



Review Article

An Overview of Central Nervous System Tumours

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Abstract

Central Nervous System (CNS) tumours refer to tumours that occur in the tissues of the brain and/or spinal cord. These tumours arise as a result of abnormal growth of cells and may begin in different parts of the brain or spinal cord. There are many types of CNS tumours, which are further divided into subtypes. Despite decades of research conducted, CNS tumours remain among the deadliest of all cancers. It is most often challenging to treat these tumours, due to the risks involved, and biological characteristics associated with them. The classification, grading, and characterisation of CNS tumour plays a pivotal role in the management thereof. The current review provides an overview of CNS tumours, classification, grading and treatment, as well as their characterisation with specific focus on gliomas, ependymomas, oligodendrogliomas, meningiomas, medulloblastomas, schwannomas, gangliogliomas, and craniopharyngiomas.

Keywords: Central Nervous System; Tumours; Gliomas; Astrocytomas; Ependymomas; Meningiomas; Medulloblastomas; Schwannomas; Gangliogliomas; Craniopharyngioma.

1. Introduction

Cancer is a disease that has been around for thousands of years with the earliest known medical description dating back to 2500 BC, in ancient Egyptian text. It was first described as a “bulging tumour in the breast, like touching a ball of wrappings”. Thousands of years later, researchers are still searching for an effective form of treatment. Cancer has become one of the leading causes of mortality worldwide. However, since then tremendous strides have been made in attempting to understand the genetics and biology of tumours, with the consensus being, that cancer develops from both genetic instability and exposure of cells to different micro-environmental factors. Simply, cancer can be defined as the uninhibited growth of cells, which results in cellular dysfunction due to the level of aggressive growth. The incidence of primary malignant brain tumours has continued to increase over the past 30 years, especially in elderly persons. Cancer metastasis to the CNS occurs more frequently, with an estimated incidence of approximately 10 times that of primary brain tumours. It has been reported that approximately 20% to 40% of patients with systemic cancer will develop brain metastases.

Cancer is known to follow a multi-stage process, from the initial emergence of cancer cells to clonal masses or tumours, and to the subsequent distribution of cancer cells from the primary tumour to distant organs or tissue via the blood and lymphatic systems through the complex processes of invasion and metastasis. Metastasis remains a challenge in terms of treatment and is a major cause of cancer related mortalities. Cancer cells often undergo genetic mutations causing activation of their oncogenes and/or inactivation of their tumour suppressor genes, allowing the cells to evade growth suppressors, resist cell death, sustain proliferative signalling, encourage angiogenesis and replicative immortality and finally induce invasion and metastasis. One of the many challenges faced by researchers in the effective treatment

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of cancer is the combination of complex signalling pathways and multiple mechanisms, which permit cancerous cells to evade programmed cell death. CNS tumours include those of the brain and spinal cord.

The causes of these tumours are yet to be identified. However, there are various factors affecting the cell cycle progression that may play a role in the development of CNS tumours which include neoplastic processes, and the accumulation of multiple genetic mutations [1]. The histological classification of CNS tumours comprises phenotypic features obtained with optical and electron microscopy, as well as immunohistochemical aspects all aiming to identify the cell of origin, and its degree of differentiation [1]. Recent studies have shown that tumours with similar microscopic and histological features may behave differently depending on their molecular characteristics and genetic individuality [1]. Brain tumours are categorised based on their primary site location. These can either be supratentorial or infratentorial except for some tumours which have the ability to form in either of these locations. Discussed in this review are CNS tumours namely gliomas, ependymomas, oligodendrogliomas, meningiomas, medulloblastomas, schwannomas, gangliogliomas, and craniopharyngiomas together with their subtypes (Table 1).

Table 1. CNS tumour types and subtypes

CNS tumour type	Subtypes
Astrocytomas (Glioma)	Pilocytic astrocytoma Subependymal giant cell astrocytoma Pleomorphic xanthoastrocytoma Diffuse astrocytoma Anaplastic astrocytoma Glioblastoma multiforme
Ependymomas (Glioma)	Subependymoma Myxopapillary ependymoma Cellular ependymoma Papillary ependymoma Clear cell ependymoma Tancytic ependymoma Anaplastic ependymoma
Oligodendrogliomas (Glioma)	Anaplastic oligodendroglioma
Meningiomas	Meningothelial meningioma Fibrous meningioma Microcystic meningioma Transitional meningioma Psammomatous meningioma Angiomatous meningioma Secretory meningioma Metaplastic meningiomas Lymphoplasmacyte plasma-rich meningioma Atypical meningioma Clear cell meningioma Chordoid meningioma
Medulloblastomas	Wingless medulloblastoma Sonic Hedgehog medulloblastoma Group 3 medulloblastoma Group 4 medulloblastoma
Schwannomas	Ancient schwannoma Cellular schwannoma Melanotic schwannoma Plexiform schwannoma Epithelioid schwannoma
Gangliogliomas	Anaplastic ganglioglioma
Craniopharyngiomas	Adamantinomas craniopharyngioma Papillary craniopharyngioma

2. Treatment of CNS Tumours

Surgery is usually one of the first steps in the treatment of CNS tumours and involves the resection of a tumour and nearby tissues from the body [2]. Surgery works best on solid tumours that are contained in a certain area removing some, but not all, of a cancer tumour [3]. Surgery is most often used to resect tumours that cause pain or pressure to an affected individual [4]. Surgical resection is believed to be beneficial in alleviating some of the symptoms associated with CNS tumours especially in patients with large tumours which are life threatening [5]. Surgery provides benefits such as the resection or isolation of tumour to establish a diagnosis [6]. In addition, it affords the opportunity to resect as much tumour as safely as possible to relieve mass effect, reduce swelling and facilitate response to adjuvant therapies, when indicated [3]. It is often the preferred method of treatment when a tumour can be resected with minimal risk of neurological damage.

In addition, radiation plays a pivotal role in the treatment of CNS tumours. Radiation therapy utilises high-dose radiation to kill cancerous cells [7]. Radiation, also referred to as X-rays, gamma rays, or photons either kills tumour cells directly or interferes with their ability to grow [7]. Radiation can affect both normal cells and tumour cells however, following standard doses of radiation, healthy cells repair themselves more quickly and completely than tumour cells [8]. As the radiation treatments continue, an increasing number of tumour cells die [9]. The tumour shrinks and the dead cells are broken down and disposed of by the body's immune system. Radiation has a more local effect targeting the deoxyribonucleic acid (DNA) in cells [10]. Radiation breaks down the DNA into pieces, which may inhibit the growth of cancer cells. Radiation therapy is complementary to surgery in a sense that radiation treats the microscopic disease that may be left behind following the resection [11].

In addition, the blood brain barrier (BBB) is known to restrict approximately 98% of small molecule therapies from entering the brain, hence radiation plays an important role in the treatment of brain cancer [12]. Radiation is also useful in shrinking a tumour before surgery or reduce tumour-related symptoms [10]. Furthermore, chemotherapy also plays a key role in the treatment of CNS tumours. It aims to kill cancerous cells by utilising medications that target rapidly dividing cells, preventing them from spreading or slowing their growth [13]. Chemotherapy is also known to shrink tumour cells however, the side effects may be severe.

Traditional or conventional chemotherapy directly kills cancer cells in a number of different ways, including induction of DNA damage, inhibition of protein synthesis, and the inhibition of cell division and new blood vessel formation [14]. Chemotherapy drugs can be administered via a number of different routes however, there are factors that may influence the efficacy, including drug resistance, and tumour factors such as mutations and metastasis [15]. Chemotherapy is commonly used following radiation in the treatment of CNS tumours however, it is often associated with adverse effects some of which can be managed [16].

3. Gliomas

Glial cells are non-neuronal cells that provide a supporting structure to the CNS and thus play an important role in the brain [17]. They are responsible for guiding neurons to their specific destination, buffering ions and chemicals that would otherwise cause harm to neurons and provide a myelin sheath around the axons [18]. As a result, neurons are unable to function without them [17]. There exists a number of subtypes of glial cells, some of which include astrocytes, oligodendrocytes and ependymal cells with each cell responsible for carrying out a particular function. Gliomas are one of the most common types of brain tumours that can occur in both the brain and spinal cord [19]. Gliomas are believed to have been derived from neuroglial stem or progenitor cells [20]. These tumours begin in the "gluey" supportive cells also known as the glial cells that surround nerve cells, helping them function and maintaining the BBB [19, 21]. Gliomas can affect the normal functioning of the brain and have the potential to be life-threatening depending on its location as well as its growth rate [22].

3.1. Classification and Grading of Gliomas

Gliomas are classified according to the type of glial cell involved in the tumour, as well as the tumour's genetic features [23]. These factors can help predict how the tumour will behave over a period of time as well as possible treatment regimens. The degrees of malignancy of tumours have been classified by the World Health Organization (WHO) and are graded I-IV on the basis of morphological and functional features with grade IV tumours being the most abnormal or aggressive cells [19, 21]. The grade of a specific tumour will ultimately determine an individual's prognosis and treatment options [24]. Gliomas are classified into three different subtypes based on their histopathologies i.e. astrocytomas, ependymomas and oligodendrogliomas [19, 21].

3.1.1. Astrocytomas

The most common gliomas are astrocytomas, a type of cancer that can form in the brain or spinal cord as a result of a tumour formed by mutated cells called astrocytes [25, 26]. Astrocytes are responsible for supporting nerve cells by

maintaining the BBB, providing nourishment to neurons as well as recycling neurotransmitters [27, 28]. Astrocytes are star-shaped cells that can give rise to astrocytomas. The symptoms associated with astrocytomas are highly dependent on the location of the tumour. Astrocytomas that occur in the brain can cause seizures, nausea and headaches whereas those that occur in the spinal cord can cause weakness and disability in the affected area [27, 29]. Astrocytomas have the ability to grow slowly however, they can also become quite rapid [29]. These types of tumours are graded to describe the degree of abnormality.

In general, tumour grading is made by analysing the tumour cells under the microscope and is based on the following features i.e. i) atypia, ii) mitosis, and iii) presence of newly vascular proliferation [30]. This is further integrated by the analysis of tumour's genetic features, i.e. DNA analysis of the tumour cells. Astrocytomas are further classified into the following subtypes namely pilocytic astrocytomas, subependymal giant cell astrocytomas, pleomorphic xanthoastrocytomas, diffuse astrocytomas, anaplastic astrocytomas and glioblastomas (GBM).

3.1.1.1. Pilocytic Astrocytomas

Pilocytic astrocytomas (PAs) are benign, slow growing tumours that stem from astrocytes [31]. They account for approximately 5-10% of diagnosed intracranial tumours taking into consideration all age groups [32]. Due to the fact that these tumours do not spread, they are categorised as grade I by the WHO making them the least aggressive type of cancer [33]. As its name suggests "pilocytic" refers to the hair-like cells with long bipolar processes found within these tumors [32]. PAs have the ability to arise anywhere in the CNS and are most typically found in the cerebellum [32, 34]. They have also been found to occur in the brainstem, near the optic nerve or hypothalamic region of the brain [34]. PAs are mostly localised and are therefore non-infiltrating into the surrounding brain tissue, it is therefore considered curative when removed completely [34], and does not require any other form of treatment such as chemotherapy or radiation. This type of tumour is most commonly found in children and young adults with symptoms including headaches, nausea and vomiting, fatigue as well as difficulty walking or balancing [34]. Essentially, a PA is a cystic tumour that is often successfully removed by surgery and has an excellent prognosis [34, 35].

3.1.1.2. Subependymal Giant Cell Astrocytomas

Subependymal Giant Cell Astrocytomas (SEGAs) are benign, grade I tumours that are composed of large ganglioid astrocytes located along the walls of the lateral ventricles of the brain [36]. These tumours comprise of spindled, epithelioid, or gemistocyte-like cells arranged in sweeping fascicles [37]. SEGAs are quite uncommon tumours and account for 1.5% of all paediatric brain tumours [38]. Tumours obstruct spinal fluid flow, thus causing hydrocephalus [39]. SEGAs usually occurs in association with a syndrome called tuberous sclerosis in approximately 6-16% of patients [36]. Patients with cerebrospinal fluid (CSF) flow do not experience any symptoms however, in patients where the CSF flow is disrupted the following symptoms namely, an increase in CSF pressure, headaches accompanied by nausea and vomiting, blurry vision, seizures as well as changes in one's personality are noted [40, 41]. Surgical resection is usually curative [39].

3.1.1.3. Pleomorphic Xanthoastrocytomas

Pleomorphic xanthoastrocytomas (PXAs) are a rare, grade II brain tumour that originate from astrocytes and primarily affects children and young adult [42]. This tumour comprises less than 1% of all astrocytoma's and has the tendency to develop in the cerebral hemisphere of the brain or the leptomeninges and are commonly associated with seizures [42, 43]. As per the WHO, these tumours are characterised by large pleomorphic and multinucleated cells, spindle and lipidised cells, a dense pericellular reticulin network, as well as a number of eosinophilic granular bodies. Some of the common signs and symptoms associated with this tumour include headaches, nausea and vomiting [45]. In comparison to diffusely infiltrative astrocytoma's, PXAs were shown to have a favourable prognosis [46]. Surgery is usually curative.

3.1.1.4. Diffuse Astrocytomas

Diffuse astrocytomas (DAs) are slow growing, grade II tumours that are believed to arise from astrocytes in the cerebral hemisphere of the brain [47, 48]. As its name suggests these tumour cells have the tendency to grow and infiltrate normal, healthy tissue making them difficult to remove completely during surgery [49]. Appearance of the tissue is only moderately different from a normal brain, however, cells appear abnormal under the microscope and slightly increased in number [50]. Some common symptoms associated with diffuse astrocytoma's include headaches and seizures [47]. Additional symptoms may occur and are dependent on the location and size of the tumour as well as its impact on a patient's neurological function. DAs can be divided into subtypes based on genetic characteristics. These tumours may present with abnormal genetic signatures such as mutations in the isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) genes which can affect patient prognosis and treatment [51, 52]. Diffuse astrocytoma's are invasive tumours which indicates that surgery alone may not be enough to have curative effects [53].

3.1.1.5. Anaplastic Astrocytomas

Anaplastic Astrocytomas (AAs) are a rare, malignant form of brain tumour [54]. These tumours are referred to as high grade astrocytomas (grade III) having acquired more aggressive features, including a higher pace of growth and a higher degree of invasiveness into the brain [55]. Their molecular pathology has further divided them into a number of molecular subtypes on the basis of interrogation of 1p/19q codeletion, transcriptional regulator (ATRX), IDH1 and mutations in the p53 gene [56]. The specific cause of this tumour is unknown [57]. However, there has been much speculation that genetic or immunological abnormalities, environmental factors, diet and stress may be contributing factors in causing this type of cancer [58]. AAs develop from astrocytes. They can develop in any area of the CNS however, they seem to have a preference for the cerebrum [56]. The symptoms of anaplastic astrocytomas vary depending on the location and size of the tumour. Many of the symptoms associated with these tumours are due to an increase in pressure within the brain which may be as a result of the tumour itself or blockages of the ventricles in the brain [59]. Some signs and symptoms include headaches, vomiting, drowsiness as well as changes in a patient's personality or mental status [56]. Surgery alone is not curative. Radiation and chemotherapy almost always follow surgery.

3.1.1.6. Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most aggressive and malignant grade IV tumour, where a large portion of tumour cells are reproducing and dividing at any given time [60]. GBM tumours are nourished by an abundant and abnormal tumour vessel blood supply. GBM is characterised by very abnormal-appearing cells, proliferation, areas of necrotic tissue and formation of new vessels [60]. GBM tumours are infiltrative and invade into nearby regions of the brain [60]. They have the ability to spread to the opposite side of the brain through connection fibres [61]. However, it is quite rare to see glioblastomas spread to other areas outside of the brain [62]. GBM can occur at any age but tends to occur more often in older adults. It can cause worsening headaches, nausea, vomiting and seizures. These tumours are quite difficult to treat and a cure is often not possible [19]. Treatments may slow down the progression of the cancer and reduce signs and symptoms. Surgery is the main form of treatment for GBM [19]. The aim of surgery is to remove the bulk of the tumour and reduce intracranial pressure without causing any neurological injury [63]. Due to the fact that GBM is surrounded by migrating and infiltrating cells, complete removal of the tumour is rather impossible [63]. Surgery is usually followed by radiation and chemotherapy. Radiation is aimed at killing the remaining tumour cells. In chemotherapy, patients are administered special drugs designed to kill tumour cells. Chemotherapy using the drug, temozolomide is the current treatment strategy for GBM [64].

3.1.1.7. Treatment of Astrocytomas

Despite multimodality in the treatment of astrocytomas, the survival rate of patients with malignant gliomas remains quite poor [4]. Apart from diagnostic therapy, surgical resection has been widely used in the treatment of astrocytomas and presents with the advantage of controlling symptoms associated with large tumours [4]. Radiation treatment has also been used and is believed to be one of the most effective forms of treatment of astrocytomas. Radiation therapy almost always follows surgery [4, 65]. Lastly, chemotherapy has been used as an adjuvant (following radiation therapy) in the treatment of astrocytomas [65]. Research studies have suggested that the use of the drug, temozolomide could potentially enhance the efficacy of radiation in the treatment of glioblastomas [4].

3.1.2. Ependymomas

An ependymoma is a type of tumour that originates in the ependymal cells in the brain or spinal cord [66]. Ependymomas line the passageways where cerebrospinal fluid that nourishes the brain flows [67]. Ependymal cells form the lining of the fluid cavities in the brain and can give rise to ependymomas [68]. These are relatively rare tumours, accounting for less than 2% of all primary brain tumours and about 7% of all gliomas [69]. These types of tumours can occur at any age, however, they are most prevalent in young children accounting for 5% of childhood brain tumours [70]. In adults, 60% of these tumours are found in the spinal cord and may cause weakness in the part of the body controlled by the nerves that are affected by the tumour [71]. In children, 90% of ependymomas are found in the brain, with the majority located in the posterior fossa [71].

These tumours have the ability to spread to other parts of the brain or spinal cord through the CSF [71]. Symptoms of ependymoma are related to the location and size of the tumour. Older children and adults experience headaches, vomiting and seizures [72]. In comparison with the outcomes of other paediatric brain tumours, the outcome for ependymomas is quite poor (5-year overall survival rate for children is approximately 39-73%) [73]. Ependymomas are graded I-IV by the WHO and are comprised of the following subtypes namely, subependymomas, myxopapillary ependymomas, cellular ependymomas, papillary ependymomas, clear cell ependymomas and tanycytic ependymomas.

3.1.2.1. Subependymomas

Subependymomas (SEs) are benign, WHO grade I tumours that are slow growing and non-invasive [74]. SEs are a rare type of ependymoma that develops from the glial cells that line the ventricles of the brain and the spinal cord [75]. Cells appear as clusters, embedded in a hypocellular fibrillary matrix [74]. These lesions have the ability to block spinal fluid flow, as a result placing pressure on surrounding structures, resulting in symptoms including headaches and confusion [76]. The actual incidence of these tumours has been difficult to establish as patients usually remain asymptomatic [74]. Tumours can occur in all age groups however, tend to occur more in middle aged and older individuals with a slight predilection for males [77]. These tumours have also been shown to occur in children [78]. Although typically asymptomatic, small lesions have been incidentally reported [77, 79]. In patients with larger tumours, elevated intracranial pressure as a result of obstructive hydrocephalus has been noted [80]. Surgery is usually curative with an overall good prognosis and survival rate [74].

3.1.2.2. Myxopapillary Ependymomas

Myxopapillary ependymomas (MPEs) are slow-growing ependymomas that are usually considered to be benign, low-grade tumours (grade I) [81]. MPEs are a variant type of ependymoma that occurs mainly in the filum terminale or conus medullaris [81]. Upon macroscopic analysis, cells are found to be encapsulated, lobulated, and sausage or oval shaped. Tumours can be found in children as well as adults [66]. The cause of ependymomas is unknown. Symptoms of an ependymoma are related to the location and size of the tumour and may include nausea, vomiting, headache, low back or leg pain, numbness, bowel or bladder symptoms [82]. In some cases CSF dissemination occurs and multiple lesions have been seen [83]. Some lesions have the tendency to become aggressive and metastasize to other part of the body. This aggressive behaviour is most commonly seen in children [84, 85]. MPEs can be cured if all of the tumour has been removed during surgery (total resection) [86] and usually presents with an excellent prognosis.

3.1.2.3. Cellular Ependymomas

Cellular ependymomas (CEs) are one of the most common intramedullary subtype of spinal cord ependymomas [87]. This tumour is the primary spinal cord tumour in adults and the second most common spinal cord tumour in children [87]. CEs are characterised by hypercellularity and a high nuclear-to-cytoplasm ratio with few rosettes however, lacks the microvascular proliferation, cellular pleomorphism, or mitoses that correspond to grade III lesions [88]. These tumours are usually identified by deletions and translocations of chromosome 22.

3.1.2.4. Papillary Ependymomas

Papillary ependymomas (PEs) are tumours that occur in the brain [89]. They are a rare variant of ependymoma resembling choroid plexus papilloma [88]. Apart from their location in the brain, there have been a few cases that have been reported in the spinal cord [90]. These tumours are classified as WHO grade II [90]. PEs present with papillae and finger-like projections that are lined by single or multiple layers of cuboidal cells with a smooth contiguous surface [89].

3.1.2.5. Clear Cell Ependymomas

Clear cell ependymomas (CCEs) are classified as grade II by the WHO [91]. Tumours are commonly supratentorial and cystic [88]. Tumour cells are non-infiltrative and have rounded nuclei with perinuclear clear halos and focal perivascular pseudorosettes [92]. In some cases these cells can present with anaplastic features [92, 93]. CCEs can be distinguished from other tumours based in their classic ependymal rosettes and perivascular pseudorosettes [92]. In comparison to most ependymomas, CCEs are known to be quite aggressive and display early recurrence despite total resection [93].

3.1.2.6. Tanycytic Ependymomas

Tanycytic ependymomas (TEs) are a rare form of ependymoma that forms within the brain or intramedullary spine and are classified as WHO grade II tumours [94]. These tumours are derived from tanocytes, common progenitor cells of both ependymal cells and astrocytes [95]. They are elongated, bipolar and bridge the ependymal lining with the capillary wall. Given its intertwined position it is believed to play a role in communication between the CSF, the brain parenchyma, and the vasculature [94]. The reported tanycytic forms of ependymoma are almost always intramedullary lesions. In these lesions fibrillar cells replace the classic ependymal rosettes and perivascular pseudorosettes [88, 94]. This tumour comprises clusters of elongated cells that form nuclear dense zones and streaming cell processes forming fibrillary zones [96]. These tumours closely resemble schwannoma and pilocytic astrocytoma's therefore making it difficult to diagnose [94].

3.1.2.7. Anaplastic Ependymomas

Anaplastic ependymoma (AEs) are fast growing, malignant, grade III types of ependymoma, that form when cells in

the CNS start to multiply rapidly [97]. An ependymoma is considered anaplastic if the cells grow very quickly and are significantly unusual in shape [88]. The exact cause of an AE is not known however, it is believed that certain changes such as somatic mutations in specific genes enable the cells to start growing quickly. Signs and symptoms of an AE vary depending on the age of the person and the location of the tumour. Some of the common symptoms associated with a brain tumour include headaches, nausea and vomiting, seizures and lethargy. Children may present with hydrocephalus [80]. Adults and children that present with anaplastic ependymoma in the spine often experience pain, weakness, neck stiffness and in some cases even paralysis. The standard treatment for AEs includes surgical resection.

3.1.2.8. Treatment of Ependymomas

The primary treatment for ependymomas include surgery however, for more aggressive tumours that are unable to be removed completely with resection, radiation therapy or chemotherapy are recommended [80]. The first step in treating ependymomas includes tumour resection which aims to remove as much of the tumour as possible [80]. Even in cases when the growth has been completely removed through surgery, radiation therapy is recommended. However, radiation is rarely performed on young children as it could potentially affect the developing brain. Radiation following surgery is therefore typically recommended for older children and adults to target tumour areas which could not be completely removed through surgical intervention [98]. Chemotherapy may also be used to treat recurring tumours, which appear following treatment with radiation. Chemotherapy is the preferred choice for use in infants and young children as opposed to radiation therapy [98].

3.1.3. Oligodendrogliomas

Oligodendrogliomas are a type of glioma that is believed to originate from the oligodendrocytes of the brain or a glial precursor cell [20]. They occur primarily in adults but are also found in children accounting for approximately 10% of all primary brain and CNS tumours [26]. These grade II tumours are predominantly found in the brain, however, can also be found in the spinal cord [99]. Oligodendrogliomas originate from oligodendrocytes. These cells produce a substance that protects nerve cells. These branches wrap themselves around neurons producing a fatty substance made of lipoprotein called myelin, which helps transmit electrical impulses along the axons [99]. Oligodendrocytes are cells with short arms forming the insulation of neurons that can give rise to oligodendrogliomas. They are genetically defined as diffuse gliomas with hallmark molecular features such as mutations in IDH1 or IDH2 genes and codeletion of chromosomes 1p and 19q [99, 100]. Signs and symptoms associated oligodendrogliomas may include seizures, headaches as well as personality changes. Weakness or disability can occur in the part of the body that is controlled by the nerve cells affected by the tumour. Oligodendroglioma treatment usually involves surgery to remove the tumour [101]. Additional treatments may however be necessary if the tumour is aggressive or is likely to recur. Oligodendrogliomas are further classified as anaplastic oligodendrogliomas.

3.1.3.1. Anaplastic Oligodendrogliomas

Anaplastic oligodendrogliomas (AODs) are classified as a grade III neuroepithelial tumour thought to originate from oligodendrocytes [99]. Statistics reveal that these tumours comprise 0.5-1.2% of all primary brain tumours [102]. These are fast growing, malignant tumours that have a preference for occurring in the frontal lobe and is also commonly found in the temporal lobe [103]. As seen with oligodendrogliomas, AODs also present with a codeletion of the short arm of chromosome 1p and the long arm of chromosome 19q [104, 105]. The most common symptom includes seizures [103]. Surgery is often carried out to help reduce some of the symptoms that are associated with the tumour.

3.1.3.2. Treatment of Oligodendrogliomas

Surgery is a mainstay therapy of oligodendrogliomas. Surgery is performed to remove as much of the oligodendroglioma as possible without interfering with healthy brain tissue [103]. Awake brain surgery, which is a specialised surgical procedure can be used to ensure that no damage or disruption occurs to sensitive brain tissue during surgery. Further treatments such as chemotherapy may be recommended following a surgical procedure should any tumour cells remain or if there is an increased risk that a tumour will recur [106]. It is often used after surgery to kill any remaining cancer cells. Chemotherapy can be combined with radiation therapy for the treatment of aggressive cancers [106]. For patients that are unable to undergo surgery, radiation therapy and chemotherapy may be used as a primary treatment.

4. Meningiomas

Meningiomas are the most common primary brain tumour originating in the CNS. Meningiomas start on the meningeal tissue that are thin membranes covering the brain and spinal cord just inside the skull [107]. Specifically, the tumour arise from the arachnoid mater of the layers of the meninges [108]. The prevalence of this tumour is higher in women than in men [109]. These tumours are graded I to III and often tend to be slow growing with as many as 90%

being benign [110]. Most meningiomas occur in the brain however, they also have the ability to grow on parts of the spinal cord. The majority of meningiomas are non-malignant, grade I, slow-growing tumours that are localised and non-infiltrating [111]. Meningiomas often present with no symptoms and do not require immediate treatment however, the growth of benign meningiomas have the ability to cause serious problems, in some cases often fatal [112]. Some meningiomas are classified as atypical [113], meaning that they are not considered to be benign or malignant however, they do possess the ability to become malignant over time. Symptoms associated with meningiomas include headaches, weakness on one side, seizures, personality and behavioural changes as well as confusion [110].

4.1. Classification and Grading of Meningiomas

Meningiomas are graded I to IV by the WHO and are divided into the following subtypes namely, meningothelial meningiomas, fibrous meningioma, microcystic meningiomas, transitional meningiomas, psammomatous meningiomas, angiomatous meningiomas, secretory meningiomas, metaplastic meningiomas, lymphoplasmacyte plasma-rich meningiomas, atypical meningiomas, clear cell meningiomas and chordoid meningiomas. Together meningothelial, fibrous and transitional meningiomas comprise approximately 80% of all meningiomas [113].

4.1.1. Meningothelial Meningiomas

Meningothelial meningiomas (MMs) are one of the most common histological subtypes of meningiomas. These tumours are classified as grade I [114] and are characterised by lobules of cells with a large cytoplasm and syncytia [115, 116]. Meningothelial cells play an important role in covering and protecting the brain and thereby assist in building the interface between the CSF and neuronal tissue. Meningothelial cells are also involved in immunological processes in the brain through the secretion of pro-inflammatory cytokines in response to various pathologically relevant stress conditions [117].

4.1.2. Fibrous Meningiomas

Fibrous meningiomas (FMs) are grade I tumours also known as fibroblastic meningiomas. They are the second most common histological subtype of meningioma and the most common intraventricular meningioma [118]. These tumours are characterised by elongated cells, with a spindly nuclei [117]. They also possess a sheet-like architecture and in many cases may not contain lobules or classic meningothelial whorls [119].

4.1.3. Microcystic Meningiomas

Microcystic meningiomas (MCMs) are a distinct histological variant of meningioma and are associated with atypical imaging appearances and therefore present with diagnostic challenges [120]. These tumours account for only 1.6% of intracranial meningiomas [117, 120]. Cells have elongated processes and loose myxoid background [121]. Overall, they resemble microcysts. The microcysts represent extracellular spaces, scattered throughout the meningioma substrate. These tumours usually also display abundant vascularity [122]. Gross total resection of the tumour is the recommended treatment of choice.

4.1.4. Transitional Meningiomas

Transitional meningiomas (TMs) (grade I) are also known as mixed meningioma. These tumours possess features of both meningothelial and fibrous subtypes of meningiomas [123]. Tumours present with admixed spindle cells [116]. They contain abundant whirling epithelioid cells or psammoma bodies [116].

4.1.5. Psammomatous Meningiomas

Psammomatous meningiomas (PMs) are a rare, grade I subtype of meningioma [111, 124]. Spinal meningiomas have been reported quite extensively and are characterised by heavily calcified spinal mass lesion together with numerous psammoma bodies. Intracranial lesions have also been identified [124, 116]. These tumours share common locations with typical meningiomas in the cranium. Surgical treatment aims for complete resection of a tumour, with the overall prognosis being heavily dependent on the resection.

4.1.6. Angiomatous Meningiomas

Angiomatous meningiomas (AMs) are another rare histological variant of meningiomas. These are grade I tumours which account for 2.1% of all meningiomas [125]. AMs are characterised by an abundance of blood vessels [126] (greater than 50% of a whole tumour) within a tumour with areas of classic meningothelial differentiation [127]. Treatment of AMs through resection has become more difficult than conventional meningiomas due to the fact that these tumours have a very rich supply of blood and there is a chance that intraoperative haemorrhage may occur.

4.1.7. Secretory Meningiomas

Secretory meningiomas (SMs) are quite an uncommon histological variant of benign (grade I) meningiomas with a

predilection for causing significant peritumoural edema which can lead to severe neurological and medical issues following postoperative management [128]. SMs are seen to contain glandular lumina with periodic acid-schiff (PAS)-positive, eosinophilic secretory globules (also known as pseudopsammoma bodies), which may be the cause of peritumoural edema [128]. These pseudopsammoma body inclusions are cytokeratin (CK) and carcinoembryonic antigen (CEA) positive. Elevated levels of CEA have been detected in peripheral blood in some patients [128].

4.1.8. Metaplastic Meningiomas

Metaplastic meningiomas (MPMs) are rare histological variants of benign meningiomas where tumour cells share the characteristics of tissues from other parts of the body. Cells are termed “metaplastic” due to the fact that their transformed neoplastic cells demonstrate the full histological characteristics of the cells they mimic [129]. MPMs are grade I tumours and their appearances are dependent on the type of tissue they express [130]. Example osseous meningiomas resemble mature bone, complete with bone marrow whereas lipomatous meningiomas contain areas of fat [130].

4.1.9. Lymphoplasmacyte Plasma-rich Meningiomas

Lymphoplasmacyte plasma-rich meningiomas (LPMs) are WHO grade I tumours, characterised by clearly visible infiltrates of lymphocytes and plasma cells as well as a proportion of meningeothelial elements [131]. These tumours have quite an unusual clinical course that mimics an inflammatory process [131]. LPMs are found more frequently in younger patients and do not possess gender predilection [131]. Despite presenting symptoms that are similar to other intracranial masses, the course is more acute mimicking an intracranial inflammatory disease.

4.1.10. Atypical Meningiomas

Atypical meningiomas (ATMs) are classified as WHO grade II and account for 20-30% of all meningiomas [132]. It is important to note that only since the WHO classification in 2007, an otherwise benign grade I tumour was promoted to grade II as a result of infiltration into brain parenchyma [133]. As a result of the new grading, the incidence of grade II tumours increased to approximately 30% [134]. ATMs are also a more aggressive form of meningioma [132]. Tumours are histologically characterised by i) 4 to 19 mitoses per ten high-power fields, ii) 3 or more of the following histologic features example sheet-like growth, necrosis, increased cellularity, small cell change, prominent nucleoli, and iii) direct invasion of brain parenchyma [110].

4.1.11. Clear Cell Meningiomas

Clear cell meningiomas (CCMs) present with a poor prognosis and a higher recurrence rate and are therefore considered WHO grade II tumours, irrespective of mitotic index, cellular atypia/anaplasia, or presence of brain invasion [135]. These tumours have been reported to occur more frequently in younger individuals [135] and are commonly found within the spinal canal and posterior fossa [49]. CCMs was shown to bear resemblance to meningeothelial meningiomas however, the tumour cells have vacuolated cytoplasm, therefore the moniker 'clear cell' [136]. Despite their benign appearing histology, tumours tend to recur locally (higher than 60% in some series), and particularly high in intracranial disease and metastasise within the CSF space [136].

4.1.12. Chordoid Meningiomas

Chordoid meningiomas (CMs) are uncommon histopathological variants of meningiomas representing about 0.5% of all meningiomas [137]. Tumours were shown to possess high proliferation and postoperative recurrence and were therefore designated grade II tumours [137]. Chordoid tumours can be found in a number of locations within the intracranial cavity accounting for approximately less than 1% of intracranial meningiomas [137]. Tumours were first described by Kepes et al. as having a chordoma-like histologic appearance with tumour cells in clusters. Tumours were also shown to have an association with Castleman's syndrome [138]. CMs were found to be histologically similar to chordomas containing cords (trabeculae) of eosinophilic vacuolated cells in a myxoid matrix [139]. The following features were also noted namely an increased cellularity, high mitotic rate, small cell change, sheet like growth, macro nucleoli and focal necrosis [137, 140].

4.2. Treatment of Meningiomas

The most common treatment for meningiomas include surgery. In cases of benign meningiomas, surgery alone is sufficient to treat the tumour. In many cases, radiation therapy follows surgery for most malignant meningiomas and has also been used in cases where surgery is not safe to perform [141]. The most common type of radiation treatment is external-beam radiation therapy. Lastly chemotherapy uses drugs to destroy tumour cells by preventing them from growing and dividing. Chemotherapy can be given intravenously or taken orally. Alternatively, it can also be given by injection into a muscle or directly into the CSF [141].

5. Medulloblastomas

Medulloblastoma is a cancerous (WHO grade IV) tumour also referred to as cerebellar primitive neuroectodermal tumour (PNET) [142]. Medulloblastoma is a fast growing, high-grade tumour that frequently spreads through the CSF to other parts of the CNS. Tumours occur in the posterior fossa but have the potential for leptomeningeal spread [142]. Gorlin's syndrome or Turcot's syndrome might increase one's risk of medulloblastoma. Medulloblastoma is the most common malignant brain tumour in children accounting for about 10% of all childhood brain tumours [142]. Signs and symptoms associated with medulloblastoma may include increased intracranial pressure such as headaches, nausea, vomiting, tiredness, dizziness, double vision, poor coordination, unsteady walk and other concerns. These symptoms may be related to the tumour itself or may be due to the build-up of pressure within the brain.

5.1. Classification and Grading of Medulloblastomas

Medulloblastomas are graded WHO IV and include the following subtypes: wingless (WNT) medulloblastoma, sonic hedgehog (SSH) medulloblastoma, group 3 medulloblastoma, and group 4 medulloblastoma.

5.1.1. Wingless Medulloblastomas

Wingless medulloblastomas (WNT) make up approximately 10% of all medulloblastomas [142]. They present with the best prognosis in comparison to the other subgroups [143]. This tumour subtype is typically located midline with involvement of the brainstem or in the cerebellar peduncle and cerebellopontine angle cistern [144]. WNT medulloblastomas are thought to arise from progenitor cells in the lower rhombic lip of the developing brainstem. They are predominantly found in children but can also be found in adults [142]. Approximately 90% of WNT tumours contain a mutation in *CTNNB1*, which encodes β -catenin [142]. This mutation causes the WNT signalling pathway to be constitutively active, driving the expression of WNT responsive genes that promote tumour proliferation.

5.1.2. Sonic Hedgehog Medulloblastomas

Sonic hedgehog (SSH) is the second most common subtype of medulloblastoma. SSH medulloblastomas are thought to arise in the cerebellar hemispheres as opposed to the midline location characteristic of other subgroups [142]. SHH tumours are believed to arise from granule cell precursors of the external granule layer. The majority of these tumours contain germline or somatic mutations or copy number alterations in the SHH signalling pathway, leading to constitutively activated SHH signalling, driving tumour development and progression [145]. Tumours occur most commonly in adults and infants but less frequently in children. There are four subtypes of SSH medulloblastomas and these include i) SHH α , found typically in children with TP53 mutations, ii) SHH β , found typically in infants, associated with a poor prognosis, iii) SHH γ found typically in infants with a good prognosis and iv) SHH Δ , found typically in adults with TERT promoter gene mutations [146, 147].

5.1.3. Group 3 Medulloblastomas

Group 3 medulloblastomas originate from a neural stem cell population and account for approximately 25% of all medulloblastoma cases [147]. Molecular characteristics associated with group 3 medulloblastomas include recurrent gene amplifications in the *MYC*, *MYCN* and *OTX2* genes [148]. These tumours are associated with high rates of metastasis (40%-45%) and are found predominantly in infants and children and very rarely in adults [147]. They are also characterised by very poor survival outcomes.

5.1.4. Group 4 Medulloblastomas

The site of origin of group 4 medulloblastomas have not yet been established, however, tumours are believed to display transcriptional resemblances to unipolar brush cells [147]. Group 4 medulloblastoma constitute about 35%-40% of all medulloblastoma cases [147]. These tumours most commonly in children and most frequently in males (3:1 sex ratio) [147, 148]. Molecular characteristics associated with group 4 medulloblastomas include the following gene amplifications namely *SNCAIP*, *MYCN*, *OTX2* and *CDK6* [148].

5.2. Treatment of Medulloblastomas

The current treatment of medulloblastoma consists of surgically resecting as much of the tumour as possible, followed by brain and spine radiation and/or chemotherapy [142]. The treatment plan is based on factors that indicate the risk of tumour recurrence, the amount of tumour remaining following surgery, the age of the patient and the amount of metastases, or tumour spread. Removing as much of the tumour is the most important step in treating medulloblastoma [149, 150]. The goals of the surgery include i) relieving CSF build-up that is caused by the tumour or swelling, ii) confirmation of the diagnosis through obtaining a tissue sample and iii) to remove as much of the tumour as possible while causing minimal or no neurological damage [151]. Radiation follows surgery in the treatment of medulloblastoma as microscopic tumour cells remain in the surrounding brain tissue even after surgery [151]. These remaining cells have

the ability to lead to tumour regrowth and spread, thus the goal of radiation therapy is to destroy any remaining cells. Chemotherapy is used to kill the medulloblastoma cells that remain after surgery and/or radiation in children reducing the risk of tumour cells spreading through the spinal fluid and the risk of the tumour returning [151].

6. Schwannomas

Schwannomas, also known as neurilemmomas or neurinomas, are benign tumours of the myelin sheath, originating from schwann cells encasing axons of the cranial nerves [152, 153]. Most schwannomas are benign, slow growing, solitary encapsulated nerve sheath tumours comprised of schwann cells [154]. They arise from the surface of neural elements in the body or within the brain, causing significant local problems on the nerves, blood vessels and adjacent structure of the bone [155]. Schwannomas can arise from the peripheral, spinal, and cranial nerves [155, 156]. They are the most common type of peripheral nerve and neurogenic tumours. The tumours grow in an eccentric fashion in relation to the nerve, and the classical histological architecture is biphasic with dense, compact areas called Antoni A, and less compact areas called Antoni B with a palisading organisation of nuclei (Verocay bodies) [157-158]. Schwannomas mainly occur in adults and equally in males and females. Although the exact cause is unknown, multiple schwannomas are known to develop from genetic disorders such as neurofibromatosis type 2, schwannomatosis, and Carney complex [156]. Schwannomas are usually solitary, slow growing, and encapsulated neoplasm generally represented as painless swellings for several years before diagnosis which may lead to difficulties in clinical diagnosis and treatment [159].

The lesions are round and quite smooth and regular in appearance and are tightly attached to the neural elements [155]. The surface of the tumour appears to be collagenous, soft, and wet. The most common locations of schwannomas are in the upper extremities including the head, trunk, and neck, retroperitoneum, mediastinum, pelvis, peritoneum, hepatoduodenal ligaments, and flexor surfaces of the upper and lower extremities [160]. The exact cause and aetiology of schwannomas is not yet known.

6.1. Classifications and Grading of Schwannomas

There are several histologic subtypes of schwannoma that have been described, including ancient, cellular, melanotic, plexiform, and epithelioid, as well as others such as neuroblastoma-like, hybrid, and pseudoglandular variants [161]. Schwannomas involving the eighth cranial nerve are termed vestibular schwannomas, and they are more frequent than spinal and trigeminal schwannomas [157].

6.1.1. Ancient Schwannomas

Ancient schwannomas (ASs) are rare, benign nerve sheath tumours characterised with degenerative atypia (i.e. schwann cell nuclei are often large, hyperchromatic, and multilobated), and diffuse hypocellular areas [162, 163]. They display pronounced degenerative changes attributed to the vascular insufficiency acquired during growth of the tumour, and the tumour size has been correlated with progressive degenerative features [164, 165]. Typically these are large tumours of long duration that lack mitotic figures, and usually show other degenerative changes including cystic necrosis, stromal edema, xanthomatous change, fibrosis, calcification, haemorrhage, and perivascular hyalinization [164, 166-167]. ASs are usually deeply located, and mostly affects the head and neck, cervical region, pelvis, retroperitoneum, and flexor aspect of the limbs [162-168]. Histologically, ancient schwannomas show areas of cellularity and areas of myxoid matrix [164]. Due to the nuclear atypia, and cystic degeneration, ASs are often confused with malignant tumours [165], however, the presence of a capsule, haemorrhagic areas, degenerative changes, and absence of mitotic activity supports the benign nature of the tumour [167]. The effects of pressure on the surrounding structures or sensory changes in the distribution of the affected nerve are the most common symptoms.

6.1.2. Cellular Schwannomas

Cellular schwannomas (CSs) are an uncommon but well recognised variant of benign schwannomas that was first described by Woodruff and colleagues in 1981 [169]. CSs accounts for approximately 5% of the benign peripheral nerve sheath tumours and predominately affects middle-aged adults [170, 171]. CSs has a predilection for middle-aged women [172]. They are extremely rare in the CNS and involve the spinal nerves more often than the cranial nerves in the peripheral nervous system [173]. The tumour has a female predominance, a median age of 55 years, and most are located in the retroperitoneum or mediastinum [174]. CSs are characterised by high cellularity, and predominance of hypercellular Antoni A areas and absence of Verocay bodies [175-177]. Type A areas are cellular and are made up of spindle cells that are often arranged in palisading fashion [178].

Typical CSs are round, oval, or nodular lesions coated with a complete fibrous capsule that has a clear border [179]. Microscopically, CSs appear to be mitotically active, but usually <4 mits/10 HPF, and lack atypia [166]. The nuclei appear to be larger, and more abundant than those of classical schwannomas [172]. They tend to have an increased rate of recurrence but they are not malignant. CSs usually present as slow growing tumours often located deep in the paravertebral region of the mediastinum and retroperitoneum [170]. They may originate from any portion of the

trigeminal nerve between the root and distal extra-cranial branches resulting in a variety of symptoms and signs, depending on the direction and extent of tumour growth [173]. CSs may be large in size, with sheets of eosinophilic cells, have bullet-shaped nuclei along with characteristic features of schwannomas i.e. hyalinised thick blood vessels and foamy histiocytes [170]. Although CSs are well-recognised entities, they are most often misdiagnosed as the well-differentiated malignant peripheral nerve tumours due to their cellularity, mitotic activity, and occasionally presence of bone destruction [171, 180, 181]. It has been suggested that the CSs should be included in the group called pseudosarcomas [174].

6.1.3. Melanotic [Pigmented] Schwannomas

Melanotic schwannomas (MSs) are rare circumscribed nerve sheath tumours of melanin producing schwann cells that accounts for approximately 1% of all nerve sheath tumours [182, 183]. They are considered as tumours of the young occurring in patients between the ages of 10-90 years with peak incidence between the fourth and fifth decade of life, with no sex predilection [184, 185]. MSs are clinically, biologically, and histologically distinct from conventional schwannomas [186]. MSs are characterised by schwann cells containing melanosomes that are immune reactive with melanocytic markers (e.g. HMB-45) [166]. They are composed of melanin producing cells with ultrastructural features of schwann cells [157, 184]. MSs may be grossly pigmented due to the accumulation of melanin in neoplastic cells, and the majority are highly cellular and contain spindled and epithelioid cells [185]. MSs often lack definite capsule, Verocay bodies, and Antoni A and B areas, often contains scattered multinucleated cells, and nuclei are often round to ovoid with delicate chromatin [166, 186-187]. Histologically, MSs are characterised by plump spindle and epithelioid cells arranged in sheets, lobules, and interlacing fascicles [187-188]. More than half of MSs patients have signs of Carney's syndrome, such as myxomas, spotty pigmentation, and endocrine hyper-activity producing Cushing's syndrome [189]. MSs are often located in the intradural extra-medullary sites and the peripheral nervous system [190]. Approximately 50% of MSs arise in close proximity to the neural axis, and are often associated with spinal nerve roots, cranial nerves or arising from the paraspinal sympathetic chain [191]. While the remaining 50% may arise in a wide variety of sites including the gastrointestinal tract, soft tissues, skin, heart, and liver. MSs may be subdivided into psammomatous and non-psammomatous types [192]. Psammomatous MSs are related to Carney complex, while the non-psammomatous type is sporadic and commonly affects spinal nerves. MSs have higher risk of malignant transformation.

6.1.4. Plexiform schwannomas

Plexiform schwannomas (PSs) are rare benign peripheral nerve sheath tumour composed of schwann cells arranged in a complex, web-like pattern [193]. PSs are a morphologically distinct variant of schwannoma comprised exclusively of schwann cells. They are characterised by plexiform growth in tissues and often intraneural, and are usually superficial, cellular with the majority containing Antoni A and/or B [157, 166]. PSs most commonly occur sporadically as solitary lesions, but have a greater incidence in patients with neurofibromatosis type 2 [NF2] and schwannomatosis [194]. They account for approximately 5% of schwannomas, with more than 23% occurring in the head and neck region, with another 15% occurring cutaneously with predilection for the head, neck, and flexor surface of the upper and lower limbs [195-196]. Clinically, the patients are usually asymptomatic, however, pain may occur due to compression of nearby nerves. The tumour usually manifest as soft mobile nodule with an average size of 3cm and grows slowly over time [195]. Histologically, they resemble conventional and cellular schwannomas [197]. PSs are commonly seen in young adults aged 30-40 years, however, it can present at birth, or in infancy [198-199].

6.1.5. Epithelioid Schwannomas

Epithelioid schwannomas (ESs) are rare variants of nerve sheath tumour composed predominantly or exclusively of epithelial-appearing schwann cells [200]. ESs are characterised by uniform epithelioid cytomorphology with predominantly round, epithelioid schwann cells arranged as single and in clusters [166, 201]. The origin of schwann cells are confirmed by strong, diffuse S-100 immunoreactivity. The most common locations of ESs are head and neck, lower and upper limbs, and the trunk [202]. It is typically a well circumscribed, encapsulated tumour with a size ranging from 0.4-20 cm (median 3.0cm) [201]. Unlike conventional schwannomas, the Antoni A and B areas, and Verocay bodies may be absent or only focal and often located subcutaneously [166]. ESs are unusual variants that often pose difficulties in diagnosis due to their increased cellularity and epithelioid morphology [203]. The main differential diagnosis of ESs is malignant peripheral nerve sheath tumour (MPNST), small size, sharp circumscription, bland morphology, and low proliferative activity. Histologically, it shows relatively uniform cellularity with cords, trabeculae, and nests of bland epithelioid tumour cells in myxoid or fibromyxoid stroma [202]. ESs mostly affect age groups a wide range of age groups of 17-73 years with a mean age of 38.6 years. Although ES has been regarded as low-grade tumour, its malignant type is highly aggressive and is associated with a high rate of recurrence and poor prognosis [204-205].

6.2. Treatment of Schwannomas

Surgery is the mainstay for the management of symptomatic schwannomas [157]. However, preoperative planning

remains crucial for successful schwannoma treatment and relies to a great extent on proper tumour classification [206]. For asymptomatic or minimally symptomatic tumours, a paradigm shift from early excision to observation is conducted depending on patient age, location, and associated symptoms [157]. In addition, schwannomas with limited pressure on the adjacent nerve may not require any treatment, however, excisional biopsy may be helpful in providing the diagnosis and prevent further problems [155]. However, larger lesions which cause nerve pressure and damage to adjacent soft tissues require wide excision. Incomplete excision of large lesions often leads to recurrence and become clinically symptomatic [207]. No chemotherapeutic agents are known to be effective. Effective treatment needs to address the entering and exiting tumour fascicle, which can often be separated from the parent nerve [207]. This permits preservation of neurologic function, even when tumours are large. In addition, stereotactic radiation is also effective in controlling tumour growth but less effective in retaining hearing in patients with vestibular schwannomas [157]. Pain is managed with neuropathic agents such as amitriptyline and gabapentin.

7. Gangliogliomas

Gangliogliomas (GGs) are well differentiated slow growing glio-neural tumours, accounting for approximately 0.4% of all CNS tumours [208-209]. GGs are diagnosed primarily in children and young adults less than 25 years, and are more common in males than females [210]. Clinical presentation depends on patient age, location, and aggressiveness of the tumour [211]. GGs usually have a benign clinical course with a long duration of symptoms prior to diagnosis, and low mortality and morbidity [212]. Patients usually suffer from seizures as a major clinical symptom, especially in those located in the temporal lobe. They are commonly associated with chronic, treatment resistant temporal lobe epilepsy, and is part of the entities grouped under long term epilepsy associated tumours (LEAT) [213]. GGs are extremely rare tumours of the CNS comprising of mixed neoplastic neural and glial components [209, 214].

Both cell populations show marked heterogeneity, ranging from predominantly neuronal phenotype to variants with a prominent glial population [215]. The glial component is variable, and may include cell types that resemble fibrillary astrocytoma, oligodendroglioma or pilocytic astrocytoma [216]. GGs tend to occur as solitary lesions and are most commonly identified in the cerebral cortex, but may also occur at subcortical sites and within the spinal cord [210]. They are characterised as hypodense lesions with calcification and a variable contrast enhancement pattern. Intracranial GGs most commonly occur in the temporal lobe (71.3%), followed by the frontal lobe (8.2%), occipital lobe (5%), and parietal lobe (4%) [210, 217]. Ultra-structurally, GGs are characterised by large neuronal cells with cell bodies contacted by numerous neuritic endings containing small clear synaptic vesicles, corresponding to the diagnostic synaptophysin staining pattern [218]. Neural cells contain numerous, dense core granules within the cell body and processes. Histologically, GGs are characterised by a dysplastic neuronal population accompanied by neoplastic glial cells. Immunohistochemically, the glial component is generally positive for glial fibrillary acidic protein (GFAP) expression, with faint or absent microtubule-associated protein-2 (MAP2) immunoreactivity, CD34, Neu-N, and synaptophysin [208, 210, 217]. The neural component can also be highlighted by immunostains and their dysmorphic features may include clustering and bi-nucleation [208]. These immunohistochemical markers, in conjunction with histopathological features, aids in the differentiation of these tumours from other gliomas such as astrocytoma, oligodendrogliomas, and dysembryoplastic neuroepithelial tumours. The molecular pathogenesis, risk factors for malignant progression, and their frequent association with drug resistant focal seizures remain poorly understood [219]. Individual cases have been described in association with family history of neurofibromatosis, in patients with Peutz-Jeghers syndrome, and in patients with Turcot syndrome [215]. However, it has been proposed that malignant GGs have a monoclonal origin, suggestive of an initial transformation of a single neuroglial precursor cell with subsequent malignant progression [215]. In addition, the loss of p19 expression and p53 gene mutations have been associated with malignant progression.

7.1. Classifications and Grading of Gangliogliomas

GGs are graded by the World Health organisation into grade I-IV. WHO grade I or II contain both neural (ganglion cell) and glial elements, and the glial component is occasionally anaplastic (grade III), and rarely glioblastomatous (grade IV) [212]. In addition, GGs may be divided into solid tumours and tumours with cystic components on the basis of their CT scan characteristics [220]. Grading of GGs has been assigned based on characteristics of the glial component of the tumour [221]. Grade II GGs has been shown to contain cellular atypia (increased cellularity and conspicuous pleomorphism), microvascular proliferation, or an elevated MIB-1 labelling index ($\geq 5\%$) [221]. While grade III GGs contains necrosis and an MIB-1 proliferation index of 10% or more. However, there are those tumours that do not meet either the criteria of grade I or III, these are known as atypical GGs [222].

Atypical GGs are often classified as grade II tumours. The histological classification of GGs remains challenging due to variable microscopic features including cellular components difficult to differentiate from pre-existing neurons, and multiple architectural growth patterns occurring in many LEAT entities such as diffuse infiltration, small cysts and/or white matter rarefaction and tumour cell nodules [223]. As previously mentioned, the most common location of GGs is temporal lobe, however, some may be located in the spinal cord.

7.1.1. Anaplastic Gangliogliomas

The WHO classifies anaplastic gangliogliomas (AGGs) as grade III, their histology exhibits anaplastic features such as hypercellularity, mitotic activity, vascular proliferation, cytological atypia and necrosis [224-225]. AGGs are very rare tumours accounting for up to 5% of gangliogliomas. The clinical course of AGGs is poorly understood, however, it has been suggested that they arrive as a low-grade tumour that has transformed into an anaplastic form. The anaplastic transformation most often occurs in paediatric population [224], however it may also occur in young adult population. AGGs typically consist of malignant transformation of the glial component and is defined by increased mitotic activity, prominent micro-vascular proliferation, necrosis, and high MIB-1, TP53, and Ki-67 labelling indices that have been associated with increased size of ganglion cells [218]. These malignant transformations are often related to radiation therapy, occurring several years after treatment [226]. However, AGGs are a controversial and poorly characterised entity with multiple differential diagnoses including diffuse glioma infiltrating the cortex, PXA with anaplastic features, atypical teratoid and rhabdoid tumour, desmoplastic infantile GG in children, and epithelioid glioblastoma [227].

7.2. Treatment of Gangliogliomas

Complete surgical excision is the standard of GG treatment, and the extent of removal is considered to be the main prognostic factor [217]. Gross total resection is the only curative treatment for both low grade and malignant GGs. Subtotal resection is often considered due to eloquent location, poor demarcation, and/or severe attachment to the neighbouring vital structures [212]. However, in the case of incomplete resection, tumour recurrence may occur and undergo malignant transformation. Radical surgery may lead to long term survival, and adjuvant therapy can probably be reserved [211, 220]. Radiation is generally reserved for incompletely resected tumours, especially those with any evidence of malignant features. Good prognostic factors include temporal localisation, complete surgical resection, and long-standing epilepsy [218]. No major benefits have been reported with conventional radiotherapy and gamma knife radiosurgery. It has been recommended that recurrent GGs should be re-operated, unless it is not resectable i.e. located within the brainstem, or hypothalamus [212]. The median overall survival for anaplastic GGs is 28.5 months, and the extent of the disease predicts the outcome. It has been reported that seizure control is reached in at least 85% of GGs, and up to 96% after gross total resection [228].

8. Craniopharyngiomas

Craniopharyngiomas (CPs) (cranio = skull, pharynx = throat, and oma – tumour) are slow growing benign tumours arising from the squamous epithelial remnants of Rathke's pouch in the sellar/suprasellar region of the brain [229-231]. CPs originate along the path of the hypophyseal-pharyngeal duct (craniopharyngeal duct) [232], however, they can extend anywhere from the nasopharynx to the tuber cinereum and may also arise within the sphenoid bone, the sella, or the suprasellar region [229]. These tumours may be cystic, solid, or a combination of the two. Although they are histologically benign tumours, clinically, they are considered partially malignant [233].

Although they are slow growing tumours, their location enables them to be large at the time of diagnosis, extending supero-posteriorly into the third ventricle and hypothalamus, compressing the supero-anteriorly the optic pathways and inferiorly the pituitary gland, impairing their functions [234]. However, the initial symptoms of CPs are frequently unspecific, and the diagnosis can be made relatively late. The most common symptoms in children are headache, visual impairment, growth failure, nausea, neurologic deficits, polydipsia/polyuria, and weight gain [234-235]. In adults, the most common symptoms of CPs are visual impairment, headache, menstrual irregularities in women, loss of energy, nausea and vomiting, lethargy, and weight gain [234]. CPs are rare, with the incidence of 0.5-2 cases per million persons per year [235].

8.1. Classifications and Grading of Craniopharyngiomas

Craniopharyngiomas (CPs) are grade 1 tumour that can be classified either according to tumour pathology or topography [236]. Pathologically, there are two main histological subtypes of craniopharyngiomas i.e. the adamantinomatous and papillary, but transitional or mixed forms have also been reported [236-237]. All these forms have different phenotypes and distinctive mutations [238]. In addition, these tumours differ clinically and pathologically. Adamantinomatous CP (ACPs) occur in both adults and children, while papillary CP (PCPs) occur almost exclusively in adults [239]. Topographically, CPs can arise anywhere along the craniopharyngeal canal, although the majorities arise in the sellar/parasellar region [236]. The majority of CPs have supra-sellar and supra-intrasellar components, however, intrasellar CPs are rare. It has been reported that both ACPs and PCPs subtypes harbour highly recurrent activating mutations [239].

8.1.1. Adamantinomatous Craniopharyngiomas

Adamantinomatous craniopharyngiomas (ACPs) are heterogeneous tumours of epithelial origin, with classic features consisting of polisading epithelium, stellate cells, nodules of anuclear cells, and large areas of regressive changes (i.e.

inflammation, calcifications, multinucleated giant cells, hemosiderin deposits, and cholesterol clefts) [240]. ACPs are composed of well differentiated epithelium, with different architectural patterns such as cords, lobules, nodular whorls, and irregular trabeculae surrounded by palisading columnar epithelium [238]. ACPs are benign tumours arising from remnants of Rathke's pouch in the sellar/suprasellar region of the brain [231]. They are the most common subtype. ACPs are characterised by collections of whorl-like nodules consisting of cytokeratin-enriched dysplastic epithelium [241]. The pathogenic mechanisms of ACPs are not well understood. However, it has been reported that ACPs may result from mutations in the Wntless (WNT) pathway gene *CTNGB1* encoding β -catenin [234]. These mutations increase the resistance of β -catenin to proteasomal degradation resulting in its intranuclear accumulation. In addition, the involvement of MAPK/ERK pathway in tumorigenesis of ACPs has been recently determined [234]. ACPs are recognised by the presence of squamous epithelium disposed in cords, nodules, and irregular trabeculae bordered by palisaded columnar epithelium [235]. These densely packed cells merge with loosely cohesive aggregates of squamous cells known as stellate reticulum.

8.1.2. Papillary Craniopharyngiomas

Papillary craniopharyngiomas (PCPs) are characterised by solid, homogenous, and monomorphic areas of well differentiated squamous epithelium without surface keratinisation, calcification, or whorls [238, 242]. The characteristic hallmarks of PCPs are their supradiaphragmatic location, and cytoplasmic/nuclear β -catenin accumulation [236, 243]. Their cellular structures resemble oropharyngeal mucosa [244]. It has been postulated that PCPs are caused by metaplasia of the adenohypophyseal cells in the pars tuberalis of the adenohypophysis, leading to the formation of squamous cell nests [235]. The majority of papillary lesions harbour BRAF V600E mutations, an oncogene regulating MAP kinase/ERK signalling and affects cell division and differentiation [242, 245]. These mutations can serve as useful guides in the management of PCPs.

8.2. Treatment of Craniopharyngiomas

Craniopharyngiomas are curable benign tumours typically treated with both surgery and radiation. The surgical approach depends on the size and sellar vs suprasellar extent. This treatment approach provides 5-year progression-free survival (PFS) rates exceeding 90% [246]. However, CPs are among the most challenging intracranial lesions to manage due to long term side effects such as endocrinopathy, hypothalamic dysfunction, visual field deficits, cerebrovascular sequelae, secondary malignancies, and neurocognitive decline which may impact the quality of life [241, 246-247]. These may be due to their close proximity to sensitive structures, such as the optic apparatus, pituitary, hypothalamus, circle of Willis, brain stem, and temporal lobes. It has been shown that adequate presurgical imaging and assessment of hypothalamic involvement of CPs plays an important role in estimating prognosis and long-term quality of life [234]. Initial tumour involvement of the third ventricular floor, mammillary bodies and/or posterior hypothalamus on imaging are associated with a worse long-term prognosis due to hypothalamic obesity, regardless of chosen treatment strategies [234]. Magnetic resonance imaging (MRI) is the standard imaging modality in CP, however, it may not discriminate between ACPs and PCPs. Computer tomography (CT) has been recommended for better calcifications within tumour. The treatment is chosen based on the paediatric grading system.

The treatment of choice for CPs without hypothalamic involvement (HI) (type 0 – no HI on MRI scan and type 1 – distorts or elevates hypothalamus) is an attempt of complete resection with preservation of visual, pituitary and hypothalamic function [234]. However, complete resection is not recommended for tumours located unfavourably (type 2 – hypothalamus not visible on MRI scan). The optimal therapeutic strategy for CPs is still controversial, and reducing long term adverse effects of radiotherapy remains a pivotal importance in treating CPs. The most recent advances in the treatment of craniopharyngioma focused on minimising treatment related toxicity, including endoscopic surgery and precision radiotherapy [246]. Despite significant advances in operative techniques, and adjuvant therapies including radiotherapy, the management of CPs remains difficult. Targeted treatment approach aimed at inhibiting certain pathway such as BRAF/MEK pathway may provide non-surgical, and non-radiotherapy treatment options.

9. Conclusion

This review provides an overview of CNS tumours, classification, characterisation, grading, and treatment thereof. CNS tumours remain among the deadliest of all cancers, and their incidence has increased. There are several types of CNS tumours, which are further divided into subtypes. The classification and grading of CNS tumours needs to be constantly updated as more subtypes are being introduced. The classification and grading of CNS tumours play an important role in the management thereof. In addition, these tumours need to be well characterised as it remains challenging to differentiate and diagnose them.

10. Nomenclature

ACPs	Adamantinomatous craniopharyngiomas	AAs	Anaplastic astrocytomas
AEs	Anaplastic ependymomas	AGGs	Anaplastic gangliogliomas
AODs	Anaplastic oligodendrogliomas	Ass	Ancient schwannomas
AMs	Angiomatous meningiomas	ATMs	Atypical meningiomas
BBB	Blood brain barrier	CEA	Carcinoembryonic antigen
CEs	Cellular ependymomas	CSs	Cellular schwannomas
CNS	Central nervous system	CSF	Cerebrospinal fluid
CMs	Chordoid meningiomas	CCEs	Clear cell ependymomas
CCMs	Clear cell meningiomas	CT	Computer tomography
CPs	Craniopharyngiomas	CK	Cytokeratin
DNA	Deoxyribonucleic acid	DAs	Diffuse astrocytoma's
ESs	Epithelioid schwannomas	FMs	Fibrous meningiomas
GGs	Gangliogliomas	GFAP	Glial fibrillary acidic protein
GBM	Glioblastoma multiforme	IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2	LPMs	Lymphoplasmacyte plasma-rich meningiomas
MPNST	Malignant peripheral nerve sheath tumour	MSs	Melanotic schwannomas
MMs	Meningothelial meningiomas	MPMs	Metaplastic meningiomas
MCMs	Microcystic meningiomas	MAP2	Microtubule-associated protein-2
MPEs	Myxopapillary ependymomas	NF2	Neurofibromatosis type 2
PCPs	Papillary craniopharyngiomas	PEs	Papillary ependymomas
PAS	Periodic acid-schiff	PAs	Pilocytic astrocytomas
PXAs	Pleomorphic xanthoastrocytomas	PSs	Plexiform schwannomas
PNET	Primitive neuroectodermal tumour	PFS	Progression-free survival
PMs	Psammomatous meningiomas	SMs	Secretory meningiomas
SSH	Sonic hedgehog	SEGAs	Subependymal Giant Cell Astrocytomas
SEs	Subependymomas	TEs	Tanycytic ependymomas
TMs	Transitional meningiomas	WNT	Wingless
WHO	World Health Organization		

11. Declarations

11.1. Author Contributions

Conceptualisation, B.T.F. and M.B.; methodology, B.T.F. and M.B.; writing—original draft preparation, B.T.F. and M.B.; writing—review and editing, B.T.F. and M.B. All authors have read and agreed to the published version of the manuscript.

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11.4. Ethical Approval

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11.5. Data Availability Statement

Data sharing is not applicable to this article.

11.6. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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