Part I

Overview and General Aspects of Therapy

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Diagnosis of Brain Tumors: Clinical and Radiographic

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Introduction

Recent epidemiologic studies by the Central Brain Tumor Registry of the United States report the rate of symptomatic brain tumors at 19 per 100,000 person-years. An estimated 64,500 new cases of primary central nervous system (CNS) tumors and 150,000 cases of brain metastases are expected to be diagnosed in the United States in 2011. Surgery, chemotherapy, and radiation are the mainstays of therapy, and early diagnosis may produce better outcomes.

This chapter focuses on the diagnosis of tumors of the CNS and reviews both presenting clinical and neuroimaging features. Clinical recognition and imaging are essential early steps in identification of CNS tumors, although pathologic evaluation of tissue samples remains the gold standard for diagnosis. Rarely, when a biopsy is not feasible (for example with pediatric brainstem tumors), imaging has an even more valuable role. Our goal is to familiarize clinicians with general principles that are useful in the clinical recognition of potential brain tumors and to review imaging modalities that help differentiate brain tumors from other mass lesions.

Clinical diagnosis of brain tumors

History

Diagnosis of CNS neoplasms begins with a good clinical history and examination. Both nonspecific and focal neurologic complaints and symptoms can alert the primary care physician or neurologist to the possibility of an underlying mass lesion and indicate the need for further work-up. Key aspects of the history that help differentiate neoplastic lesions from other diagnoses include timing of symptom onset, tempo of progression, and severity of symptoms. Systemic symptoms and the presence of other diseases or hereditary syndromes are additional valuable pieces of information that can help narrow the diagnosis by their association with specific CNS tumors.

Symptoms produced by brain tumors may be either nonspecific or focal, and in general tend to be subacute in onset. The presentation varies widely and neither a normal neurologic exam nor presentation with acute onset of symptoms rules out a brain tumor. At the outset many brain tumors produce minimal or no symptoms. In

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contrast, brain tumors can also present with acute onset stroke-like symptoms. This type of acute presentation is usually the result of a focal seizure or hemorrhage into the tumor bed. Less common causes include infarction or intraparenchymal hemorrhage resulting from stroke or venous sinus thrombosis, two conditions to which brain tumor patients are predisposed given their inherent hypercoagulable state.

The rate of progression of symptoms is also quite variable but tends to be gradual over weeks to months, helping to differentiate neoplasms from other more static disorders such as degenerative disease or more rapidly progressing infectious conditions. By paralleling the growth and spread of CNS neoplasms, the rate of symptomatic progression can serve as a rough clinical estimate to tumor grade. Typically, benign tumors such as meningiomas, or low-grade neoplasms such as oligodendrogliomas, will have a slower progression of symptoms than more malignant tumors such as glioblastomas.

Various other historical factors associated with brain tumors that can be elicited in the history are helpful in the formulation of a differential diagnosis. A careful review of systems, for instance, should identify symptoms such as weight loss, lethargy, and night sweats that are nonspecific but can be associated with many types of cancers. When combined with neurologic symptoms, these symptoms should raise suspicion of primary or metastatic CNS neoplasms, though should not rule out subacute infectious, inflammatory, or autoimmune CNS processes. Likewise, a detailed review of past medical history may identify genetic syndromes or other conditions with a higher than normal incidence of CNS neoplasms. Li–Fraumeni syndrome, resulting from germline mutations in the p53 tumor suppressor gene, is associated with a strong family history of multiple cancers including breast cancer, sarcoma, and leukemia, and associated with glioblastomas. Neurofibromatosis type 1 is associated with gliomas and cutaneous manifestations, neurofibromatosis type 2 is associated with vestibular schwannomas and meningiomas, while von Hippel–Lindau syndrome is associated with hemangioblastomas. Other systemic illnesses increase the risk for specific CNS neoplasm; one of the best examples of this is the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Neurologic symptoms in immunocompromised patients, and in particular those with HIV/AIDS, should raise concern for primary CNS lymphoma (PCNSL). Likewise, focal neurologic symptoms in patients with a prior history of systemic cancers or lymphoma raises suspicion for brain metastases or CNS lymphoma. Lastly, knowledge of prior exposure to ionizing radiation can be helpful. Irradiation of the cranium is the only environmental exposure or behavior that is known unequivocally to increase the risk for intracranial tumors, specifically meningiomas, glial tumors, and schwannomas.

Clinical presentation and symptoms

Though classically patients with mass lesions are thought to present with focal or lateralizing symptoms, the reality is that many patients present with impairments reflecting multifocal, global, or nonspecific cerebral dysfunctions. The variety of symptoms and symptom subtypes reflect the diverse actions of tumors, either directly or indirectly, on brain function. Tumors such as gliomas or lymphomas can directly invade and destroy brain parenchyma. Others, such as meningiomas, directly compress and distort brain tissue. Such direct effects can result in a disruption of brain functioning at the cellular or circuit level resulting in focal neurologic signs. Alternatively, compression or invasion of other intracranial structures such as blood vessels, leptomeninges, and CSF outflow tracts is possible, and could lead to infarctions, venous sinus thromboses, elevated intracranial pressure, and hydrocephalus. Disruption of the blood–brain barrier (BBB) is another frequent occurrence that leads to vasogenic edema and thus increases the territory of brain parenchyma that becomes affected. Importantly, other factors inherent to the tumor itself, including location, size, and growth rate, impact the clinical presentation. Tumor size will determine how much of the brain is affected, which can correlate with both the number and severity of symptoms. The rate of tumor growth impacts the brain's ability to adapt to pathologic changes, and slower growing tumors often produce milder symptoms.

Generalized non-focal symptoms

Generalized tumor-associated symptoms are global and nonlocalizable. Often, patients with intracranial neoplasms have generalized impairments of cerebral function and present with vague complaints, making accurate diagnosis difficult. Headaches, nausea, vomiting, and changes in mental status, cognition, and level of consciousness usually reflect raised intracranial pressure from mass effect or hydrocephalus. Other symptoms and signs, such as global mental status changes, are quite pervasive and include apathy, change in personality, irritability, psychomotor retardation, lethargy, and forgetfulness. Such nonspecific impairments in mental function have been linked to lesions in the frontal and temporal lobes, corpus callosum, thalamocortical fibers, and reticular formation, among others. Occasionally, increased intracranial pressure can present in a similar fashion though usually alongside other indicative signs such as papilledema or with progressive altered levels of consciousness. Still other nonlocalizable presentations are the result of multifocal tumors, often seen in metastatic disease, presenting with a mixture of focal signs and symptoms that can be confused for generalized clinical manifestations.

Headache is one of the most pervasive symptoms in neuro-oncology, occurring in over 50% of this patient population. Pre-existing headache conditions appear to predispose patients to tumor-related headaches, making it difficult to distinguish between tumor and nontumor-related complaints. Some clues, such as change in headache character and increasing frequency or severity of headache, can help with diagnosis and point to the need for further work-up. Importantly, most tumor-related headaches do not appear in isolation. Recent estimates indicate that just 2% of brain tumor patients present with headache as their only clinical manifestation. The association of focal neurologic signs or symptoms with headache is another indication for prompt work-up.

Unfortunately, the character of the headache is not especially helpful in diagnosis. The classical teaching is that headache attributable to an intracranial neoplasm will be progressive, worse in the morning, or wake the patient from sleep, and may be aggravated by coughing, straining, or bending forward. These characteristics were thought to reflect raised intracranial pressures and theoretically to help identify tumor-related headaches. Recent reviews, however, have not corroborated an association between intracranial tumors and headache that is worse in the morning or with cough. Instead, tension-type headaches that are dull, moderate in intensity, and not particularly localizable are found to be the most common headache type in patients with intracranial tumors.

CAUTION!

Patients with headaches that wake them at night or are worse in the morning, or who have focal neurologic deficits, require urgent neuroimaging. However, many patients with brain tumors present with headaches that are indistinguishable from tension headaches.

Nausea and vomiting occur most frequently in association with severe tumor headache, but can also be present in isolation. These symptoms typically manifest first thing in the morning and are only rarely associated with food intake. Usually, tumor-associated vomiting reflects an increase in intracranial pressure or compression of the area postrema, a chemoreceptive trigger zone for vomiting, located in the inferolateral portion of the fourth ventricle. Specific tumor types with a predilection for the fourth ventricle and thus for inducing nausea and vomiting include medulloblastomas and ependymomas. Projectile vomiting without preceding nausea is fairly specific to posterior fossa childhood tumors and is rarely seen in adults. Tumors of the brainstem can also lead to similar symptoms via their effect on the nucleus solitarius.

Dizziness is another frequent complaint in brain tumor patients which can be either vague and ill-described or consistent with frank vertigo. A complaint of classic vertigo should raise suspicion of a tumor in the cerebellopontine angle such as a schwannoma, meningioma, or metastasis, or tumors in the pons or posterior fossa. Posterior fossa tumors sometimes present with vertigo and concomitant headache or dizziness.

Concomitant signs of incoordination such as dysmetria or ataxia are highly suggestive of a cerebellar or pontine lesion. Tumors that are supratentorial may at times also present with dizziness, though this is usually of the vague, ill-defined type that is more consistent with a sensation of lightheadedness and can be related to elevations in intracranial pressure.

Seizures are another common clinical manifestation of intracranial tumors. Although they are the result of a focal lesion, their frequent secondary generalization often prevents accurate localization. There may be post-ictal clues, such as Todd paralysis or post-ictal aphasia, which aid in localization of the lesion. If secondary generalization does not occur, or if the seizure semiology prior to generalization is clear, localization may be possible. The frequency of seizures in patients with brain tumors is around 30%, with significant variability by tumor type. Typically, slow-growing low-grade tumors are most epileptogenic and cause seizures that are often difficult to manage clinically. As an example, low-grade gliomas have a seizure frequency of 65–85% whereas the incidence of seizures in glioblastoma is 30–50%, closer to the average across all tumor types. The reason for the higher frequency in lower grade tumors remains elusive but may simply be related to the longer survival times of these patients. About 10–25% of patients with meningiomas or metastasis also develop seizures, with some variation by location. High convexity meningiomas and cortical metastasis are associated with higher seizure frequencies. Seizure frequencies for other specific tumor types have been less well defined, though brain lesions in close proximity to the cortex will be more epileptogenic than lesions deeper in the brain parenchyma.

Focal symptoms

Focal signs and symptoms may not be present initially in brain tumor patients but almost always develop as the disease progresses. There is great variety in symptom type based on location of the lesion (Table 1.1), and we describe some of the more typical signs and symptoms.

Supratentorial lesions frequently result in motor, sensory, language, or visual impairments. Hemiparesis, for instance, can occur in up to 50% of patients with brain metastasis and 36% of patients with glioblastoma. Of course, the severity and side of the paresis, as well as the presence of concomitant signs and symptoms, depends on both the location and size of the tumor. Gross sensory disturbances are typical of tumors in the sensory cortex or thalamus, whereas higher level impairment in sensory discrimination or processing are typical of tumors in the parietal lobes. Diverse aphasias are possible when tumors affect the dominant postero-inferior frontal lobe or superior, perinsular, or insular regions of the dominant temporal lobe. When the aphasia presents in isolation of other symptoms it should raise concern for seizure and be further evaluated with an electroencephalogram (EEG). Visual impairments such as hemianopsias can be caused by lesions in the occipital lobes or parieto-temporal regions where the optic radiations may be impacted. Tumors of the hypothalamic or pituitary regions can compress the optic chiasm, producing bitemporal hemianopsia. Double vision can result from involvement of cranial nerves III, IV, and VI, usually with tumor invasion of the cavernous sinus, but also with tumors in the brainstem. Notably, double vision can present as a false localizing sign from VIth nerve palsy when increased intracranial pressure is the culprit.

Several tumor types frequently occur in specific locations and tend to produce a characteristic constellation of associated localizing symptoms. Their symptom pattern makes them readily recognizable. For example, craniopharyngiomas, slow-growing suprasellar tumors, can damage the pituitary and hypothalamus and compress the nearby optic chiasm, producing hormone imbalances manifesting with excessive thirst and urination or stunted growth, along with the classic bitemporal hemianopsia. Pituitary tumors can have a similar presentation though often the hormone imbalance is brought about by an overproduction of the hormone corresponding to the specific tumor cell type. Schwannomas are benign nerve sheath tumors that have a predilection for cranial nerve VIII, often causing hearing loss, tinnitus, and vertigo. Pineal gland region tumors, including pineal parenchymal tumors and germ cell tumors, present with symptoms of obstructive hydro-

Table 1.1. Symptom type based on location of lesion.

Frontal lobe	Seizures
	Headaches, nausea, vomiting
	Abulia
	Personality and behavioral changes
	Hemiparesis
	Aphasia (Broca [inferior frontal gyrus], conduction, or transcortical)
Temporal lobe	Seizures
	Headaches, nausea, vomiting
	Aphasia (Wernicke [superior temporal gyrus]; conduction
	Memory loss
	Visual field loss (superior quadrantinopsia)
Parietal lobe	Headaches, nausea, vomiting
	Sensory loss
	Seizures
	Visual field loss (inferior quadrantinopsia or homonymous hemianopsia)
	Visual spatial problems; problems with directions, dressing apraxia
Occipital lobe	Visual field loss (homonymous hemianopsia)
	Headaches, nausea, vomiting
	Seizures
Cerebellum	Ataxia
	Headaches, nausea, vomiting
Brainstem	Dizziness
	Diplopia
	Dysarthria
	Weakness
	Numbness
	Ataxia
Pineal region	Headaches, nausea, vomiting (from tumor and hydrocephalus)
	Visual problems
Pituitary/ hypothalamic region	Headaches
	Visual field loss (bitemporal hemianopsia)
	Hormonal disturbance (overproduction or underproduction of hormones)

cephalus including headache, nausea and vomiting, and lethargy. These tumors frequently compress the midbrain, potentially resulting in Parinaud (dorsal midbrain) syndrome, characterized by a group of specific eye and pupil abnormalities including impaired upgaze, light-near dissociation, convergence nystagmus, and eyelid retraction.

Radiographic diagnosis of brain tumors

Clinical clues can help formulate a differential diagnosis that includes intracranial neoplasms,

but the differential remains vast and other tools are required to help narrow the diagnosis. Imaging with computerized tomography (CT) and/or magnetic resonance imaging (MRI) should be the next step in the confirmatory process of a suspected intracranial mass lesion. To date, MRI with gadolinium represents the best noninvasive and sensitive tool in the evaluation and characterization of intracranial neoplasms. Several specific MRI characteristics, along with more advanced imaging techniques, which are discussed below, are especially useful in differentiating among various types of intracranial masses such as brain tumors, demyelinating or inflammatory lesions, abscesses, and other infections. They do so by approximating lesion cellularity, invasiveness, metabolic rate, and vascularity. Many of these imaging characteristics can also be used to differentiate between specific tumor types and grades, and are helpful for preoperative planning, monitoring of treatment effect, and assessment of tumor recurrence.

Computer tomography imaging

Despite the many advantages of MRI, CT remains the most commonly used imaging modality in the initial evaluation of patients suspected of having a brain tumor. The reasoning behind this includes the speed and ease of CT scanning, the availability of scanners across emergency departments and hospitals, and the relatively low cost of CT compared with MRI. Occasionally, when an MRI is contraindicated such as when a patient has a pacemaker or metallic foreign body or implanted device, CT may be the only imaging modality available for use. CT scans can identify enhancing brain lesions that are larger than 5 mm. Lesions that are small or located in the posterior fossa can often be missed. CT scan can also readily identify tumors that are calcified such as oligodendrogliomas and craniopharyngiomas and can detect bony abnormalities-associated skull-based tumors. In the acute setting this imaging modality is essential for the rapid identification of mass effect, midline shift, vasogenic edema, hemorrhage, herniation, and hydrocephalus. The speedy identification of these complications is crucial to providing patients with appropriate and sometimes life-saving treatments.

Brain magnetic resonance imaging

MRI with gadolinium provides a great deal of information about intracranial tumors and their effects on surrounding brain parenchyma. Basic MRI sequences, such as T1, T2, and fluid attenuated inversion recovery (FLAIR), can identify the number, location, and size of lesions, the amount of associated vasogenic edema, and the presence of mass effect, midline shift, and hydrocephalus. T1 post-gadolinium sequences and more advanced sequences can provide detailed information that help differentiate among diverse types of mass lesions and intracranial tumors.

Contrast enhancement

The evaluation of an intracranial lesion with MRI should be performed with and without contrast, unless contraindicated. Gadolinium, a chelated rare earth element, is the contrast material of choice for MRI. The BBB acts as a first line of defense by impeding entrance of toxic substances, including gadolinium, into brain. Contrast enhancement of brain parenchyma thus reflects a breakdown in the BBB leading to increased permeability. The degree of enhancement should parallel the amount of BBB permeability, though imaging technique and contrast dose result in significant variability.

Neoplastic lesions, and in particular higher grade tumors, increase permeability and cerebral capillary blood volume via the cooption of existing capillaries and the formation of new distorted blood vessels with abnormal endothelium and incomplete basement membranes. This results in a leaky BBB that is permeable to gadolinium, making high-grade neoplastic lesions more apt to enhance on T1 post-gadolinium sequences. Theoretically, higher grade tumors with increased angiogenesis should result in higher degrees of contrast enhancement than lower grade lesions. In practice, however, the correlation between the degree of enhancement (aside from present or absent) and grade of glial tumors can be variable. Some low-grade tumors, such as pilocytic astrocytomas, gangliogliomas, and hemangioblastomas, enhance with contrast while a very small minority of glioblastomas do not.

Various other pathologic states increase BBB permeability including active inflammation from

infectious and noninfectious causes, cerebral ischemia, and increased pressure states. Specific tumor types, however, tend to possess unique patterns of enhancement that can differ from patterns in these other disease states (Table 1.2). Extra-axial tumors, for instance, can produce pachymeningeal enhancement through a reactive process that results in increased dural thickness. Meningiomas, one type of extra-axial tumor with a broad-based dural attachment, are often identifiable by their characteristic "enhancing dural tail" on MRI. Leptomeningeal enhancement is another pattern of enhancement seen when neoplasms spread into the subarachnoid space, a process often referred to as "leptomeningeal metastases or neoplastic meningitis." Occasionally, this type of enhancement will be more nodular, helping to differentiate it from the

Table 1.2. Differential diagnosis of brain tumors.

SINGLE BRAIN LESION	Brain metastases
Tumors	Primary CNS lymphoma
Primary brain tumor (including primary CNS lymphoma)	Intravascular lymphoma
Metastatic brain tumor	Lymphomatoid granulomatosis
Hamartoma	Multifocal glioma
Vascular	Leptomeningeal metastases
Cerebral hemorrhage	**Vascular**
Cerebral infarction	Multiple cerebral infarction
Aneurysm	Small vessel disease
Arteriovenous malformation	Cavernous angiomas
Cavernous angioma	Multiple hemorrhages (amyloid angiopathy, blood dyscrasias, anticoagulation)
Infection	**Inflammatory**
Abscess	Systemic lupus erythematosus
Progressive multifocal leukoencephalopathy (PML)	Vasculitis
Lyme disease	Demyelination
Syphilis	Multiple sclerosis
Viral encephalitis (e.g. herpes simplex encephalitis)	Acute disseminated encephalomyelitis
Inflammation	Behçet
Multiple sclerosis	Sarcoidosis
Post-infectious encephalomyelitis	**Infections**
Systemic lupus erythematosus (SLE)	Abscesses
Sarcoidosis	Bacterial
Vasculitis	Tuberculosis
Degenerative disorders	Syphilis
Trauma	Fungal
Benign cyst	*Toxoplasma*
MULTIPLE BRAIN LESIONS	Cysticercosis
Tumor	Progressive multifocal leukoencephalopathy (PML)
	Developmental
	Heterotopia
	Trauma

smooth leptomeningeal enhancement caused by infectious forms of meningitis. The presence of small nodular cortical and subcortical enhancing lesions at the brain gray–white junction is typically seen in parenchymal brain metastasis. The gray–white matter junction is usually a transition zone between abundant and sparse vasculature creating a filtration zone for intravascular particulate matter in the region, including hematogenously spread neoplasms. However, brain metastases may occur anywhere in the brain parenchyma.

Another classic pattern of enhancement is ring enhancement, which can be associated with numerous types of benign and malignant intraparenchymal brain lesions. Ring enhancing lesions can be both superficial or deep and can represent high-grade gliomas, metastasis, abscesses, and other infections as well as demyelinating diseases, usually in that order of frequency. Both metastases and glioblastomas may appear initially as nodular and solidly enhancing lesions which become ring-enhancing with further growth as a result of central necrosis. Glioblastomas are usually single lesions, while metastases, demyelinating disease, and infections more frequently present as multiple lesions.

Patterns of ring enhancement can also vary, providing another clue in diagnosis. A smooth thin ring of enhancement is typically seen with abscesses and other infectious lesions. An open ring pattern can be quite characteristic of tumefactive demyelinating lesions. Thick irregular and nodular rings are usually seen in high-grade gliomas. Both glioblastoma and primary CNS lymphoma can present as expansile masses involving the corpus callosum, making it sometimes difficult to distinguish the two entities.

Diffusion MRI

Diffusivity measures the anisotropic movement of water molecules through tissues and is greater in extracellular than intracellular compartments. Lower diffusivity, which on MRI corresponds to a dark area on the apparent diffusion coefficient (ADC) sequence and a bright area on diffusion-weighted imaging (DWI) sequence, can thus serve as an approximation for higher cellularity and help to distinguish neoplastic lesions from non-neoplastic ones. It is particularly useful when attempting to distinguish hypercellular neoplasms, such as lymphomas and some high-grade gliomas, from less cellular lesions such as tumefactive demyelinating lesions. Diffusivity can also be used to differentiate solid viable tumors from tumors with necrotic centers. Importantly, abscesses are hypercellular lesions and will exhibit restricted diffusion on MRI. Low diffusivity will be seen both at the periphery and core of the abscess, helping to distinguish it from high-grade gliomas, which can have a similar ring enhancement pattern but a necrotic high-diffusivity core. Acute strokes also presents with restricted diffusion secondary to cytotoxic injury and may be difficult to differentiate from tumor, though the vascular distribution of the former is an important clue. Information from patterns of enhancement described above, diffusivity and appearance of lesions in other MRI sequences and other advanced imaging techniques must be taken into account in the radiographic diagnosis of intracranial lesions.

Identification of postoperative injury by noting new areas of restricted diffusion in the tumor resection cavity is also valuable to the clinician. Intraoperative injury can occur for numerous reasons, and areas of injury will subsequently evolve both physiologically and radiographically. Specifically, an area of injury with low diffusivity can evolve to become contrast enhancing. Without knowledge of prior tissue injury to the area it would be almost impossible to distinguish the lesion from tumor recurrence.

Perfusion MRI (dynamic susceptibility MRI)

Perfusion MRI techniques help identify the degree of tumor angiogenesis and capillary permeability by approximating cerebral blood volume and flow. Because increased tumor vascularity (with some notable exceptions especially among extra-axial tumors such as meningiomas) correlates with malignancy, this imaging technique provides additional hemodynamic information that can help distinguish neoplastic from benign lesions. Perfusion imaging also provides valuable information for preoperative tumor grading and planning, with more accurate estimates of the degree of vascularity than contrast enhancement provides. Biopsies can be obtained

from regions of high perfusion, increasing the likelihood of obtaining tissue from regions corresponding to the highest grades. The technique has also been used with some success to differentiate tumor recurrence from radiation effect, including "pseudoprogression," and to measure response to antiangiogenic therapies.

Dynamic contrast-enhanced MRI

Although not routinely used in the diagnosis of brain tumors, dynamic contrast-enhanced (DCE) MRI provides useful information on tumor vascular permeability and is occasionally used to follow the effects of antiangiogenic therapies.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy is a noninvasive MRI technique that measures freely mobile metabolites within a specific area of interest in the brain, thereby relaying information about the regional biochemical milieu. The major metabolites of interest in the study of brain tumors include *N*-acetyl aspartate (NAA), choline, creatine, and lactate. Each of these provides unique biochemical information of the area of interest. Specifically, NAA, which is high in normal brain tissue, is a marker of neuronal integrity and will be decreased in regions corresponding to brain tumors. Creatine levels correspond to energy stores. Malignant tumors with high metabolic activity will usually have decreased levels of this metabolite. Choline is a marker of membrane turnover that is low in normal parenchymal tissue and will increases within brain tumors. Lactate and lipid levels vary in the typical spectra of malignant gliomas, with lactate representing the presence of anaerobic glycolysis and lipids reflecting any type of tissue necrosis.

Magnetic resonance spectroscopy may occasionally be useful in the radiographic diagnosis of brain tumors but generally has only limited value in the differentiation of intracranial masses. This is because spectroscopic patterns may be similar for gliomas, demyelinating disease, ischemia, and infection. Some niche applications of this technique include the differentiation of meningiomas, dural-based metastasis, and high-grade gliomas. More common clinical applications have included tumor grading, assessment of tumor recurrence, and preoperative planning. Elevation of lipid within a malignant lesion corresponds to tissue necrosis suggesting a high grade. Information about metabolite levels in regions of T2 hyperintensity just beyond areas of contrast enhancement is also helpful in differentiating between tumor infiltration and vasogenic edema. The same pattern of low NAA and creatine with high choline characteristic of a neoplastic lesion will correspond to tumor infiltration, a mechanism of tumor spread characteristic of high grade but not low grade or metastatic lesions. Metabolite analysis can further help to differentiate areas of radiation necrosis from areas of tumor recurrence, a common clinical diagnostic dilemma. Radiation changes will typically exhibit low NAA and creatine similar to tumors, but will also have low choline levels in contradistinction to neoplasms. Lastly, magnetic resonance spectroscopy can be clinically useful in preoperative planning, where regions that appear most metabolically active can be identified for brain biopsy thereby decreasing the likelihood of false negatives based on sampling error.

Positron emission tomography

Positron emission tomography (PET) is a functional nuclear medicine imaging modality that can provide information about glucose metabolic activity, blood flow, and oxygen consumption. ^{18}Fluorodeoxyglucose (FDG) is the most available and commonly used tracer. It concentrates in regions of high glucose metabolism, thus highlighting lesions with high metabolic activity such as malignant neoplasms. Importantly, inflammatory lesions may also display increased FDG uptake, which can complicate the diagnosis of brain tumors. Amino acid tracers such as ^{11}C-methionine (MET) and ^{18}F-fluoroihydroxyphenylalanine (DOPA) are being developed as alternative tracers. As with FDG, increased concentrations of these tracers can be seen in neoplastic lesions known to upregulate carrier-mediated transport of amino acids.

In addition to its utility in the diagnosis of intracranial neoplasms, PET can be used to distinguish between radiation necrosis and tumor recurrence, and in monitoring response to treatment, although its sensitivity and specificity are limited. PET is also used occasionally in

preoperative planning by highlighting regions of high metabolic activity, which can be targeted for biopsy.

Conclusions

Accurate diagnosis of intracranial tumors is challenging and usually requires histopathologic evaluation of sampled tissue. The process of diagnosis begins with a detailed clinical evaluation and continues with imaging. Both of these steps are crucial to the identification of intracranial lesions and provide significant information that helps formulate a differential diagnosis, sometimes narrowing the possibilities to one or two entities. The clinical history provides information regarding symptoms, their onset and progression that can begin to point in the direction of an intracranial neoplasm. The exam then provides direct observation of neurologic deficits and impairments, which allows for corroboration of the history and localization of potential brain lesions. Imaging confirms the presence of intracranial pathology. The use of a combination of standard and advanced imaging modalities provides anatomic, metabolic, functional, and physiologic information about intracranial pathologies that is frequently necessary to make an accurate diagnosis.

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