM with a prototype-driven learning and also this algorithm seems to be simple in its computation. The parameter selection is on the basis of exponential separation strength among clusters.

10. High speed parallel fuzzy c-means algorithm is more advantageous both in the sequential FCM and parallel FCM which employs the clustering process in the segmentation techniques. When the image size is so large, the proposed algorithm works very fast and it requires minimum execution time.

11. Back propagation neural network is one of the best performing approaches in terms of execution performance, computational costs, and accuracy.

12. Fast neural network: an iterative-free training approach is followed in this network using the Huang's neural network. The convergence time period is considerably reduced since the weights are determined analytically rather than through conventional weight adjustment procedure.

13. Watershed transform and level set method combines the watershed transform and region-based level set method. The watershed transform is first used to presegment the image. The region-based level set method is then applied for extracting the boundaries of objects on the basis of the presegmentation. The consumed time does not depend on the size of the image but the number of presegmented regions. This method is computationally efficient.

14. Bayes-based region growing algorithm is an algorithm that estimates parameters by studying characteristics in local regions and constructs the Bayes factor as a classifying

criterion. The technique is not fully automatic, and this method fails in producing acceptable results in a natural image. It only works inhomogeneous areas. Since this technique is noise sensitive, therefore, the extracted regions might have holes or even some discontinuities.

15. Marker controlled watershed segmentation is a quite versatile, fast and simple to use method. This method can be applied to all type of 2D MR images representing all tumours irrespective of their location in human body and their size.

16. Deformable models: The segmentation efficiencies reported in this approach is very low and the report also concluded that the proposed approach is a failure in case of symmetrical tumours across the mid-sagittal plane.

17. Colour based segmentation method that uses a K-means clustering technique to track tumour objects in MR images can successfully achieve segmentation for MR brain images to help pathologists distinguish exactly lesion size and region.

18. LVQ neural network: The concept of GA is incorporated in this technique to improve the performance of conventional LVQ.

19. Support vector machine is a promising technique in image segmentation because of its good generalization performance, especially when the number of training samples is very small, and the dimension of feature space is very high.

20. A fuzzy kohonen neural network is completely dependent on the input features which are the drawback of this system. The qualitative and quantitative analysis results are inadequate when compared with the other techniques.

21. Marker controlled watershed segmentation model is quite versatile, fast and simple to use. This method can be applied to all type of 2D MR images representing all tumours irrespective of their location in human body and their size.

22. Modified-FCM segmentation is an improved segmentation technique based on the FCM clustering algorithm. The neighbour pixels of targets are varied by applying the Sigma filter principle. The proposed algorithm is compared with FCM algorithm in visual evaluation and quantitative evaluation thereby the efficacy of the proposed method was demonstrated.

23. The improved FCM algorithm is based on the concept of data compression where the dimensionality of the input is highly reduced. Since the modified FCM algorithm uses a reduced dataset, the convergence rate is highly improved when compared with the conventional FCM.

24. Vector quantization segmentation method is a very effective model for image segmentation process. Vector quantization is a classical quantization technique from signal processing which allows the modelling of probability density functions by the distribution of prototype vectors.

25. Gaussian smoothing based FCM algorithm approach has incorporated a feature selection algorithm for improved accuracy. Experimental analysis has revealed the suitability of this approach for noisy MR images. But the computational complexity of this approach is significantly high due to the bootstrap-based feature selection techniques.

26. Spatial information with fuzzy c-means clustering approach utilizes histogram based fuzzy c-means clustering algorithm for the segmentation of medical images. The spatial probability of the neighbouring pixels is incorporated in the objective function of FCM to increase the robustness against noise.

27. Hierarchical self-organizing map with FCM is a hybrid technique that combines the advantages of hierarchical self-organizing map with FCM. The hybrid approach is accurately identifying the principal tissue structures in the image volumes.

4.5 AUTOMATIC DETECTION OF INTRA-CRANIAL LESIONS WITH PRINCIPAL COMPONENT ANALYSIS AND SUPPORT VECTOR MACHINE HYBRID MODAL

In our study, we have created a hybrid model using two different methods to analyse magnetic resonance images with the highest possible processing performance, lowest computational cost and highest accuracy.

One of the major problems facing medical image processing solutions is that all magnetic resonance images do not have the same resolution and the presence of noise that significantly reduces analysis consistency and renders the analysis unreliable. In order to analyse the magnetic resonance image in as much resolution as possible in our study, we preferred to use the wavelet transform method, although it imposes some additional burdens on computing costs. In order to reduce computational costs and increase the performance of our modal, we decided to use a dimensionality-reduction method (PCA-principal component analysis) to reduce the dimensionality of our data set by transforming the broad set of variables into a smaller one that still contains most of the information in the large data set.

Recent classification studies fall into two main categories. First is the supervised classification, which also includes the support vector machine modal that we prefer to use. The other category is unsupervised classification, including popular fuzzy c-means and self-organisation feature map modals. All methods are advanced enough to provide high accuracy levels, but almost most of the existing methods have an overall accuracy level of below 95 percent, which leads us to search for a more accurate approach.

Although the most important criteria for our study is the overall accuracy, the support vector machine provides some other benefits beside overall accuracies like mathematical tractability and direct geometric interpretation when compared to other models like the artificial neural network, Bayesian network and decision tree. Support vector machine also provides higher accuracy with a smaller number of training samples.

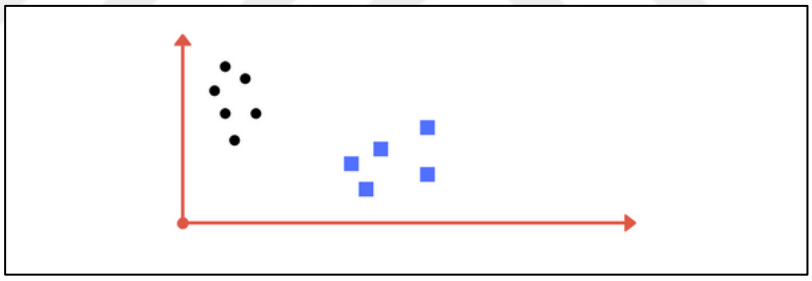
Because the vector support machines are linear and we require to fit the maximum-margin hyperplane in a transformed feature space, we prefer to use the kernel support vector machine approach which is ideal in the cases that the transformation may or may not be linear and the transformed space high dimensional; thus the classifier is a hyperplane in the high dimensional feature space, it may be nonlinear in the original input space.

Before proceeding with kernel support vector machines, we will define the support vector machine first.

4.5.1 Support Vector Machine

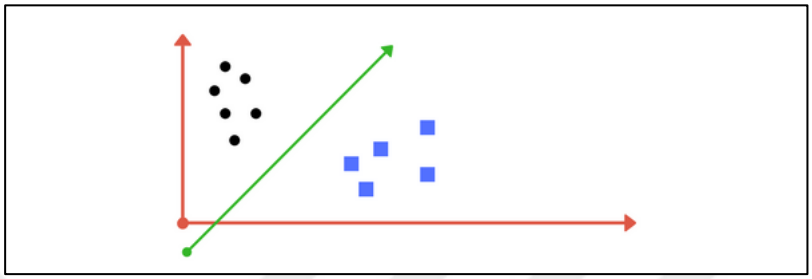
The purpose of the support vector machine is to identify the separating line for the following two classes at image 9.

Image 4.2: The Classes



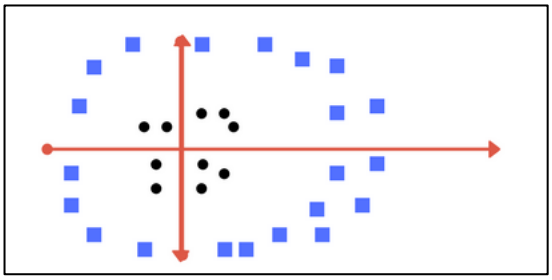
The expected drawing would be something like the green line at Image 9 which separates the two classes. The points at the left of the line will fall into black circle class and the points placed at the right side of the green line would fall into blue square class. The main purpose of Support Vector Machine is simple like that. Separation of the classes in a given context. If finds out a hyperplane (in multidimensional space, the line that separate the classes, the green line in Image 10).

Image 4.3: The Hyperplane



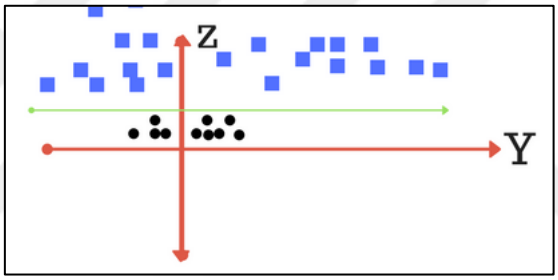
When the space gets more complex, we may need more than one hyperplane. Image 11 is an example of that scenario and in order to separate the classes in this example, we will add an additional dimension which we will call as z-axis.

Image 4.4: More Complex Scenario



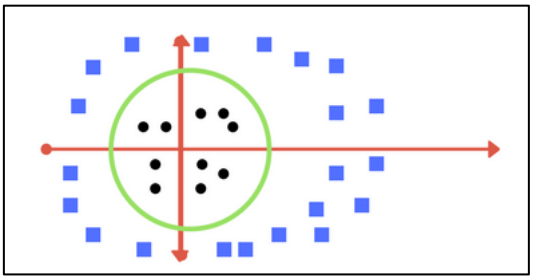
Let's assume that the value of points on z-plane, $w = x^2 + y^2$ so we can manipulate it as distance of point from z-origin. So, if we plot in z-axis, we will have a clear separation and the hyper-plane can now be drawn.

Image 4.5: Plot of zy axis.



When we transform back this line to original plane, it maps to circular boundary as shown in image 13. These transformations are called kernels.

Image 4.6: Transformed back to Z-Y plane.



In real-life scenarios, our data plot usually is not simple like these examples, and our data overlap very often. So, in real-life applications, finding the perfect class for millions of training data set takes lots of time. So, we use the regularisation parameter and gamma

(which are the tuning parameters in SVM) to prioritise accuracy or computation performance. The third parameter in SVM is the kernel.

The equation for prediction for a new input using the dot product between the input (x) and each support vector (xi) is calculated for the linear kernel as follows:

$$f(x) = B(0) + sum(ai * (x, xi))$$

This equation involves calculating the inner products of a new input vector (x) with all support vectors in training data.

The polynomial and exponential kernels calculate separation line in the higher dimension (kernel trick), and they can be formalized as follows;

Polynomial kernel

$$K(x, xi) = 1 + sum(x * xi)\text{^}d$$

Exponential kernel

$$K(x, xi) = \exp(-gamma * sum((x - xi^2))$$

4.5.2 Our Solution Approach

In our study, we have a three-step process for each magnetic resonance image. In the first phase, we pre-process the input magnetic resonance images for feature extraction and wavelet transform, and feature reduction. In the second phase we train the kernel support vector machine and process the input images and finally we apply a cross validation of the given training dataset against other datasets to avoid overfitting to increase the reliability of the results of our solution.

4.5.2.1 Fourier transform vs. Wavelet transform

Fourier transform is one of the most convenient tools for signal analysis that breaks down a time-domain signal into constituent sinusoids of different frequencies to transform a

signal from a time domain to frequency domain. Fourier transform discards the time information of the signal, which makes impossible for us to tell when a particular event took place. Because the time information is lost, the classification performance decreases significantly. To prevent this, Gabor proposed a solution called windowing or short-time Fourier signal where only a small section of the signal analysed at a time. This approach provides information regarding both time and frequency, but in this case, the precision of the information is limited by the size of the window.

Wavelet transform is a windowing technique with variable size. It enables us to preserve both time and frequency information of the signal. It also does not produce a time-frequency view but a time-scale view of the signal, which is a different and better approach to view data compared to frequency. Also, large/small scale is easy to understand than in low/high frequency.

We define the continuous wavelet transform of $x(t)$ relative to a given wavelet $\psi(t)$ as (Zhang and Wu 2012);

$$W_{\psi}(a,b) = \int_{-\infty}^{\infty} x(t)\psi_{a,b}(t)dt$$

where

$$\psi_{a,b}(t) = \frac{1}{\sqrt{a}}\psi\left(\frac{t-a}{b}\right)$$

The wavelet $\psi_{a,b}(t)$ is calculated from the parent wavelet $\psi(t)$ by translation and dilation where a is the dilation factor and b is the translation parameter. We can discretize the first equation by restraining a and b to a discrete lattice ($a = 2^b$ & $a > 0$) to give the DWT. The following is the equation of one-level decompose, which is the fundamental of wavelet decomposes that decomposes signal $x(n)$ into two signals, the approximation coefficients $ca(n)$ and the detail components $cd(n)$:

$$ca_{j,k}(n) = DS\left[\sum_{n} x(n)g_j^*(n-2^j k)\right]$$

$$cd_{j,k}(n) = DS\left[\sum_{n} x(n)h_j^*(n - 2^j k)\right]$$

This decomposition process can be iterated with successive approximations being decomposed in turn so that one signal is broken down into various levels of resolution. DWT is applied to each dimension of 2D images separately, which results in four sub-band images. The sub-band LL is the approximation component of the image and used for the next 2D DWT iteration. The other sub-bands (LH, HL, and HH) are detailed components. Increased decomposition levels result in more compact and coarse approximation component. We also implemented border distortion method. Then we used PCA to reduce the dimension of our dataset. The PCA transforms dataset to a new set of ordered variables according to their importance but retains most of the variations.

As mentioned before, traditional support vector machines construct a hyperplane to classify data, which limits the capability of classifying different types of data located at different sides of a hypersurface. The equation is very similar to a difference of every dot product is replaced by a nonlinear kernel function. The KSVMs allow fitting the maximum-margin hyperplane in a transformed feature space. This transformation does not need to be linear; it can be nonlinear and the transformed space higher-dimensional.

Because the classification algorithm is trained with the given dataset, it shows a high consistency on that dataset, but may not show the same consistency when working with other datasets. To avoid this overfitting situation, a cross-validation method is needed. There are three cross-validation methods: random subsampling, K-fold cross-validation, and leave-one-out validation. We used the K-fold validation which creates a K-fold partition of the whole dataset, repeats K times to use K-1 folds for training and a left fold for validation, and then average the error rates of K experiments. The K folds are partitioned randomly. Number of K has a significant effect on overall performance. During our study, we used values from 2 to 10 and selected 5 as the K value as the optimal value for the best performance/accuracy rate.

4.5.3 Dataset, Experiments and Results

We implemented our algorithm in MATLAB 2019a version using wavelet, biostatistical, and SVM toolboxes.

We used two different databases during implementation and tests. Our test database includes the following collections from cancer imaging archive;

i. Low- and high-grade gliomas: 537 cases.
ii. Glioblastoma: 520 cases.

Additionally, 1.641 cases (484 of them used at final experiments) from our university hospital's medical records have been used. We also used 359 cases reported with no intra-cranial lesions for validation purposes.

Some examples from our tumour database are shown below to demonstrate the processed images of different tumour types.

a. Acoustic neuroma

Image 4.7: Axial T2 of Acoustic Neuroma

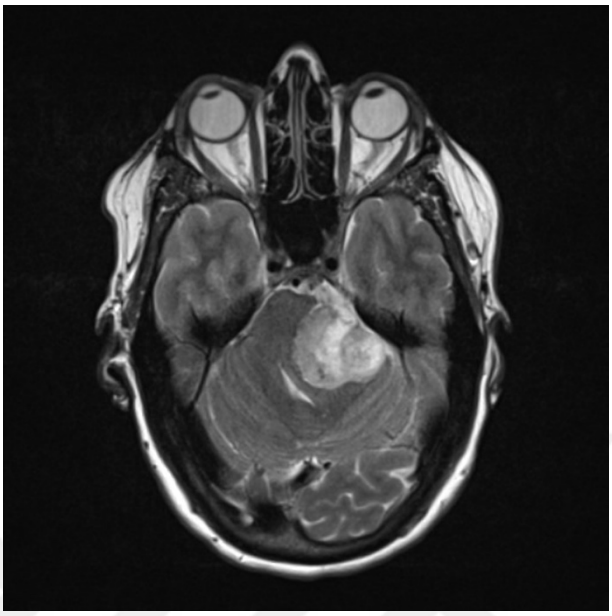


Image 4.8: Axial FLAIR of Acoustic Neuroma

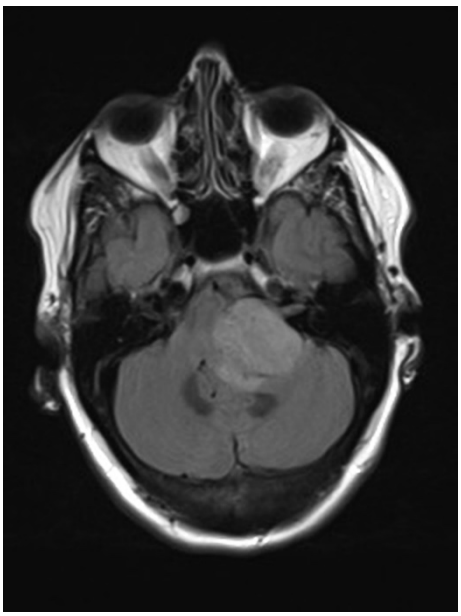


Image 4.9: Axial T1 of Acoustic Neuroma

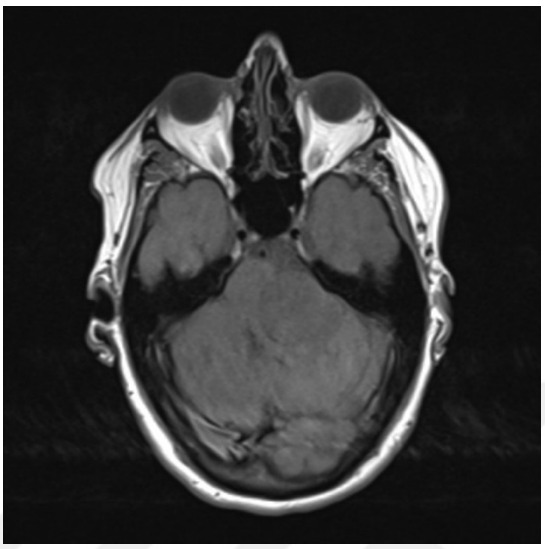
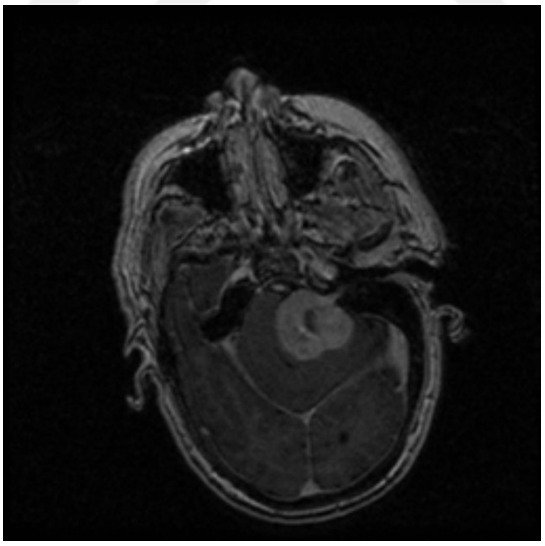


Image 4.10: Axial T1 C+ of Acoustic Neuroma



Source: Case courtesy of Dr Henry Knipe, Radiopaedia.org, rID: 40063

b. Anaplastic Oligodendroglioma

Image 4.11: Axial T1 of Anaplastic Oligodendroglioma

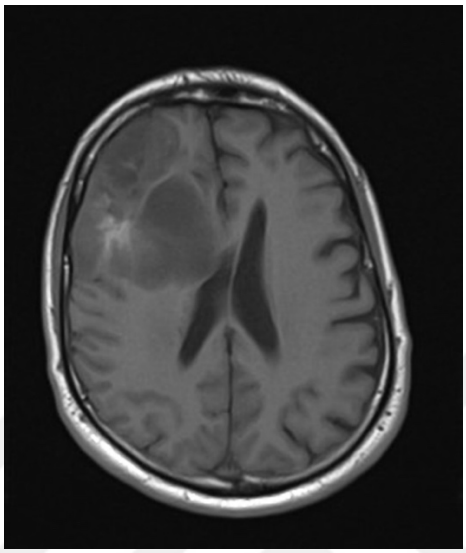


Image 4.12: Axial T1 C+ of Anaplastic Oligodendroglioma

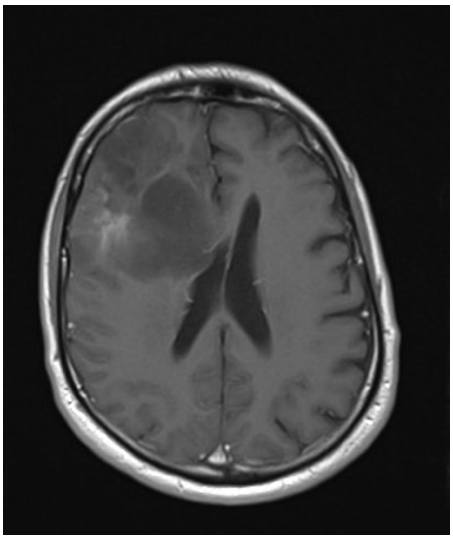


Image 4.13: Axial FLAIR of Anaplastic Oligodendroglioma

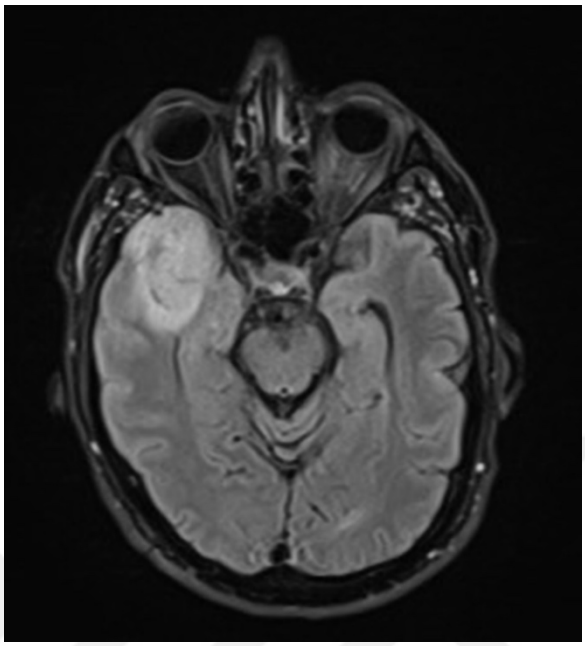


Image 4.14: Axial T2 of Anaplastic Oligodendroglioma

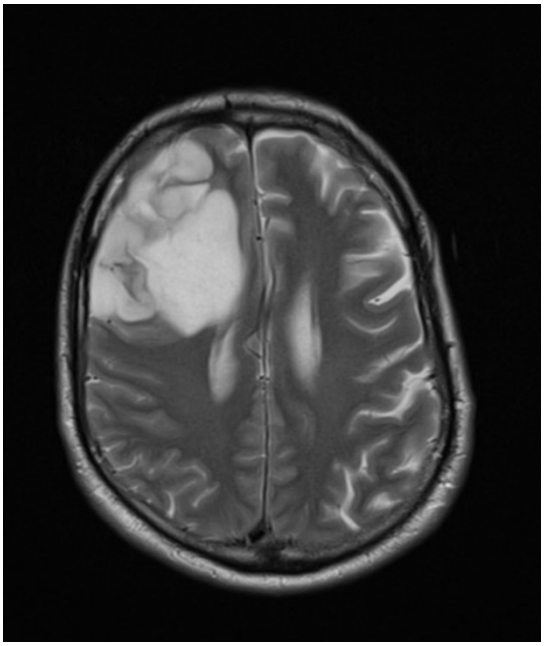


Image 4.15: Axial DWI of
Anaplastic Oligodendroglioma

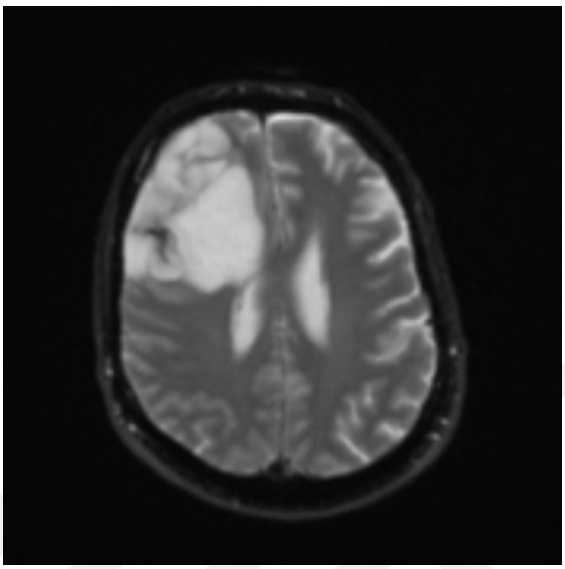


Image 4.16: Axial ADC of
Anaplastic Oligodendroglioma

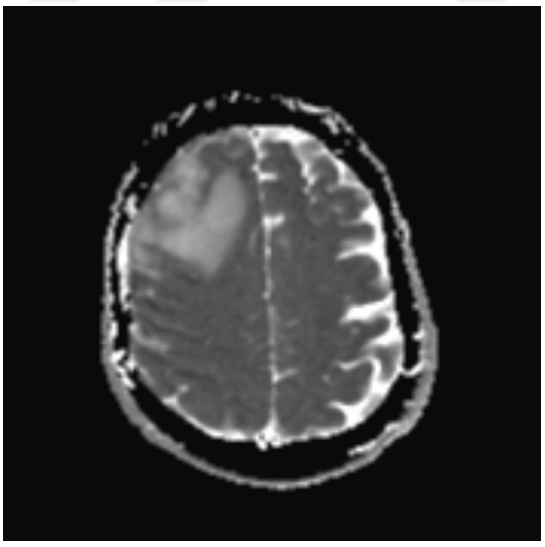


Image 4.17: Saggital T1 of Anaplastic Oligodendroglioma

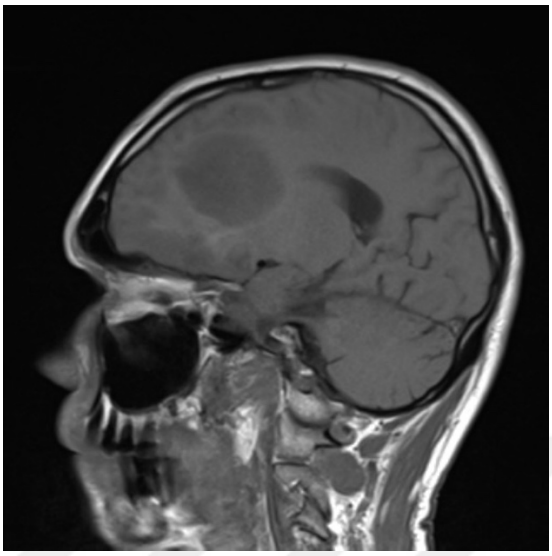
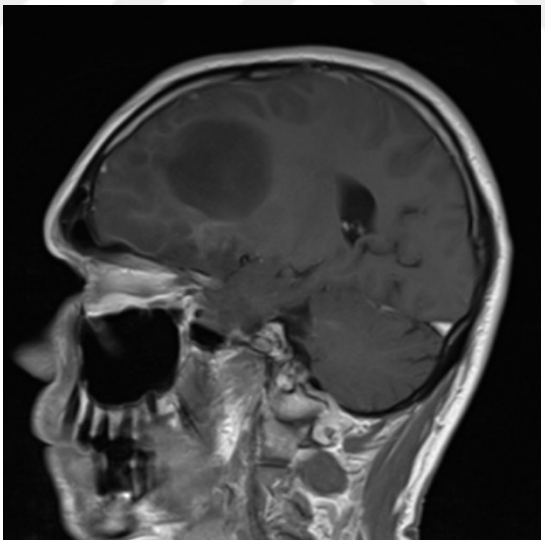


Image 4.18: Saggital T1 C+ of Anaplastic Oligodendroglioma



Source: Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 55579

c. Glioblastoma

Image 4.19: Axial FLAIR of Glioblastoma

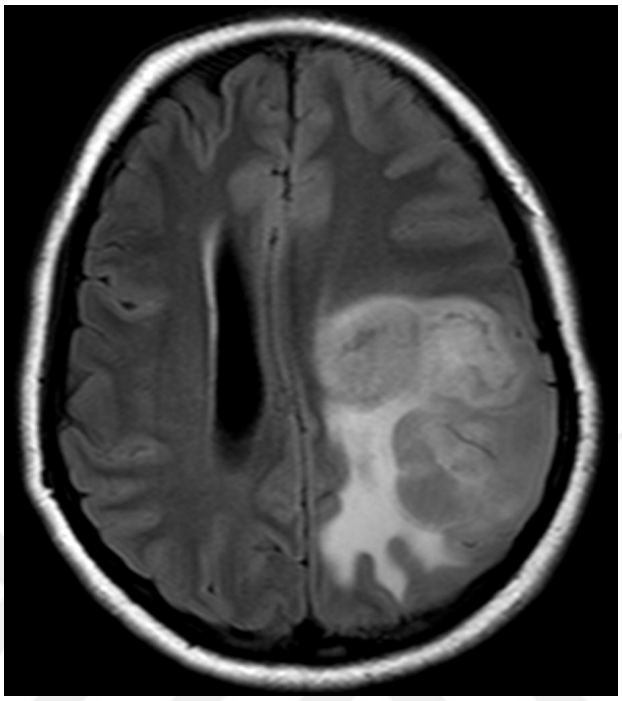


Image 4.20: Axial Inversion Recovery of Glioblastoma

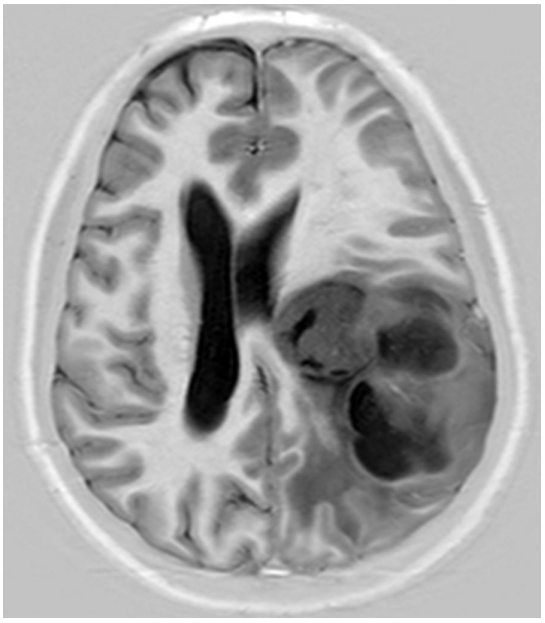


Image 4.21: Axial T1 C+ of Glioblastoma

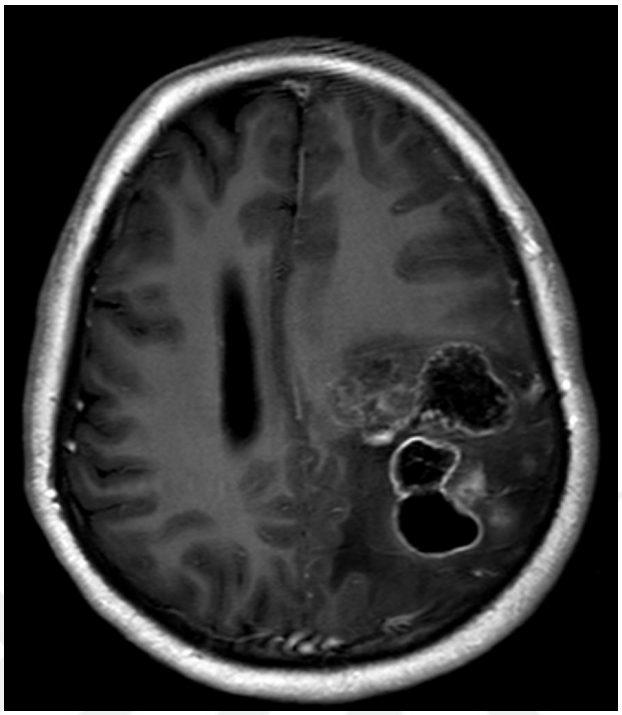


Image 4.22: Coronal T1 C+ of Glioblastoma

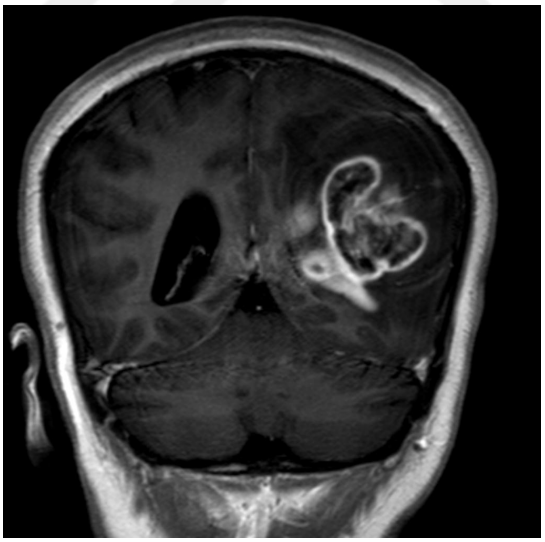


Image 4.23: Axial DWI of Glioblastoma

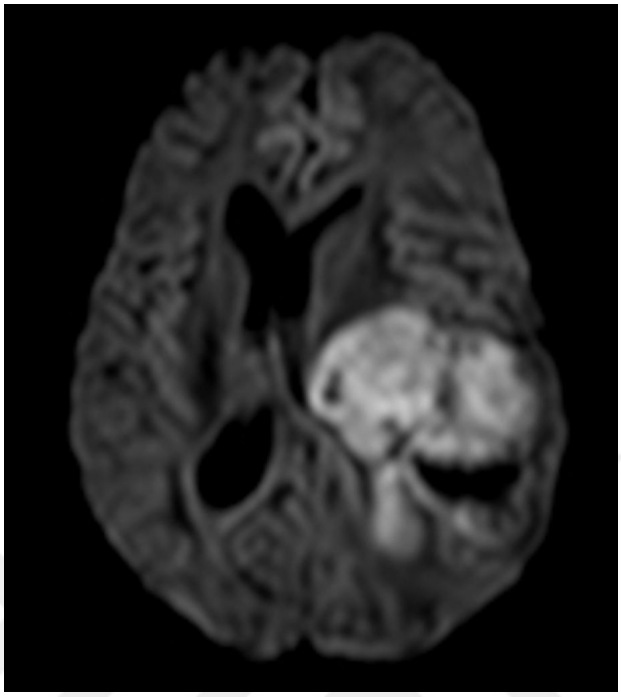
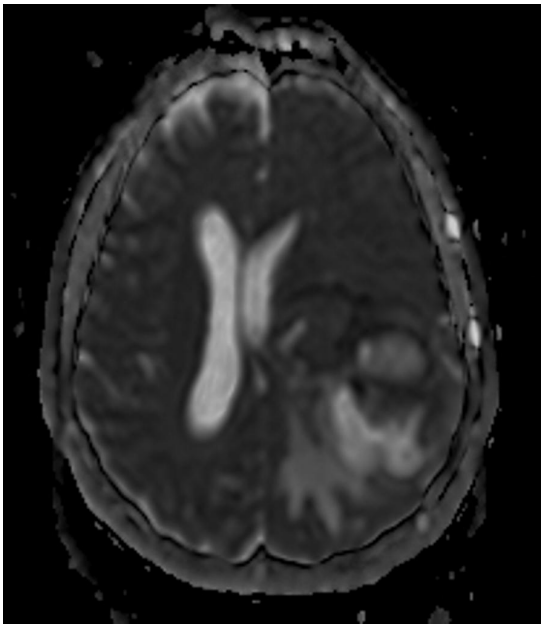


Image 4.24: Axial ADC of Glioblastoma



Source: Case courtesy of Dr Hani Salam, Radiopaedia.org, rID: 12502

d. Low Grade Glioma

Image 4.25: Axial T2 of Low Grade Glioma

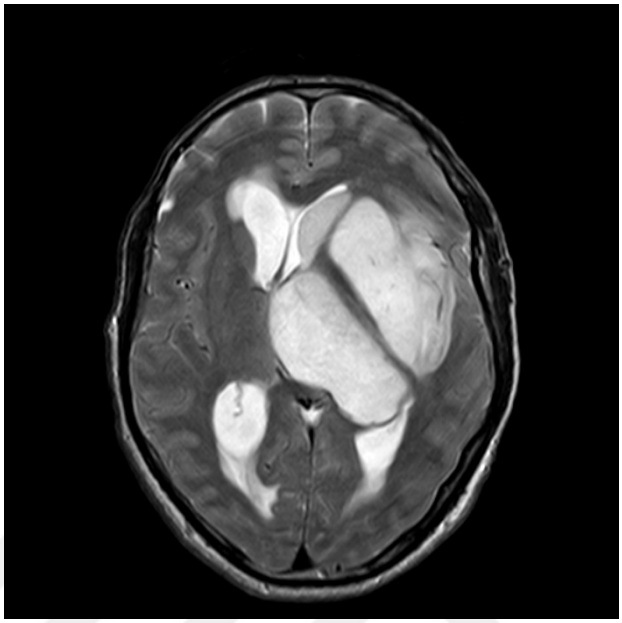


Image 4.26: Axial FLAIR of Low Grade Glioma

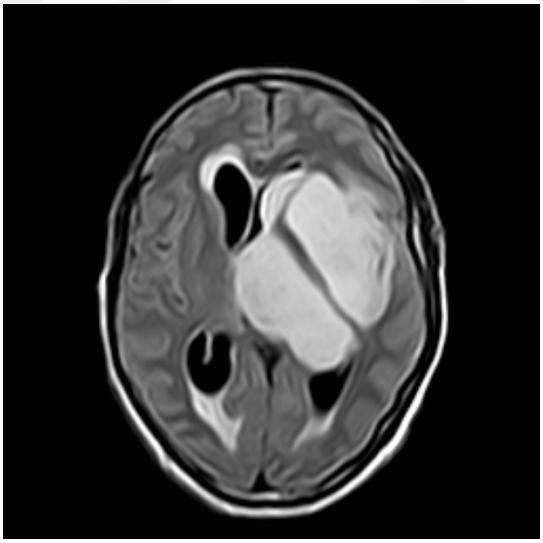


Image 4.27: Saggital T1 of Low Grade Glioma

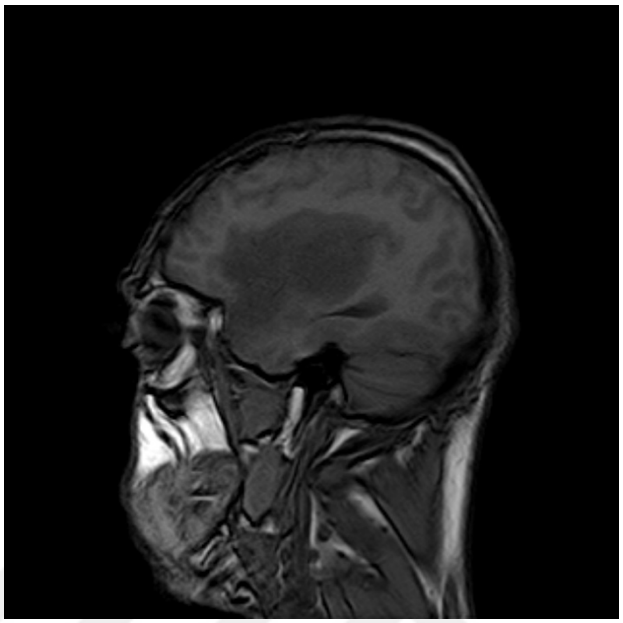
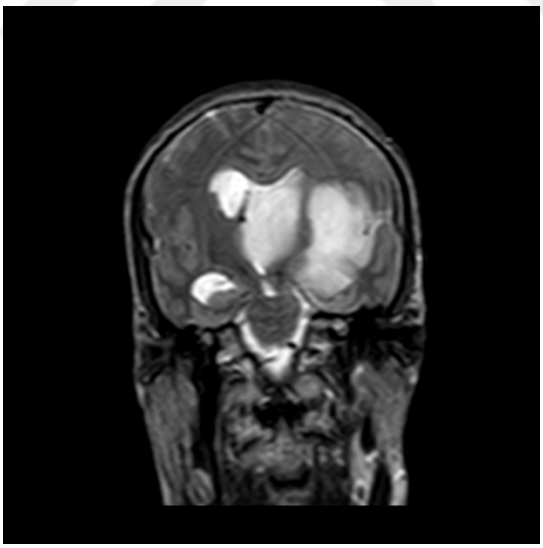


Image 4.28: Coronal T1 of Low Grade Glioma



Case courtesy of Dr Ahmed Abdrabou, Radiopaedia.org, rID: 36657

e. Meningioma

Image 4.29: Axial FLAIR of Meningioma

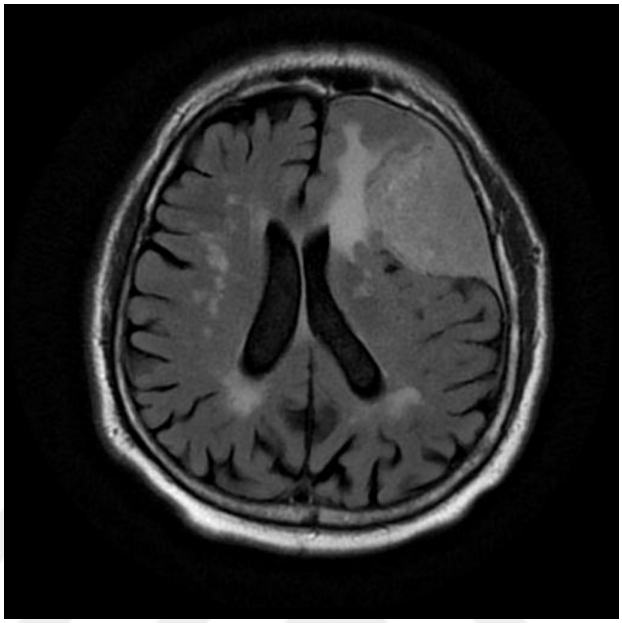


Image 4.30: Axial T1 of Meningioma

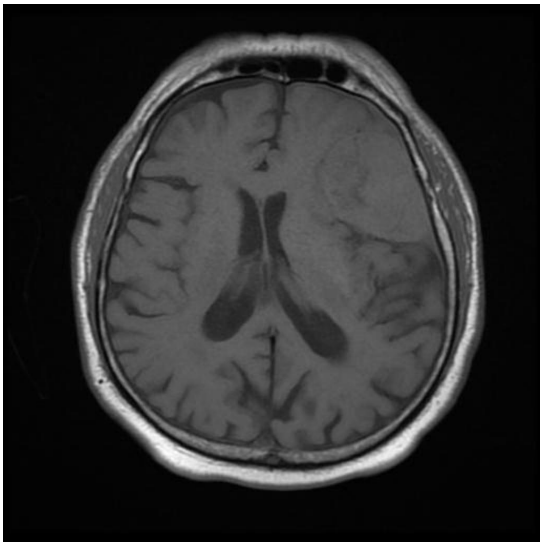


Image 4.31: Axial T1 C+ fat sat of Meningioma

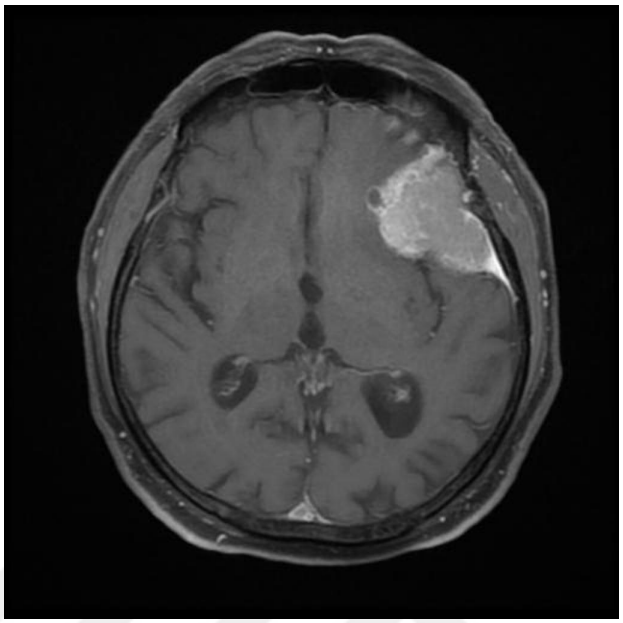
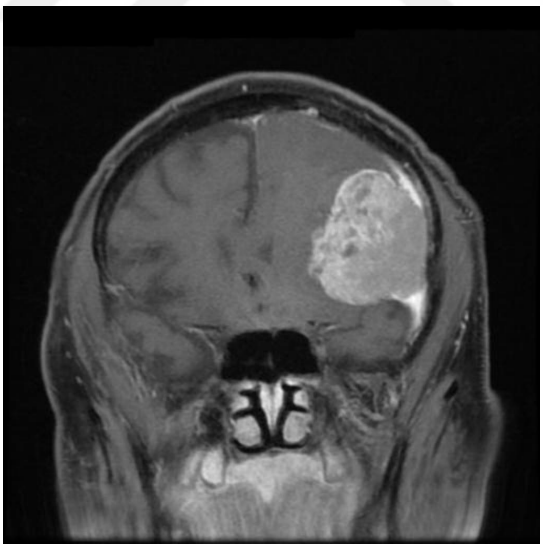


Image 4.32: Coronal T1 C+ fat sat of Meningioma



Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 30745

f. Pituitary Adenoma

Image 4.33: Saggital T1 of Pituitary Adenoma

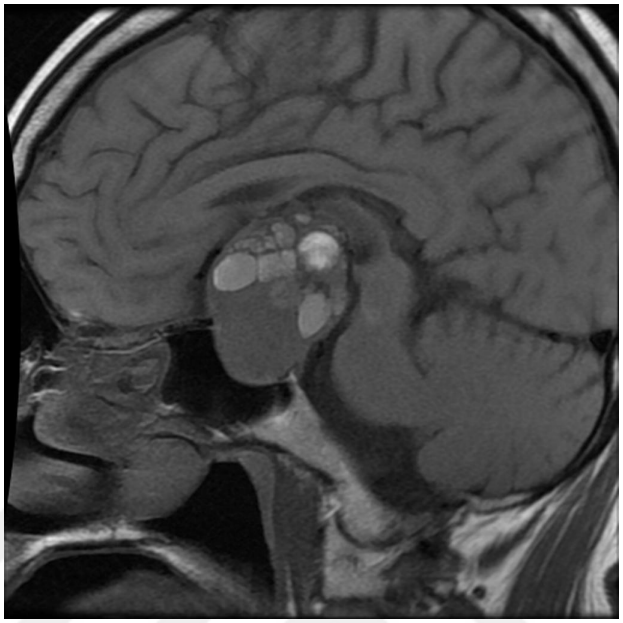


Image 4.34: Saggital T1 C+ of Pituitary Adenoma

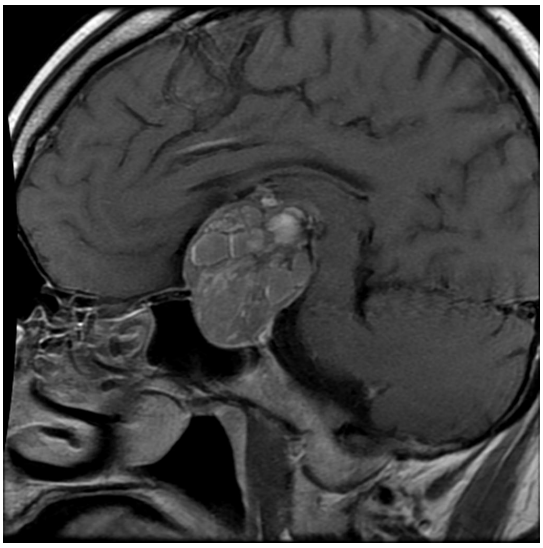


Image 4.35: Axial FLAIR of Pituitary Adenoma

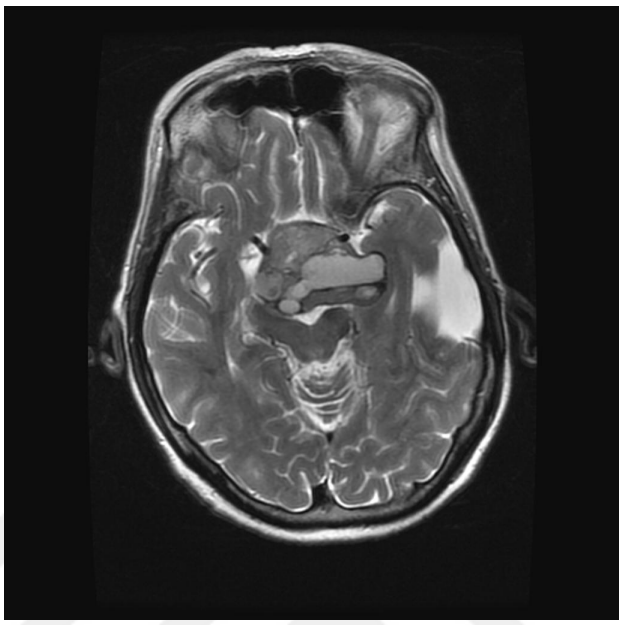
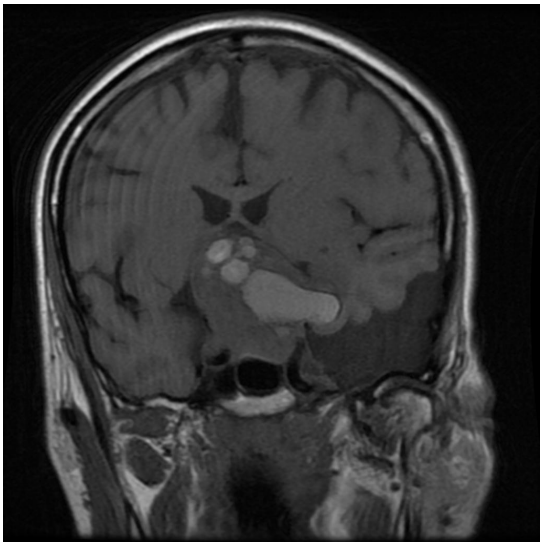


Image 4.36: Coronal T1 of Pituitary Adenoma



Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 4976

We used the following configuration for our experiments.

CPU	Intel i7 8th Generation 3.5 GHz
Memory	32 GB 2133 MHz LPDDR3
Storage	1TB Dedicated Flash Storage

5. RESULTS

In our experiments, magnetic resonance images of 1.900 cases were analyzed with the algorithm and the following results were obtained. Of these, 1,641 patients with radiology-confirmed brain tumours were operated and 359 were included in the test dataset for validation purposes, and the radiology department confirmed that there were no brain tumours.

Table 5.1: Experiment Results

Tumour Type	**Cases M**	**Cases F**	**Cases T**	**Accuracy M**	**Accuracy F**	**Accuracy O**
Acoustic Neuroma	51	18	69	94,0192%	89,8327%	91,92595%
Pilocytic Astrocytoma	11	18	29	89,5412%	90,0107%	89,77595%
Low-grade Astrocytoma	24	47	71	90,5713%	89,9894%	90,28035%
Anaplastic Astrocytoma	4	7	11	90,2878%	91,8994%	91,0936%
Glioblastoma	211	109	320	96,8764%	94,6802%	95,7783%
Ependymoma	16	24	40	89,4351%	88,8273%	89,1312%
Optic Nerve Glioma	6	19	25	84,8724%	83,8301%	84,35125%
Medullablastoma	2	1	3	84,3732%	82,1283%	83,25075%
Meningioma	68	98	166	91,2304%	91,1912%	91,2108%
Glioma (Low Grade)	381	232	613	90,2383%	90,1381%	90,1882%
Oligodendroglioma	41	57	98	88,1913%	86,1123%	87,1518%
Pineal Tumour	17	6	23	81,1931%	80,1831%	80,6881%
Pituitary Glioma	32	41	73	78,1927%	79,2911%	78,7419%
Healthy	187	172	359	98,8126%	99,1109%	98,96175%
	Total			**Average**		
	1.051	**849**	**1.900**	**89,131071%**	**88,3732%**	**88,752136%**

6. CONCLUSION

In this study, we aimed to implement a decision support application for the diagnosis of brain tumours from neuro-oncology processes by investigating the potential of information technologies to contribute to clinical processes. For this purpose, our algorithm has a remarkable capacity even when it is operated with limited hardware. The analysis of a magnetic resonance scan using the hardware specified by the algorithm takes approximately 107.3 seconds. This means with the given configuration; our approximate capacity is about 33 analysis per hour and 804 analysis per day. When we compare the capacity reached for an investment of approximately 800 USD with the investment costs in the field of health, we see that it is possible to reach a very high analysis capacity with an extremely low investment cost.

In our study, the results obtained by processing magnetic resonance images of different resolutions obtained from different sources reveal the necessity of study for use in clinical processes. However, considering the non-standard, complex structure and different resolution levels of the mean consistency level that we have reached, it is possible to achieve higher consistencies and higher process performances if our studies are carried out with more samples.

When this study has reached sufficient maturity, we think that in neuro-oncology, it can support clinicians by playing an essential role in minimizing the error rate in diagnosis and accelerating the diagnostic process.

6.1 LIMITATIONS AND FUTURE WORK

The most important limitation of our study was the insufficient number of cases we studied. The main reasons for this restriction are:

Magnetic resonance images of the cases belong to the patients treated by the Neurosurgery team of Bahçesehir University Faculty of Medicine. These magnetic resonance images over a wide range of time vary considerably due to the equipment and imaging parameters used.

Another limitation was the fact that we only used the data obtained from open sources for the optimization of the algorithm and the limited number of patients with data on the treatment process.

Since we are working with real and validated cases, we have not used a data transformation or an anomaly correction technique to optimize the algorithm.

In the upcoming period, we aim to train our model with more patient data to increase the consistency rate of different tumour types and to perform staging of the tumour by including magnetic resonance spectroscopy data.