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REVIEW ARTICLE

Central nervous system malignancies

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Abstract:
Central nervous system (CNS) tumours are the second most common malignancy in children and the most common form of solid tumours in childhood. Astrocytomas accounting for 52% are the most common entity throughout childhood and adolescence, with juvenile pilocytic astrocytomas accounting for about 20% of all tumours. Anaplastic astrocytomas and glioblastomas achieve about 15%. Embryonal tumours: medulloblastomas and PNETs, are the second most common entity (21%) and the most frequent type among high-grade tumours. Ependymomas are the third most frequent tumours (9%) and very common in the first 3 years of life. Rarer entities included germ cell tumours, gangliogliomas, craniopharyngiomas, atypical teratoid/rhabdoid tumours, choroid plexus tumours, and dysembryoplastic neuroepithelial tumours (DNT). Computed tomography is still an excellent initial study for brain tumours and may serve as an important complementary study to magnetic resonance imaging (MRI). MRI has revolutionized the diagnosis of brain tumours in children and nowadays it is widely considered as the gold standard for the imaging of all brain tumours. The traditional treatment modalities in paediatric neurooncology are surgery, radiotherapy and chemotherapy, applied either alone or in various combinations and sequences. The use of high dose chemotherapy has changed an approach to the treatment of young children with newly diagnosed medulloblastoma, PNET and possibly other malignant brain tumours of early childhood, as well as selected patients with recurrent germ-cell tumours. Despite significant advances in treatment modalities, CNS tumours are still the leading cause of cancer-related death in this age group. Many of children fortunate enough to survive their CNS tumours are left with lifelong deficits resulting from their intensive treatments. New therapeutic approaches will more specifically target the tumours, resulting in better tumour kills with fewer long-term side effects and improving the survivors quality of life. Patients with brain tumours represent everything that is positive and negative about current treatment: increasing cure rates, the promise of new treatments, deleterious effects of therapy, and a lack of understanding about the impact of current treatment on long-term survivorship. Patients, their parents and caregivers need to be oriented to the relative merits of all treatment options based on peer-reviewed data. The major hope for future improvements in childhood brain tumour management rests on the ability to translate laboratory advances, especially new understandings in the molecular genetics and biology of brain tumours, into more effective therapeutic approaches.

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Inroduction

Central nervous system (CNS) malignancies are the second most common malignancy in children and the most common form of solid tumours in childhood. Yet, brain tumours in children are the second leading cause of cancer-related death in this age group [1]. Over the last three decades, advances in neuroradiologic and other diagnostic and prognostic modalities, neurosurgical and radiation therapy (RT) techniques, and the application of chemotherapy, are responsible for the considerable improvement in the long-term survival of children with brain tumours. Currently the rate of 5-year survival achieves 74% among patients (ages 0-19 years) with CNS tumours [1].

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Epidemiology

Although overall incidence is rare and central nervous system tumours represent only 2% of all cancers, primary brain tumours in children, contrary to adults, comprise almost 20% of all paediatric neoplasms. As recent data suggest the overall incidence rate for childhood brain tumours (ages 0-19 years) is 3.2 (per 100,000 person-years). Among this population brain tumours are more

common in males than females (3.4 vs 3.0/100,000). The incidence for all brain tumours is highest among 0-4 year olds (3.9/100,000) and lowest among 15–19 year olds (2.1/100,000) [1]. The increase in CNS cancer rates in the past three decades has been the subject of numerous reports. One concern is that changes in environmental exposures may be responsible for the increasing incidence rates, although epidemiologic evidence to support this hypothesis currently is lacking. An alternative explanation is that improvements in diagnostic technology and case ascertainment may be contributing to the increasing trend.

Etiology and risk factors

The etiology of paediatric brain malignancies remains largely unknown. There is no specific risk factor known to explain a substantial proportion of brain tumour occurrence. The most clearly established risk factors are the specific hereditary neurological disorders including neurofibromatosis, nevoid basal cell syndrome, tuberous sclerosis and the familial cancer Li-Fraumeni syndrome. However, these diseases are rare, and not all children with genetic predispositions go on to acquire cancer [2, 3]. Although a somewhat increased risk has been observed when a sibling or parent has had a brain tumour, the association with family history is not strong or consistent [4]. Thus, from a population perspective, known inherited genetic factors explain only a small percentage (2-4%) of childhood CNS cancer incidence. Another risk factor considering as an established one is a high-dose ionising radiation for cancer therapy [5, 6]. Children treated in the past for tinea capitis experienced 2.5-6-fold increased risk [7]. Currently, those at risk are children treated with radiation to the head for leukaemia or a previous brain tumour [8, 9]. The knowledge about the risks of radiation-induced neoplasms has been accumulated over decades. Recent studies have suggested that even very low levels of ionizing radiation, such as those associated with computed tomographic (CT) scans, are capable of inducing cancer [10, 11]. Children are at greater risk than adults, because the use of adult scan protocols leads to higher effective doses in children, due to of children's greater sensitivity to the same effective dose and because their longer life expectancies create longer time frames in which to develop radiation-induced cancers [12, 13]. Radiological examinations during pregnancy have in some studies been associated with a slightly increased risk of brain tumours in offspring [14, 15]. However, meta-analyses have found no clear associations [16, 17]. For other potential risk factors that have been studied, the evidence is limited and/or conflicting. These factors include maternal diet during pregnancy, pesticides, products containing N-nitroso-compounds, electromagnetic fields, polyomaviruses, parental occupational exposures, history of head injury and family history of epilepsy or mental retardation [18-22].

Histologic classification

The pathologic classification of paediatric brain tumours is a specialized area that is undergoing evolution; review of the diagnostic tissue by a neuropathologist who has particular expertise in this area is strongly recommended. Assessment of the histologic characteristics of a tumour by light and sometimes electron microscopy, is necessary for their diagnosis/classification, and aids in grading the degree of anaplasia for those tumours in which grade is useful for prognosis.

Recently, the detection of molecular genetic traits of paediatric brain tumours is providing new information to classify tumours and predict prognosis. This should translate to more accurate risk stratification than traditional tumour grading and staging, and ultimately, to better treatment outcomes. Some genetic markers of paediatric brain tumours that are thought to correlate with prognosis are listed in Table 1 (acc. to [23, 24]).

Table 1. Selected genetic markers of malignant paediatric brain tumours

Tumour type	Genetic alteration	Prognostic relevance
High-grade glioma	p53 mutation	worse prognosis
	p53 overexpression	poor prognosis
	bFGF high expression	poor prognosis
	Topoisomerase II alfa low expression	poor prognosis
Medulloblastoma	Trk C high expression	good outcome
	C-myc amplification	poor prognosis
	ErbB-2 high expression	poor prognosis
	HER2 and HER4 coexpression	poor prognosis
	p53 overexpression	poor prognosis

bFGF, basal fibroblast growth factor; Trk, tyrosine kinase; ErbB, Epidermal Growth Factor (EGF) family of receptor tyrosine kinases (RTKs); HER, Human Epidermal growth factor Receptor

According to the 4th edition of the World Health Organization classification, primary brain tumours are classified on the basis of their cellular origin, the clinical course and histological appearance, immunophenotypic features, and molecular/cytogenetic profile [25]. Therefore, six different groups are recognized as shown in Table 2 (acc. to [25]). Astrocytomas accounting for 52% are by far the most common entity throughout childhood and adolescence, with juvenile pilocytic astrocytomas accounting for about 20% of all tumours. Anaplastic astrocytomas and glioblastomas achieve about 15%.

Embryonal tumours (medulloblastomas and PNETs) are the second most common entity (21%) and the most frequent type among high-grade tumours. Ependymomas are the third most frequent tumours (9%) and very common in the first 3 years of life. Rarer entities included germ cell tumours, gangliogliomas, craniopharyngiomas, atypical teratoid/rhabdoid tumours, choroid plexus tumours, and dysembryoplastic neuroepithelial tumours [18].

Table 2. Histological classification of tumours of the central nervous system

1. Tumours of neuroepithelial tissue

Astrocytic tumours
- juvenile pilocytic astrocytoma
- anaplastic astrocytoma
- glioblastoma

Oligodendroglial tumours
- oligodendroglioma
- anaplastic oligodendroglioma

Mixed gliomas
- oligoastrocytoma
- anaplastic oligoastrocytoma

Ependymal tumours
- ependymoma
- anaplastic ependymoma
- myxopapillary ependymoma

Choroid plexus tumours
- choroid plexus papilloma
- choroid plexus carcinoma

Glial tumours of uncertain origin
- astroblastoma

Neuronal and mixed neuronal-glial tumours
- ganglioglioma
- anaplastic ganglioglioma
- dysembryoplastic neuroepithelial tumour (DNT)

Neuroblastic tumours

Pineal parenchymal tumours
- pineocytoma
- pineoblastoma

Embryonal tumours
- medulloblastoma
- primitive neuroectodermal tumour (PNET)
- atypical teratoid/rhabdoid tumour

2. Tumours of peripheral nerves

Schwannoma (neurinoma)
Neurofibroma
Perineurinoma
Malignant peripheral nerve sheat tumour

3. Tumours of meninges

Tumours of meningothelial cells
- meningioma
- anaplastic meningioma

Mesenchymal, non-meningothelial tumours
- lipoma, angiolipoma
- fibrosarcoma
- rhabdomyoma, rhabdomysarcoma
- haemangiopericytoma

Primary melanocytic lesions

Tumours of uncertain histogenesis
- hemangioblastoma

4. Primary lymphomas and hematopoietic neoplasms

5. Germ cell tumours
- germinoma
- embryonal carcinoma
- yolk sac tumour
- choriocarcinoma
- teratoma
- mixed germ cell tumours

6. Tumours of the sellar region
- craniopharyngioma
- pituitary adenoma and carcinoma

Clinical presentation

Identification and diagnosis of brain tumours in children can be difficult. Many of the initial symptoms and signs of CNS tumours also occur with other more common and less serious childhood disorders such as gastroenteritis, migraine, and behavioural problems. In general, clinical presentation of a brain tumour is mainly determined by the age of the sick child and tumour location. Conventional teaching is that CNS tumours present with symptoms of raised intracranial pressure (ICP) (early morning headache with vomiting, mental status changes and papilloedema) with or without focal neurological signs [3]. Raised ICP is present in about 40% of all intracranial tumours, 80% of posterior fossa tumours, 30% of brainstem tumours and 7% of spinal cord tumours**.** Other alerts to a possible CNS tumour include: abnormal gait and coordination, seizures, squint, change in behavioural or school performance, macrocephaly, cranial nerve palsies, lethargy, abnormal eye movements (nystagmus, Parinaud's syndrome), hemiplegia, weight loss, focal motor weakness, unspecified visual or eye abnormalities, and altered level of consciousness [26, 27].

Increasing awareness of the varied and complex symptomatology that often occurs with CNS tumours could speed up the diagnosis and reduce the extended symptom interval experienced by many children. Recognition that specific combinations of symptoms and signs indicate a focal CNS lesion is crucial to the diagnosis of many CNS tumours (Table 3) [3, 26, 28].

Table 3. CNS tumour presentation

Tumour location and frequency		Most common clinical presentation
Supratentorial 40-50 %	**cerebral hemispheres (25-40%)**	seizures focal neurological signs (motor or sensory disturbances) headache signs of increased intracranial pressure speech disorders macrocephaly
	midline (10-20%)	endocrine symptoms sleeping and eating disorders signs of increased intracranial pressure abnormal eye movements behavioural change or school difficulties altered level of consciousness
Infratentorial 45-60 %	**cerebellum (25-50%)**	signs of increased intracranial pressure abnormal gait and coordination difficulties ataxia abnormal eye movements weight loss, focal motor weakness vertigo or auditory symptoms
	brainstem (10-20%)	abnormal gait and coordination difficulties cranial nerve palsies pyramidal signs ataxia squint, focal motor weakness stiff neck

Diagnostic imaging

An accurate diagnosis is of obvious importance in selecting optimal therapy for a child with a brain tumour. Thus, advances in diagnostic and prognostic modalities are integral to progress in the treatment and outcomes of children with brain tumours. In general, the diagnosis of a brain tumour is made with an imaging study. A variety of methods are available; each with advantages and shortcomings. For a long time, computed tomography (CT) has been regarded as the best clinical tool to image brain tumours because of its capacity to define neoplasm localization, its extension, and the relation between tumour and surrounding parenchyma [29]. Moreover, CT is available in most of clinical centers. However, some brain regions (ie, infratentorial, sellar, temporal, meningeal) are poorly assessed by CT, which is not very sensitive also in areas near bone of irregular shape. CT is still an excellent initial study for brain tumours and may serve as an important complementary study to magnetic resonance imaging (MRI). MRI has revolutionized the diagnosis of brain tumours in children and nowadays it is widely considered as the gold standard for the imaging of all brain tumours and the precise definition of their intra- or extra-axial origin.

Molecular imaging techniques, including Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and MR spectroscopy (MRS) are adding a new dimension to the anatomical information obtained from conventional CT and MRI scans and probe the biochemistry, metabolism and even the genetic signature of tumours [30]. MR spectroscopy permits the measurement of multiple chemical metabolites (i.e. N-acetyl aspartate, choline, creatinine) in normal and abnormal brain parenchyma. In the management of brain tumours, MRS is most valuable in the evaluation of whether MRI changes represent treatment-related effects or recurrent disease; it may also prove useful in the assessment of tumour response to therapy [31].

Although normal brain exhibits high FDG ([18F]-2-fluoro-deoxy-D-glucose) uptake due to its high glucose utilization, there is even higher uptake in malignant CNS neoplasms, which depend on anaerobic glycolysis and upregulate glucose transport mechanisms. For brain tumours, FDG PET has some relation to tumour grade, although its more important role is distinguishing recurrent or residual tumour from the effects of treatment, particularly radiation necrosis [32]. Although FDG PET is of limited use in following response to therapy for brain tumours, some molecular techniques are now being adapted to PET imaging which will greatly improve the utility of PET especially in medulloblastoma [30].

Treatment modalities

The traditional treatment modalities in paediatric neurooncology are surgery, radiotherapy and chemotherapy, applied either alone or in various combinations and sequences. Treatment modalities will depend upon the tumour type, disease extent, extent of resection and patient characteristics.

Surgical resection remains a first step following the diagnosis of a brain tumour. Surgery has two goals. The first, and most important, is to obtain a tissue diagnosis that will guide further management. The second objective is resection, if it is possible. Complete resection should be attempted for all lesions that are surgically accessible. In some cases, tumour location may prohibit a complete resection because of the risk of injuring critical neural or vascular structures. For tumours where an extensive resection would result in unacceptable morbidity, it is still often possible to obtain a diagnostic stereotactic needle biopsy.

Radiotherapy remains the major nonsurgical treatment modality for majority of paediatric CNS tumours. The use of radiotherapy is predicated on a differential effect on tumour vs. normal tissue, the therapeutic ratio. Modern external beam radiotherapy benefits from technical advances in quality control, such as the simulator, CT- or MRI-based target volume definition, computer assisted three-dimensional radiotherapy planning and dosimetry, verification analysis, custom-made immobilisation devices, compensators and attenuators. This permits more precise tailoring of the dose to irregular tumour contours and reduces its administration to surrounding brain. The recommended daily fraction in children ranges from 1.5 to 1.8 Gy, delivered 5 days per week. The dose to local fields ranges from 30 to 40 Gy (in the case of germcell tumours) to 54 Gy (for medulloblastoma and high grade glioma). Craniospinal irradiation remains essential only in embryonal tumours as these tumours are likely to spread within the neuroaxis. However, this treatment modality remains controversial in other tumours, such as anaplastic ependymomas and germ-cell tumours. Stereotactic radiosurgery, the gamma knife and proton beam radiotherapy may all be considered as investigational radiation modalities. Their aim is to achieve better tumour control through significantly higher local doses while sparing the surrounding brain. These methods have been useful for the treatment of unresectable brain tumours which are small and well circumscribed, and where the ablation of normal tissue very close to the target does not cause unacceptable toxicity. Another approaches to improve the efficacy of radiotherapy is the use of biologic response-modifiers that increase tumour sensitivity to

radiation or decrease radiation resistance. Pretreatment with temozolomide, carboplatin and gemcitabine were found to enhance the effect of irradiation on tumour cell killing [24].

The use of chemotherapy is supplemental for most tumour types and considered critical for some, especially when it can be used to delay irradiation in the very young, lower the total dose required to achieve disease control, or work synergistically to improve outcome. Conventional chemotherapeutic agents have made considerable improvement in the outcome of germ cell and embryonal tumours (including medulloblastoma), low grade optic pathway gliomas, malignant tumours in infants and high grade gliomas [24, 33]. Another approach in treating brain tumours has been the use of very high dose chemotherapy followed by stem cell rescue. The rationale for such trials relates to the potential benefits of dose intensification leading to better penetration of the bloodbrain barrier by cytotoxic agents. The use of high dose chemotherapy has changed our approach to the treatment of young children with newly diagnosed medulloblastoma, PNET and possibly other malignant brain tumours of early childhood, as well as the retrieval of select patients with recurrent germ-cell tumours. Myeloablative chemotherapy has also been attempted in children with diffuse pontine gliomas and ependymomas but has not been shown to increase either survival or duration of survival [34]. High-dose chemotherapy with autologous hematopoietic stem cell transplant can result in long-term survival with satisfactory functional status especially in those children who can achieve complete remission before transplant [34, 35].

Current and historical results of therapy of children with CNS tumours with respect to histo-pathology diagnosis is shown in Table 4 [1].

Table 4. 5-year relative survival rates for CNS tumours age <20 by type and period time, SEER 1975-84 and 1999-2005

ICCC Group	1975-1984	1999-2005
All CNS malignancies	60%	74,2%
Astrocytomas	70%	82,6%
Other gliomas	47%	52,8%
Ependymomas	39%	69,6%
Medulloblastomas/PNETs	52%	61,8%
Intracranial germ-cell tumours	nd	83%

ICCC, International Classification of Childhood Cancer; nd – no data

Investigational therapies

Recent advances in molecular biology have identified critical cellular changes within paediatric brain tumours, suggesting that molecularly targeted therapy may have a role in the treatment of these patients. Agents directed at specific targets theoretically should be more selective for cancer cells, less toxic to normal cells, and more effective than current agents that typically rely on cell division and primarily effect dividing cells. The "targeted" therapies inhibit tumour growth by various approaches, including immunotherapy, inhibition of signal transduction pathways, anti-angiogenic therapy, and regulation of gene expression (Table 5) [24, 36-38].

Several different targeted strategies for treating CNS tumours are currently under investigation. CNS tumours pose multiple challenges that must be overcome for these therapies to be effective. While certain targets have been identified we are maybe at a crossroads in clinical drug development. More works is needed to better understand how to increase the efficacy of these strategies and how best to incorporate them into the overall treatment plan for paediatric brain tumour patients.

Late effects and quality of life

Although impressive gains in survival have been achieved, late effects of brain tumour treatment remain significant for the growth and development of children and for the health of the adults that they become. The impact of long-term sequelae on functional outcome is particularly important in children who are expected to have long-term survival.

Brain tumour patients are vulnerable to wide-ranging side effects from therapy that are magnified especially in young children and enhanced by tumour and treatment type. Side effects range from treatable deficits that rarely impact long-term function to severe and debilitating side effects that result in the loss of functional independence. The late effects of therapy result in motor, sensory, coordination, hearing, visual and cognitive deficits, endocrine disorders, emotional and behavioural disturbances, as well as the increased risk of secondary malignancies [3, 39]. The long-term sequelae of treatment influence the posttreatment health-related quality of life (HRQoL) of brain tumours survivors. Some studies demonstrate that they reported much more problems resulting in significantly poorer HRQoL than their healthy peers and children with other types of cancer [40-42]. Thus, ongoing and future clinical trials with novel therapies should continue to improve quality of life of children with brain tumours.

Table 5. Possible targeted therapies for paediatric brain tumours.

Immunotherapy	
passive	monoclonal antibodies to EGFR (nimotuzumab), VEGF (bevacizumab) radiolabeled I^{131} anti-tenascin antibody ligands for tumour specific receptors conjugated with toxins (TGF-α, transferrin)
adoptive	ex-vivo expanded tumour specific T-cells (expressing CARs for HER2)
active	peptide vaccines or tumour lysates
Inhibition of tumour signal transduction pathways	
gefitinib (ZD1839, Iressa)	targets the EGFR tyrosine kinase
imatinib mesylate (STI-571, Glivec)	targets the PDGFaR tyrosine kinase
erlotinib (OSI-774, Tarceva)	targets the ErbB2 receptor tyrosine kinase
tipifarnib (R115777, Zarnestra)	inhibits the Ras signaling pathway
rapamycin (Sirolimus) rapamycin derivative (RAD001, Everolimus)	inhibit the PTEN/PI3K/ras/AKT/mTOR pathway
lonafarnib (SCH 66336, Sarasar)	inhibitor of farnesylation
lapatinib (GW572016)	targets both the EGFR and HER2 tyrosine kinases
Anti-angiogenic therapy	
vinblastin	inhibits endothelial cell function
cilenglitide (EMD121974)	integrin receptor antagonist
thalidomid	inhibits endothelial proliferation
SU5416, AZD2171	small molecule inhibitors of VEGF
Gefitinib (ZD1839, Iressa)	small molecule inhibitor of EGFR
metronomic chemotherapy	inhibits VEGF, bFGF, COX-2 and endothelial proliferation
imatinib mesylate (STI-571, Glivec)	small molecule inhibitor of PDGFR
Gene therapy	
prodrug activation	herpes simplex virus vector expressing thymidine kinase (HSVtk)
tumour suppressor gene therapy	replaces the missing or mutated tumour suppressor protein (i.e. p53, PTEN)
antisense gene therapy	inhibits genes responsible for tumourigenesis (i.e. urokinase plasminogen activator receptor and cathepsinB)

EGFR, Epidermal Growth Factor Receptor; VEGF, Vascular Endothelial Growth Factor; TGF, Transforming Growth Factor; CAR, chimeric antigen receptor; HER, Human Epidermal growth factor Receptor; PDGFaR, platelet-derived growth factor alfa receptor; ErbB, Epidermal Growth Factor (EGF) family of receptor tyrosine kinases (RTKs); PTEN, phosphatase and tensin homolog deleted on chromosome ten; PI3K, Phosphoinositide 3-kinase; ras, name of gene family; AKT, name of protein family; mTOR, mammalian target of rapamycin; bFGF, basal fibroblast growth factor; COX, Cyclooxygenase

Summary

Brain tumour is a well recognized diagnosis in paediatric oncology and these patients represent everything that is positive and negative about current treatment: increasing cure rates, the promise of new treatments, deleterious effects of therapy, and a lack of understanding about the impact of current treatment on long-term survivorship. Patients, their parents and caregivers need to be oriented to the relative merits of all treatment options based on peer-reviewed data. The major hope for future improvements in childhood brain tumour management rests on the ability to translate laboratory advances, especially new understandings in the molecular genetics and biology of brain tumours, into more effective therapeutic approaches.

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