B.2. Diagnosis and Management of Brain Tumor and Abscess

a. Neuroepithelial tumors

i. 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. The 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.

ii. 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.

iii. 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.

iv. 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.

v. 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.

vi. 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.

vii. 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.

viii. 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.

b. Tumors of cranial and spinal nerves

i. 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.

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.

iii. 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.

c. 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.

d. 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.

e. 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.

f. 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.

g. Brain Abscess

Brain abscesses arise by several mechanisms including hematogenous spread, penetrating trauma, surgery, or local spread from the paranasal sinuses, mastoid air cells or emissary veins. The peak incidence is in young men due to the occurrence of middle ear and paranasal sinus infections in addition to congenital heart disease. Other predisposing factors include Osler-Weber-Rendu syndrome with pulmonary arteriovenous fistulae, endocarditis, congenital heart disease, dental work and immunosuppression. Symptoms consist of headache, fever, seizures and/or neurological deficit. The majority of brain abscesses are solitary.

Aerobic and anaerobic bacterial abscesses occur. Abscess cultures in one third of patients grow multiple organisms. Common organisms based on the site of origin include Streptococcus species from the frontal/ethmoid sinus; Bacteroides fragilis from chronic mastoiditis/otitis; Staph. aureus or enterobacteriacea following penetrating trauma or surgery; Strep. viridans and Strep. pneumonia in cases of congenital heart disease; Staph aureus and Strep. pneumonia in cases of endocarditis. In immunosuppressed patients, toxoplasma gondii, nocardia, mycobacteria, yeast and fungal abscesses occur. Outside the US, tuberculomas, cysticercosis, echinococcus, schistosomiasis and strongoloidiasis are more common.

In the first stage of brain infection, there is inflammation of the brain, termed early cerebritis. This stage occurs in the first 3-5 days after inoculation. The CT scan appearance of cerebritis is that of an ill-defined hypodense contrast enhancing area. This coalesces to a late cerebritis stage during days 4-13 with irregular rim enhancement. This is followed, at approximately day 14, by a collagen reticulum encapsulation with a necrotic center (early capsule stage) On CT scan or MRI scan this appears as a ring enhancing mass often with the abscess wall facing the ventricle appearing the thinnest. The final stage is the late capsule stage in which there is a three-layer capsule: an outer gliotic layer, a middle collagenous layer and an inner granulation layer. These can persist for months on imaging studies before ultimate resolution.

Antibiotics are the mainstay of treatment in all cases. Empiric treatment of a presumed bacterial abscess requires coverage for both aerobes and anaerobes. Surgery is usually indicated to confirm the diagnosis of an abscess and for culture and sensitivity of specific organisms. Stereotactic aspiration is the treatment of choice. Aspiration may need to be repeated before resolution occurs. Often two to three weeks of antibiotic treatment are needed before a size decrease is seen on imaging studies. In general 4 – 6 weeks of intravenous antibiotics are often used, followed by a period of oral antibiotics. Patients with nocardia abscesses, or patients in whom treatment has failed after the third aspiration, should consider surgical resection when accessible. Often, aspiration alone can treat significant mass effect and prevent rupture of the abscess into the ventricular system. Ventricular rupture of a bacterial brain abscess is often fatal.