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Tumors of the nervous system

Learning guide for students
Faculty of Medicine

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Introduction

Significant advances have been made in neuro-oncology in terms of understanding the genetic origins and evolution of brain tumors, particularly gliomas. In addition, continuing advances in technologies have allowed more refined and nuanced resections of tumors with sparing of normal brain function. In combination with the increased use of functional imaging and intraoperative imaging technologies, the work of the neurosurgical oncologist is increasingly precise.

This section contains several outstanding and up-to-date basic/translational chapters related to the pathobiology and pathogenetics of brain tumors. The bulk of this section, however, is dedicated to clinical neuro-oncology and clinical neuro-oncologic surgery. The histology, genetics, diagnosis, management, surgery, and adjuvant therapies are presented in a systematic manner. Ultimately, the objective is to provide the reader with the knowledge accumulated since the early 2000s, so that future advances can be reported in the context of past battles in the fight against brain cancers.

CLASSIFICATION OF TUMOURS OF THE NERVOUS SYSTEM

Beginning with the classification of brain tumours by Bailey and Cushing (1926) a number of classification have been proposed, including those by Penfield, Cone and Elvidge (1931), Kerrohan, et al. (1949), Zulch (1965), Russell and Rubinstern (1971), more recently who has reported a series of classification from time to time.

The Revised 4th Edition of the WHO Classification of the nervous system (2016) is the latest published classification of the tumours of the nervous system.

1. Tumors of neuroepithelial tissue
    - Astrocytic tumours
    - Oligodendroglial tumours
    - Ependymal tumours

- Choroid plexus tumours
- Neuronal tumors
- Tumors of the pineal region
- Embryonal tumors

2. Tumors of cranial and paraspinal nerves
   - Schwannoma
   - Neurofibroma
3. Tumors of the meninges
   - Meningioma
   - Fibrosarcoma
4. Lymphomas and hematopoietic neoplasms
   - Lymphoma
   - Plasmacytoma
5. Germ cell tumors
   - Germinoma
   - Teratoma
6. Tumors of the sellar region
   - Craniopharyngioma
   - Pituitary adenoma
7. Metastatic tumors
   - Lung
   - Breast
   - Melanoma
   - Renal cell
   - Lymphoma
   - Gastrointestinal

GRADING OF CENTRAL NERVOUS SYSTEM TUMOURS

In the CNS, tumours are graded from I to IV. Grade I tumours are those with low proliferative potential and could possibly be cured by surgical resection alone. Grade II tumours are usually infiltrative, have a lower proliferative potential, but often progress to higher grade malignancy and recur, for example, diffuse astrocytoma (DA) (Grade II) which can progress to anaplastic astrocytoma (Grade III) and GBM (Grade IV). Grade III tumours are malignant and these patients have to receive appropriate radiotherapy and/or chemotherapy. Grade IV tumours are cytologically malignant, with brisk mitosis, often associated with necrosis. These patients have a poor prognosis and a fatal outcome. Examples for Grade IV tumours are GBM and most of the embryonal tumours.

PATHOGENESIS

Precise pathogenetic mechanisms in the development of human malignant cerebral neoplasms are still not well defined. Understanding of the processes such as cell-cycle control, programmed cell death and angiogenesis, together with the discovery of oncogenes and TSG have provided insight into the mechanisms of initiation, proliferation and progression of the tumour. Tumourigenesis is a multistep process caused by genetic changes that are either inherited or acquired. The identification of the genes responsible for hereditary syndromes associated with tumours such as p53, Rb and NF genes and the elucidation of their functional role have been extended to understanding the pathogenetic mechanisms underlying sporadically occurring brain tumours. In addition, analysis of genetic changes, such as gene amplification or loss of heterozygosity, allow the identification of markers that can be used as more accurate tools for diagnosis and the assessment of tumour prognosis.

The pathogenetic mechanisms in CNS tumours are discussed under the following heads: (1) Molecular pathogenesis (oncogenes and tumour suppressor genes); (2) Hereditary factors; (3) Oncogenic viruses; (4) Radiation; (5) Chemical carcinogens; (6) Immunosuppression; (7) Hormones and (8) Trauma.

CLINICAL ASPECTS

Most brain tumors present with:

● Progressive neurologic deficit, usually motor weakness

● Headache

● Seizures. Often focal in onset (due to cortical irritation in the area of the tumor), may generalize secondarily.

Focal neurologic deficits associated with brain tumors

In addition to nonfocal signs and symptoms (e.g. seizures, increased ICP…), as with any destructive brain lesion, tumors may produce progressive deficits related to the function of the involved brain.

Some characteristic syndromes:

1. *frontal lobe*: abulia, dementia, personality changes. Often nonlateralizing, but apraxia, hemiparesis or dysphasia (with dominant hemisphere involvement) may occur.
2. *temporal lobe*: auditory or olfactory hallucinations, déja vu, memory impairment. Contralateral superior quadrantanopsia may be detected on visual field testing.
3. *parietal lobe*: contralateral motor or sensory impairment, homonymous hemianopsia. Agnosias (with dominant hemisphere involvement) and apraxias may occur.
4. *occipital lobe*: contralateral visual field deficits, alexia (especially with corpus callosum involvement with infiltrating tumors).
5. *posterior fossa*: cranial nerve deficits, ataxia (truncal or appendicular).

Headaches with brain tumors

Headache (H/A) may occur with or without elevated ICP. H/A are present equally in patients with primary or metastatic tumor (≈ 50% of patients). Classically described as being worse in the morning (possibly due to hypoventilation during sleep), this may actually be uncommon. Often exacerbated by coughing, straining, or bending.

Associated with nausea and vomiting in 40%, may be temporarily relieved by vomiting (possibly due to hyperventilation during vomiting). These features along with the presence of a focal neurologic deficit or seizure were thought to diferentiate tumor H/A from others.

Etiologies of tumor headache.

The brain itself is not pain sensitive. H/A in the presence of brain tumor may be due to any combination of the following:

1. increased intracranial pressure (ICP): which may be due to
    a) tumor mass efect
    b) hydrocephalus (obstructive or communicating)
    c) mass efect from associated edema
    d) mass efect from associated hemorrhage
2. invasion or compression of pain sensitive structures:
    a) dura
    b) blood vessels
    c) periosteum
3. secondary to difficulty with vision
    a) diplopia due to dysfunction of nerves controlling extra-ocular muscles
        - direct compression of III, IV, or VI
        - abducens palsy from increased ICP,
        - internuclear ophthalmoplegia due to brain stem invasion /compression
    b) difculty focusing: due to optic nerve dysfunction from invasion /compression
4. extreme hypertension resulting from increased ICP (part of Cushing's triad)
5. psychogenic: due to stress from loss of functional capacity

Supratentorial tumors

Signs and symptoms include:

1. those due to increased ICP:
    a) from mass effect of tumor and/or edema

b) from blockage of CSF drainage (hydrocephalus): less common in supratentorial tumors (classically occurs with colloid cyst, may also occur with entrapped lateral ventricle)

2. progressive focal deficits: includes weakness, dysphasia
    a) due to destruction of brain parenchyma by tumor invasion
    b) due to compression of brain parenchyma by mass and/or peritumoral edema and/or hemorrhage
    c) due to compression of cranial nerve(s)
3. headache
4. seizures: not infrequently the first symptom of a brain tumor. Tumor should be aggressively sought in an idiopathic first time seizure in a patient > 20 years (if negative, the patient should be followed with repeat studies at later dates). Rare with posterior fossa tumors or pituitary tumors
5. mental status changes: depression, lethargy, apathy, confusion
6. symptoms suggestive of a TIA (dubbed "tumor TIA ") or stroke, may be due to:
    a) occlusion of a vessel by tumor cells
    b) hemorrhage into the tumor: any tumor may hemorrhage
    c) focal seizure
7. in the special case of pituitary tumors:
    a) symptoms due to endocrine disturbances
    b) pituitary apoplexy
    c) CSF leak

Infratentorial tumors

Seizures are rare (unlike the situation with supratentorial tumors, seizures arise from irritation of cerebral cortex).

1. most posterior fossa tumors present with signs and symptoms of increased intracranial pressure (ICP) due to hydrocephalus (HCP). These include:
    a) headache:

b) nausea/vomiting: due either to increased ICP from HCP, or from direct pressure on the vagal nucleus or the area postrema (so-called "vomiting center")

c) papilledema: estimated incidence is ≈ 50– 90% (more common when the tumor impairs CSF circulation)

d) gait disturbance/ataxia

e) vertigo

f) diplopia: may bedue to VI nerve (abducens) palsy which may occur with increased ICP in the absence of direct compression of the nerve

2. S/S indicative of mass effect in various locations within the p-fossa

a) lesions in cerebellar hemisphere may cause: ataxia of the extremities, dysmetria, intention tremor

b) lesions of cerebellar vermis may cause: broad based gait, truncal ataxia, titubation

c) brainstem involvement usually results in multiple cranial nerve and long tract abnormalities, and should be suspected when nystagmus is present (especially rotatory or vertical)

Evaluation / Posterior fossa (infratentorial) tumors

In pediatric patients with a posterior fossa tumor, an MRI of the lumbar spine should be done pre-op to rule out drop mets (post-op there may be artifact from blood). In adults, most intraparenchymal p-fossa tumors will be metastatic, and work-up for a primary should be undertaken.

Treatment of associated hydrocephalus

In cases with hydrocephalus at the time of presentation, some authors advocate initial placement of VP shunt or EVD prior to definitive surgery (waiting ≈ 2 wks before surgery) because of possibly lower operative mortality.

PEDIATRIC BRAIN TUMORS

Among all childhood cancers, brain tumors are the second only to leukemias in incidence (20%) , and are the most common solid pediatric tumor, comprising 40 – 50% of all tumors.

Types of tumors

The common pediatric brain tumors are gliomas (cerebellum, brainstem, and optic nerve), pineal tumors, craniopharyngiomas, teratomas, granulomas, and primitive neuroectodermal tumors (PNETs, primarily medulloblastoma). Meningiomas: 1.5% of meningiomas occur in childhood and adolescence (usually between 10– 20 years), comprising 0.4 – 4.6% of intracranial tumors.

Infratentorial vs. supratentorial

It has traditionally been taught that most pediatric brain tumors (≈ 60%) are infratentorial, and that these are equally divided among brain stem gliomas, cerebellar astrocytomas, and medulloblastomas. In reality, the ratio of supratentorial to infratentorial tumors is dependent on the specific age group studied.

Astrocytomas are the most common supratentorial tumor in pediatrics as in adulthood.

MEDICATIONS FOR BRAIN TUMORS

Steroid use in brain tumors

The beneficial effect of steroids in metastatic tumors is often much more dramatic than with primary infiltrating gliomas.

Prophylactic anticonvulsants with brain tumors

20– 40% of patients with a brain tumor will have had a seizure by the time their tumor is diag-nosed.

Antiepileptic drugs (AEDs) are indicated in these patients. 20–45% more will ultimately develop a seizure.

Prophylactic AEDs are not indicated for isolated posterior fossa tumors.

Alkylating agents

Temozolomide (Temodar ®) is a derivative of Dacarbazine and is an oral alkylating agent.

Temozolomide is a prodrug which undergoes rapid non-enzymatic conversion at phisiologic pH to the active metabolite monomethyl

triazenoimidazole carboxamide (MTIC). The cytotoxice effect of MTIC is associated with alkylation.

IMAGING STUDIES FOLLOWING SURGERY OF TUMOR

At many academic centers, it is common to get a noncontrast CT scan within 6–12 hours of surgery to assess for acute complications (primarily blood – within brain or epidural or subdural hematoma, amount of pneumocephalus, hydrocephalus...).

Then to assess the extent of tumor removal, a post-op brain CT or MRI without and with contrast should either be obtained within 2– 3 days, or should be delayed at least 30 days. The non-contrast scan is important to help differentiate blood from enhancement. The contrast images demonstrates areas of enhancement, which may represent residual tumor. After 48 hours, contrast enhancement due to post-operative inflammatory vascular changes ensues, which may be difficult to differentiate from tumor. This usually subsides by 30 days, but may persist for 6 – 8 weeks.

This recommendation regarding the timing of post-op imaging does not apply to pituitary tumors. The effect of steroids on contrast enhancement is controversial, and may depend on many factors (including tumor type).

CRANIOTOMY FOR SUPRATENTORIAL TUMOR

1. position: (depends on location of tumor)
2. pre-op embolization (by neuroendovascular interventionalist) for some vascular tumors including some meningiomas
3. equipment:
    a) microscope
    b) ultrasonic aspirator
    c) image guidance system
4. blood availability
5. post-op: ICU
6. consent (in lay terms for the patient – not all-inclusive):

a) procedure: surgery through the skull to remove as much of the tumor as is safely possible

b) alternatives: nonsurgical management, radiation therapy for some tumors

c) complications: usual craniotomy complications plus inability to remove all of the tumor

DIAGNOSIS AND MANAGEMENT OF BRAIN TUMOR BY TYPE

Neuroepithelial tumors

Astrocytoma

Astrocytomas, which arise from astrocytes, are the most common primary brain tumor. Astrocytomas are histologically graded based on cellularity, anaplasia, mitotic figures, endothelial proliferation and necrosis. Well-differentiated astrocytomas (WDA) have mild hypercellularity and minimal nuclear pleomorphism. They typically occur in children and young adults who present with a seizure or headaches. On CT or MRI scan they usually appear as a non-enhancing mass lesion. Anaplastic Astrocytomas (AA) have moderate cellularity and nuclear pleomorphism with mitotic activity. Moderate endothelial proliferation can be present but no necrosis. These lesions are typically found in mid-life as enhancing lesions with mass effect. They often present with seizures, headaches and/or focal neurological findings. Glioblastoma multiforme (GBM) is characterized by hypercellularity, dramatic nuclear pleomorphism, endothelial proliferation, mitotic figures and necrosis. These patients are usually older adults who present with headaches, seizures or focal neurologic findings. On CT or MRI scan a GBM typically appears as an irregular ring-enhancing lesion with significant mass effect and edema.

Survival correlates with grade: WDA 5-10 years, AA 2-3 years and GBM 1-1.5 year. Astrocytomas can initially present as a low-grade tumor and subsequently convert to a higher grade. De novo AA and GBM tumors occur as well.

Treatment is based on grade. Controversy exists for the optimal treatment of WDA. Most agree that a WDA in non-eloquent brain with mass effect should be resected. A stereotactic brain biopsy for diagnosis is an option for symptomatic

lesions in areas of the brain where open surgery carries an increased risk of causing a deficit. Radiation is controversial in stable tumors but is often used if growth is demonstrated. AA and GBM are typically treated by surgical resection followed by radiation and BCNU chemotherapy. Surgery is indicated for diagnosis, to relieve mass effect, and, possibly, to decrease the "tumor burden". AA or GBM in the motor strip, language areas or other eloquent brain regions are often biopsied rather than resected because of the high risk of surgery in these areas. It has been difficult to prove that the extent of tumor resection has an effect on patient survival. As a rule, surgery is never curative. BCNU impregnated wafers implanted in the tumor bed after resection of a recurrent AA or GBM have proven to be efficacious. Recurrence within a centimeter or two of the resection site is typical regardless of the treatment given after surgical resection. Surgery for recurrent AA and GBM is controversial. Most surgeons agree that reoperation is indicated for the relief of headaches or neurological deficits due to mass effect.

Pathologically, several types of astrocytomas exist, such as fibrillary, protoplasmic and gemistocytic astrocytomas. Glioblastomas also have giant cell and gliosarcoma variants.

A separate group of astrocytoma is the juvenile pilocytic astrocytoma (JPA). This group is either not graded or considered Grade 0. JPA are distinct because they behave in a more benign fashion and when completely resected can be cured by surgery alone. They are typically discrete cystic lesions with an enhancing mural nodule. Histologically, JPA are composed of loose and dense regions of stellate astrocytes. These have Rosenthal fibers that indicate slow growth. JPA are typically found in children and young adults. They tend to occur in the cerebellar hemisphere, optic nerve, hypothalamus and brainstem. Cerebellar JPA often present with signs of increased intracranial pressure (headache, nausea, vomiting) due to hydrocephalus. JPA also can present with cerebellar dysfunction such as gait ataxia or ipsilateral extremity dysmetria. Rarely, JPA can undergo malignant degeneration. Subarachnoid seeding does occur rarely with JPA and probably

carries a poorer prognosis. This has been seen with hypothalamic tumors. Optic nerve JPA and WDA tumors are associated with neurofibromatosis type II.

Pleomorphic xanthoastrocytomas are astrocytic neoplasms found in young adults with a long history of seizures. They are usually superficial in the cerebral cortex and may consist of a mural nodule associated with a cyst. They are typically slow growing but malignant transformation does occur. Subependymal giant cell astrocytomas are typically found at the foramen of Monro in patients with tuberous sclerosis.

Gliomatosis cerebri is a condition where there is diffuse infiltration of the entire brain with an astrocytic tumor.

Oligodendroglial tumors

The majority of oligodendrogliomas present in young adulthood with the onset of seizures. Radiographically, calcifications are typical. The classic histologic appearance is of homogeneously appearing cells with a "fried egg" appearance and "chicken wire" vessel pattern. Similar to WDA, patients can have long term survival. Malignant transformation does occur. These tumors are called anaplastic oligodendrogliomas. In general, surgical resection is recommended when possible for diagnosis, to relieve mass effect, and resect as much tumor as safely as possible. Radiation therapy is controversial, but is probably beneficial. PCV (procarbazine, CNU, & vincristine) chemotherapy has been shown to be beneficial in the treatment of oligodendrogliomas.

Ependymal tumors

Ependymomas typically arise from the lining of the ventricular system and usually occur in children and young adults. The floor of the fourth ventricle is a common location. Ependymomas typically present with hydrocephalus and increased ICP. Presenting symptoms include nausea, vomiting, headache, gait ataxia, diplopia and vertigo. Ependymomas have a significant potential for CSF seeding and thus "drop metastasis". Complete surgical resection has been shown to improve survival and should be attempted if there is minimal brainstem invasion. Postoperative radiation and chemotherapy is usually administered. No clear

consensus exists for grading ependymomas but the term anaplastic ependymoma is sometimes used for more malignant appearing tumors. Paradoxically, intramedullary spinal cord ependymomas, which are histologically identical, may be cured by surgery alone.

Myxopapillary ependymomas are a variant of ependymomas. This tumor occurs in the conus or filum terminale of the spinal cord. Complete resection is probably curative. Subependymomas occur in anterior lateral ventricles or posterior fourth ventricle. They are benign slow growing tumors that are typically found incidentally at autopsy. However subependymomas can cause hydrocephalus from obstruction of cerebrospinal fluid pathways. Symptomatic or enlarging tumors should be removed. In elderly patients insertion of a VP shunt is a viable option if obstruction of CSF pathways is present.

Mixed gliomas

Mixed gliomas occur and appear histologically as a combination of neoplastic oligodendrocytes and astrocytes. These tumors are referred to as oligo-astrocytomas or anaplastic oligo-astrocytomas. Often the name is shortened to the dominant cell type only.

Choroid plexus tumors

Tumors of the choroid plexus are called choroid plexus papillomas (CPP). In children less than 2 years of age, they usually are located in the lateral ventricle and present with hydrocephalus. In adults CPP usually occur in the fourth ventricle, foramen of Luschka or cerebellopontine angle. The treatment is surgical resection, though elderly patients with an asymptomatic cerebellopontine angle tumor may be followed with serial imaging studies. Recurrence should be treated aggressively with reoperation, when possible, due to a favorable prognosis. One or two percent of choroid plexus tumors are carcinomatous. Choroid plexus carcinoma carries a poor prognosis.

Neuronal and mixed Neuronal-glial tumors

Gangliocytoma is a tumor composed of large abnormal mature neurons. They are primarily supratentorial with the most common location being the

temporal lobe. The majority of patients are in their first two decades of life. Surgical resection, when complete, is curative. Variable radiographic features occur, ranging from an enhancing mural nodule to a ring enhancing mass with calcifications.

Dysplastic gangliocytoma of the cerebellum (Lhermite Duclos Disease) is a non-neoplastic mass of hypertrophic granular cell neurons which expands the cerebellar folia. These tumors can cause mass effect and hydrocephalus and typically occur in young adults. Resection (total or subtotal) and/or shunting are therapeutic options.

Dysembryoplastic neuroepithelial tumors (DNET) are a "hamartomatous", supratentorial, predominantly temporal lobe lesion composed primarily of glial cells. They usually present with seizures. Radiographically these tumors often lack edema and have a multinodular appearance. Inner table skull erosion or deformation may be present.

Gangliogliomas are tumors consisting of large mature neurons and a neoplastic glial component. This tumor affects patients of all ages with the majority diagnosed in young adults who often have a long history of seizures. Surgical resection even if subtotal can be curative. Surgery is recommended for diagnosis and, on occasion, for control of seizures.

Pineal tumors

Pineal tumors are tumors arising from pineocytes. The well-differentiated pineocytoma occurs in mid-life as a discrete contrast enhancing mass in the posterior third ventricle/pineal region. The poorly differentiated pineoblastoma has a similar location and enhances with contrast but shows signs of local invasion and is prone to CSF dissemination. The complex of pineoblastoma and bilateral retinoblastoma is called trilateral tumor. In general, pineocytomas have a good prognosis while pineoblastomas with subarachnoid spread are aggressive and carry a poor prognosis. Pineal tumors often present with hydrocephalus due to obstruction of the aqueduct of Sylvius. Compression of the dorsal midbrain by a

pineal tumor can result in Parinaud's syndrome of pupillary mydriasis, paralysis of upgaze, and convergence retractorius.

Embryonal tumors

Neuroblastoma is a small cell neoplasm with neuroblastic differentiation arising in the deep cerebral hemispheres of young children (<5 yrs. of age). A variant is the ganglioneuroblastoma that has a preponderance of ganglion appearing cells.

The olfactory neuroblastoma (esthesioneuroblastoma) is a neuroblastic tumor arising from the nasal epithelium with cribiform plate involvement. There is a bimodal age distribution in adolescents and older adults. Patients present with nasal obstruction and or epistaxis. Complete surgical resection with combined cranio-facial resection is the treatment of choice, with a generally favorable prognosis. Adjuvant radiation therapy is generally recommended.

Ependymoblastoma is a rare small cell embryonal neoplasm with prominent ependymoblastic rosettes. It typically occurs in the cerebrum of children less than five years of age. Its propensity for craniospinal dissemination often leads to death within a year.

Retinoblastoma is a retinal neoplasm that occurs in children < 3 years of age. Ophthalmoscopic exam is diagnostic, giving the characteristic white reflex. These tumors have both hereditary (earlier onset and bilateral) and sporadic forms. Surgical resection with or without radiation can be curative.

Medulloblastoma or primitive neuroectodermal tumor (PNET) of the cerebellum is a small cell neoplasm believed to arise from the external granular layer of the cerebellum. This tumor arises in the vermis of children and young adults although cases in older patients have been reported. Radiographically, these are homogeneously enhancing masses of the cerebellar vermis. CSF tumor seeding can produce drop metastases, even at the time of diagnosis. Surgical resection, combined with radiation and chemotherapy, may lead to significant long-term survivals. Rarely, metastasis to bone, lymph nodes and lung have been reported. Variants include desmoplastic medulloblastoma, medullomyoblastoma, and

melanocytic medulloblastoma. Medullomyoblastoma occurs in children, with a propensity for boys. Cerebral (supratentorial) and spinal PNET's occur, but with much less frequency.

Tumors of cranial and spinal nerves

Schwannomas

Schwannomas (neurinoma, neurilemmoma) are tumors composed of Schwann cells that arise along cranial or spinal nerves. The vestibular schwannoma (acoustic neuroma) is probably the most common schwannoma and arises typically from the superior vestibular nerve. Vestibular schwannomas typically present with tinnitus and sensori-neural hearing loss. Facial numbness follows when the tumor reaches approximately 2.5 cm. Ipsilateral coordination difficulties and mild facial nerve weakness typically do not occur until the tumor diameter is greater than 3 cm. Radiographically, these tumors enhance with contrast and extend into the internal auditory canal. Complete surgical resection is curative. Hearing and facial nerve preservation is dependent on tumor size and preoperative level of nerve function. In older patients or poor surgical candidates, stereotactic radiosurgery is an effective treatment for tumor size < 2.5cm. Some proponents of radiosurgery feel that it should be used as the primary treatment for all but the largest tumors. Bilateral vestibular schwannomas occur with neurofibromatosis type II.

Neurofibromas

Neurofibromas are a nerve sheath tumor composed of Schwann cells, fibroblasts and perineural cells. This tumor can occur in isolation or in associated with neurofibromatosis. This tumor may be solitary, plexiform or occur as a mixed neurofibroma/schwannoma. These tumors arise from nerves in the subcutaneous tissue or in the neuroforamena. Classic spinal tumors have a dumbbell appearance when they extend across the neuroforamena. Surgical resection is indicated in symptomatic lesions. Malignant transformation in neurofibromas is rare but should be suspected with increasing size or pain.

Malignant peripheral nerve sheath tumors

Malignant peripheral nerve sheath tumors: neurogenic sarcoma, anaplastic neurofibroma, and malignant schwannoma are rare malignant tumors arising from the non-neural elements of nerves. These have a poor prognosis with death resulting within the year. Complete resection is usually not feasible.

Tumors of the meninges

Meningioma (subtypes: meningothelial, transitional, fibrous, psammomatous, angiomatous, microcystic, secretory, clear cell, choroid, lymphoplasmacyte-rich, metaplastic variants, atypical, anaplastic).

Meningiomas are typically solitary, benign, slow growing, extra-axial tumors arising from arachnoid cap cells in the cranium and spine. The most common locations are parasagittal, convexity, tuberculum sella and sphenoid ridge. A small percentage may be intraventricular. Meningiomas rarely occur in children but when they do there is a predilection for the posterior fossa and ventricle. Less than five percent of meningiomas are malignant, characterized by brain invasion and increased mitotic activity. Meningiomas are most common in middle age and elderly women. Common symptoms include headache, seizures, weakness, and mental status changes. Focal neurologic deficits on presentation depend on the site of origin of the tumor. Radiographically these tumors are well circumscribed, homogeneously enhancing lesions. There may be hyperostosis of the underlying skull. There is often a tail of dural enhancement at the edge of the tumor after contrast administration on imaging studies. The primary treatment of symptomatic surgically accessible tumors is surgical resection. Surgery if complete is often curative. Large lesions may require embolization of intra-operatively inaccessible vascular supply prior to surgical resection to decrease intraoperative bleeding. Small or asymptomatic meningiomas in older individuals can be followed and treatment recommended if growth is demonstrated. Radiation therapy and/or radiosurgery are treatment alternatives for recurrent tumors or if surgery carries an increased risk of complications. There is an association between meningiomas and neurofibromatosis type 2 and an abnormality in the long arm of chromosome 22.

Cysts and tumor-like lesions

Numerous cysts and tumor-like lesions can occur in the brain including Rathke's cleft cyst, epidermoid cyst, dermoid cyst, colloid cyst of the third ventricle, enterogenous cyst (neuroenteric cyst), neuroglial cyst, other cysts, lipoma, granular cell tumor (choristoma, pituicytoma), hypothalamic neuronal hamartoma, nasal glial heterotopias.

Tumors of the anterior pituitary

Pituitary adenomas are slow growing, benign tumors that arise in the anterior pituitary gland. Pituitary tumors are divided into hormone secreting tumors and non-secretors. Tumors less than 1 cm in diameter are referred to as microadenomas while tumors larger than 1 cm are called macroadenomas. Prolactinomas are pituitary adenomas that secrete the hormone prolactin. Prolactinomas often present with amenorrhea in women and loss of libido in men. The primary treatment for prolactinomas is medication, usually bromocryptine analogues. Bromocryptine often results in a decrease in tumor size but does not kill tumor cells. It usually must be continued for life or tumor recurrence is the rule. Adenomas that secrete growth hormone produce gigantism if present before puberty and acromegaly if present after puberty. ACTH secreting adenomas result in Cushing's disease. Hypercortisolism is characterized clinically by centripetal obesity, moon facies, buffalo hump, glucose intolerance, hypertension and impaired wound healing. Non-secreting macroadenomas with suprasellar extension can compress the optic chiasm. Compression of the optic chiasm from below often produces a bitemporal hemianopsia. Spontaneous hemorrhage or infarction of a pituitary adenoma is referred to as pituitary apoplexy and can result in sudden visual loss or hypocortisolism. Emergent surgery is sometimes necessary for pituitary apoplexy.
The primary treatment for patients with secreting pituitary adenomas producing Cushing's disease, acromegaly, or symptomatic non-secreting tumors is surgical resection. Surgery is typically performed through the transsphenoidal route. Cavernous sinus invasion by adenoma cells often makes a surgical cure difficult.

Recurrent tumors or those with cavernous sinus invasion can be treated with re-operation or radiation therapy.

Metastasis

Metastases are the most common brain tumor. Tumors that frequently spread to the brain, in order of decreasing incidence are: lung, breast, skin, colon, and kidney. Commonly, lung, thyroid, renal cell and melanoma metastases can become hemorrhagic. The treatment of solitary lesions is surgical resection followed by radiation therapy. For patients with multiple asymptomatic lesions, surgery is reserved for diagnosis only. For patients with controlled systemic disease but multiple brain metastases, a large symptomatic accessible lesion could be considered for resection. Whole brain radiation is generally given for multiple brain metastases.

PREOPERATIVE EVALUATION AND MANAGEMENT

The initial evaluation of a patient with a brain tumor includes a detailed history, a general examination and a detailed neurological examination, and evaluation of the available radiologic studies. While carrying out the evaluation, the surgeon should be trying to answer the following questions:

1. What is the most likely pathology of the tumor? What are the other possibilities?

2. Does the patient need surgery, or is observation appropriate? If surgery is indicated, is the indicated procedure an open resection or stereotactic biopsy?

3. When should the surgery take place? Is there any urgency?

4. What other radiologic or laboratory studies are necessary for the surgeon to be maximally prepared to perform the surgery?

When these four questions have been answered, the surgeon can counsel the patient about what should be expected from surgery and initiate the surgical treatment plan.

PREOPERATIVE IMAGING INTERPRETATION

Interpretation of the preoperative imaging studies is important in terms of planning the surgery, setting surgical goals, and educating the patient. Most

patients have already had gadolinium-enhanced magnetic resonance imaging (MRI) scans when they are seen by the neurosurgeon. When the surgeon evaluates the MRI scan, answers to the following questions are invaluable:

1. What is the location of the tumor: supratentorial or infratentorial; deep or superficial; frontal, temporal, or parietal?

2. Is the tumor intra-axial or extra-axial?

3. Is there a mass effect on normal brain structures? Are brain structures shifted across the midline? This is important in determining how quickly the tumor has grown and how rapidly the problem needs to be addressed.

4. Does the tumor enhance on imaging with administration of contrast material?

5. Is vasogenic brain edema seen surrounding the tumor? This is best visualized on the fluid-attenuated inversion recovery (FLAIR) and T2-weighted MRI scans.

6. What is the relationship of the tumor to vascular structures and the draining sinuses?

Answering these six questions allows the surgeon to identify the most plausible disease, assess the urgency of the problem, plan the surgical approach, and schedule any additional preoperative imaging studies that are needed. While studying the MRI findings and answering the six questions, surgeons should begin to organize their thoughts about the biologic behavior of the tumor. For example, is it a slow-growing tumor, such as an intrinsic low-grade astrocytoma, or is it a more aggressive intrinsic brain tumor? The presence of brain edema, mass effect, and contrast enhancement argues against a slow-growing process and for a high-grade, fast-growing tumor. Surgeons must be aware, however, that there are always exceptions to such rules. The surgical issues and approach will differ, depending on the probable diagnosis, and surgeons must constantly test their diagnostic hypothesis by looking for clues that suggest a different diagnosis. For example, meningiomas are enhancing lesions that can reach a large size and have a significant mass effect, but the surgical goals for affected patients differ from those

for patients with high-grade gliomas. Although the extradural location leads the surgeon to the diagnosis of meningioma, the pace and severity of symptoms provide important clues about the biologic behavior of the tumor. Slow-growing tumors can reach a very large size and cause impressive shifts in normal brain structures without causing many symptoms. Growth of the tumor over a long period allows the brain to accommodate and adjust and maintain its function at a normal or nearly normal level. Symptoms that arise over a short period and increase in severity suggest a more ominous pathologic process and a fast-growing lesion. Correlating the pace and severity of symptoms with the radiologic findings is critical for formulating a surgical treatment plan and its timing.

TIMING OF SURGERY

The timing of surgery is dictated by the type of symptoms and their pace. Progressive symptoms over a short period indicate that the tumor and edema are expanding faster than the brain is able to compensate. Recognition of this situation is critical because affected patients are at risk for rapid deterioration. According to the Monro-Kellie principle, introduced to neurosurgery by Harvey Cushing, changes in brain volume cause reciprocal changes in the blood and cerebrospinal fluid (CSF) compartments within the rigid cranial sphere to maintain intracranial pressure (ICP) within a normal range.

As brain volume increases in response to a mass such as a tumor, a compensatory decrease in CSF or blood volume occurs to maintain ICP within the normal range. As the tumor expands, ICP increases slowly until there is no further displaceable volume (i.e., CSF or blood). At this point, further increases in brain volume result in an accelerated increase in ICP.

It is unusual for a brain tumor to necessitate emergency surgery. The two exceptions are (1) a marked increase in ICP as a result of the tumor mass and brain edema and (2) the presence of acute or subacute obstructive hydrocephalus. In both circumstances, ICP is elevated. Patients with increased ICP can have marked alterations in mental status. Patients with obstructive hydrocephalus need either a temporary ventriculostomy before a planned resection or a ventriculoperitoneal

shunt. A third option is to proceed directly to tumor resection, with the goal of relieving the hydrocephalus. Patients with marked brain edema require high doses of steroids; this regimen usually results in neurological improvement.

SURGICAL PLANNING: IMAGING STUDIES

After deciding that the patient needs surgery, the surgeon must determine whether additional imaging studies are needed to better define the relationship between the tumor and the patient's normal anatomy. The studies that might be obtained are (1) angiography, magnetic resonance angiography, or venography to assess the relationship of the tumor to the blood vessels; (2) MRI for use with a frameless stereotactic system; (3) functional MRI to assess the tumor's relationship to areas controlling eloquent brain functions; and (4) diffusion tensor imaging to assess the relationship of critical cortical pathways to the tumor.

The use of angiography for the diagnosis and evaluation of brain tumors has diminished significantly with the advent of MRI. Preoperative embolization represents another indication for preoperative angiography.

Typically, routine enhanced MRI is the imaging modality used interactively in the operating room. However, additional imaging modalities can now be used in the navigation system to increase the likelihood of success in the operation (i.e., maximal tumor resection with no neurological sequelae). Such modalities include functional MRI, diffusion tensor imaging with fiber tract images, positron emission tomography, and ultrasonography. It is critical to understand the limitation of this technology in terms of the brain shifts that occur during surgery, as well as the accuracy and reliability of using the different imaging modalities. Although it is most useful with intra-axial tumors, we have also found it valuable for extra-axial tumors, particularly meningiomas.

Intraoperative MRI is becoming increasing available. Intraoperative MRI allows the surgeon to use an updated MRI scan obtained during surgery to determine whether additional resection is necessary. Intraoperative computed tomography can provide similar information, but the ability to differentiate the tumor margin and estimate the extent of resection is limited. Whether

intraoperative MRI also improves tumor resection and outcomes remains to be determined.

Functional imaging is playing an increasing role in surgical planning. Functional MRI and fiber tract localization with diffusion tensor imaging allows localization of eloquent brain areas and tracts in relation to the tumor and to the planned surgical approach. This information is used to assess the patient's risk with surgery and to assist the surgeon in approaches to resection. The data can be loaded onto the intraoperative navigation system in order to use the information in real time. There are limitations to functional MRI that involve the specificity of the data. The study is based on changes in blood flow that occur when a person is carrying out a task; thus the accuracy of the result depends on the assumption that the measured increase in blood flow identifies the area of the brain responsible for the activity being performed. This assumption may not be correct in the setting of certain tumors with increased blood flow and perfusion because there may be no relationship between blood flow and function around the tumor. The surgeon must discuss the functional MRI results with an experienced radiologist.

SURGICAL PREPARATION

We prefer to pretreat patients with steroids for several days before surgery when symptomatic brain edema or mass effect is present. In the absence of symptoms, steroids are started at the time of surgery. If steroids are started preoperatively, the typical dose is 16 mg/day or 4 mg four times a day.

In addition to steroids, anticonvulsant therapy is started, usually phenytoin (Dilantin) or levetiracetam (Keppra). Patients with high-grade lesions undergo surgery within 7 to 10 days of initial evaluation. In patients undergoing more elective surgery, such as those with schwannomas and meningiomas, surgery may not be performed for several weeks or longer, and anticonvulsant treatment is not started preoperatively. In addition to clearing any cardiac or pulmonary issues before surgery, the surgeon should review the patient's medications to check for any that might be contraindicated by surgery: in particular, aspirin, fish oil, and some antipsychotic agents.

Once the patient is under general anesthesia, an arterial line and a Foley catheter are placed. For most craniotomies, central venous access is not indicated. When the patient's head is positioned significantly higher than the heart, central venous access can be important because there is a real risk of venous air embolism and the central venous line is helpful in treating this problem. In addition to anesthetic needs, neuromonitoring electrodes for evoked potentials, electromyography, and electroencephalography are placed on the patient. Somatosensory evoked potentials are the most common neurophysiologic monitoring data used in craniotomies for brain tumors. One derivation of somatosensory evoked potentials is to localize the motor strip with a strip electrode by means of phase reversal. This is valuable in planning where to make the cortical incision for an intrinsic tumor near the central sulcus. If frameless stereotaxy is to be used, registration of the machine to the patient is performed after the patient's head has been positioned in the head-holding device.

POSITIONING

Positioning is an important but often overlooked part of the surgical procedure. The four body positions are supine, lateral, prone, and sitting. The sitting position is rarely used today. In the past, it was used primarily for pineal tumors, but it has been replaced by the prone Concorde position.

Several general principles apply to all craniotomies for tumor removal. First, the position of the patient should not put any extremity, muscle, or body part at risk for injury. For example, it is better to position the patient laterally for a posterior frontal-parietal lesion than to turn the head in the supine position so that the neck and shoulder are under stress and stretch. Included in this principle is the use of padding and protection of the patient's elbows, hands, and eyes. The second general principle is that the position should promote venous drainage from the brain back to the heart. This includes (1) positioning the patient's head so that the neck is supple and (2) elevating the head so that it is above the level of the heart. In the prone and lateral positions, in which the neck is flexed and sometimes bent laterally, the neck veins can be compromised. Poor venous drainage results in

increased blood volume within the intracranial cavity. If the surgeon is dealing with a large tumor with vasogenic edema, the extra venous blood will result in brain swelling and make the surgery more difficult. The corollary of this principle can be used to achieve brain relaxation when the brain is swelling and pushing out through the dural opening. Elevation of the patient's head and improvement in venous return can lead to brain relaxation. The third principle is that whenever possible, the approach through the brain to the tumor should be perpendicular to the floor. Positioning the patient in this way results in a minimal amount of brain retraction during resection. In addition, this is often the most comfortable position for the surgeon. Positioning the patient in this way is most useful for intrinsic supratentorial tumors. For extra-axial tumors, the goal of patient position is, again, to allow the surgeon to remove the tumor with minimal brain retraction. However, for extra-axial lesions, this is usually a position in which gravity, as well as removal of CSF, will assist in brain relaxation.

CRANIOTOMIES

Frontotemporal

A frontotemporal craniotomy is a standard approach to intrinsic tumors located in the frontal or temporal lobes. It is also used for tumors in the suprasellar area and the anterior skull base. A modification of this approach is the orbitozygomatic or modified orbitozygomatic approach, in which the orbital rim is removed to facilitate access to the skull base and minimize brain retraction.

Parieto-Occipital

Parieto-occipital craniotomy allows exposure of the entire parietal lobe, the posterior temporal lobe, and the occipital lobe. Tumors located in the parieto-occipital area are best approached with this craniotomy. In addition, intraventricular tumors located in the posterior horn of the ventricle, as well as thalamic tumors, are approached with this craniotomy.

Parasagittal

Intra-axial and extra-axial tumors located in the parasagittal region are approached with a parasagittal craniotomy. This is also the craniotomy for

approaching intraventricular tumors in the anterior horn and body of the lateral ventricle, as well as tumors located in the region of the foramen of Monro and third ventricle.

Midline Cerebellar

The midline approach is used for tumors located in the fourth ventricle, in the vermis, or in the pineal region. The exposed cerebellum includes a portion of both cerebellar hemispheres, and so a tumor located medially in the cerebellar hemisphere could also be approached with this craniotomy.

Lateral Cerebellar

Tumors located in the lateral cerebellar hemisphere and tumors in the cerebellopontine angle are exposed with the lateral cerebellar approach.

TUMOR REMOVAL

Removal of the tumor is the culmination of the operative process. All the presurgical planning, positioning of the patient, and size of the craniotomy are aimed at putting the surgeon in the best position to safely remove the tumor. Intraoperative adjuvant techniques that facilitate maximal safe surgical resection include intraoperative navigation with frameless stereotactic systems, intraoperative ultrasonography, and intraoperative MRI. These tools provide imaging feedback that the surgeon can use to evaluate the extent of resection. These tools should be used to complement the visual feedback that the surgeon is receiving from the gross appearance of the tumor.

POSTOPERATIVE CARE

After surgery, most patients spend 1 day in the neurological critical care unit before returning to a regular hospital room. During this time, the patient is monitored for signs and symptoms of elevated ICP or for any change in neurological function. Routine postoperative orders for patients with brain tumors include high-dose steroids, H2 blockers, antibiotics for 24 hours, anticonvulsants, and intravenous fluids at two-thirds maintenance requirements.

As mentioned earlier, the most valuable parameter to follow is the findings of the neurological examination, particularly the level of consciousness, papillary

responses, and the motor responses. Any changes in the neurological parameters should be investigated to determine the cause, and the neurosurgeon should be notified.

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