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Anatomic, Physiologic and Metabolic Imaging in Neuro-Oncology

Sanjeev Chawla, Harish Poptani, and Elias R. Melhem

1 Introduction

Primary brain tumors arise from various cell types of the brain, including glial cells, neurons, neuroglial precursor cells, pinealocytes, pericytes of the vessels, cells of the hypophysis, lymphocytes and the meninges [1, 2]. The incidence of primary brain tumors varies between subtypes, with the most common primary brain tumors in adults being gliomas and meningiomas.

Gliomas can be histologically classified into astrocytomas, oligodendrogliomas, mixed oligoastrocytomas, ependymal tumors and tumors of the choroid plexus. Tumor malignancy or grade is generally assessed according to the World Health Organization (WHO) criteria, taking into account the presence of nuclear changes, mitotic activity, endothelial proliferation and necrosis [1, 3]. The most fatal and common primary brain neoplasm is the glioblastoma multiforme (GBM), which corresponds to WHO grade IV. Despite aggressive multimodal treatment strategy (surgery, radiation and chemotherapy), median survival of patients with GBM is limited to less than 14 months. A complex series of molecular events occur during tumor growth resulting in dysregulation of the cell cycle, alterations in apoptosis and cell differentiation, neo-vascularization as well as tumor cell migration and invasion into the normal brain parenchyma. Genetic alterations also play an important role in the development of glioma, including a loss, mutation or hypermethylation of the tumor suppressor gene, such as p53 or other genes involved in the regulation of the cell cycle. During progression from low-grade to high-grade, step-wise accumulation of genetic alterations occurs. Growth of certain tumors seems to be related to the presence of viruses and familial diseases that accelerate the progression of molecular alterations, or exposure to environmental chemicals, pesticides, herbicides and fertilizers [4-6].

A better understanding of tumorgenesis is crucial for the development of specific molecular therapies that specifically target the tumor and reduce patient morbidity and mortality. Positron emission tomography (PET), computed tomography (CT) and magnetic resonance imaging (MRI) are generally used for non-invasive diagnosis and

Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States

understanding of tumor growth mechanism. Cranial CT and MRI, with and without contrast media, are widely used for primary diagnosis of brain tumors. CT is used for detection of calcifications in oligodendrogliomas, meningiomas or craniopharyngiomas, and for tumors that are located at the base of the skull. However, the discrimination of tumor boundaries from normal tissue or vasogenic edema, as well as the evaluation of tissue heterogeneity and tumor grading are often a challenge and are not adequately reflected on CT. Furthermore, the use of ionizing radiation and image acquisition only in the axial plane, limits its applicability.

PET uses various radioactive agents to detect differences in metabolic and chemical activity in the body. PET measures a wide range of physiologic processes critical in understanding the pathophysiology of brain tumors with high sensitivity. It allows for detection of metabolic changes that occur prior to structural changes visible on CT and conventional MR images. However, the major limitation of PET is its relatively poor spatial resolution and a high incidence of false positives.

Continuous developments in MRI provide new insights into the diagnosis, classification and understanding of the biology of brain tumors. MRI offers several advantages compared to CT and PET. MRI offers excellent spatial resolution ($1 \times 1 \times 1 \, mm^3$ in humans), very high gray-white matter contrast and acquisition of multiplanar images. MRI is particularly accurate in establishing the intra- or extra-axial origin of tumors. The use of three-dimensional (3-D) image acquisition and reconstruction with MRI is not only limited to diagnosis, but is also useful for pre-surgical planning, stereotactic procedures and radiotherapy. Despite optimization of sequences and protocols, the classification and grading of gliomas with conventional MRI is sometimes unreliable, with the sensitivity for glioma grading ranging from 55.1 percent to 83.3 percent [7]. Integration of diagnostic information from advanced MRI techniques like proton magnetic resonance spectroscopy (^{1}H MRS), diffusion and perfusion-weighted imaging and functional MRI (fMRI) can further improve the classification accuracy of conventional anatomical MRI [8]. Advanced MRI techniques are also being used to gain additional information on metabolic and molecular tumor markers [9, 10]. In selected patients, MRI and PET are being used in conjunction to define the real extent of the tumor [11].

2   Magnetic Resonance Imaging

2.1   *Diagnosis and Grading of Brain Tumors*

2.1.1   Conventional MRI

General Features of Brain Tumors

Due to the excellent soft tissue contrast and high spatial resolution, MRI provides exquisite anatomical details that aid in diagnosis, classification and understanding the biology of brain tumors. A routine MRI examination of patients with brain

tumors includes long TR/long TE (T2-weighted), short TR/short TE (T1-weighted), fluid-attenuated inversion recovery (FLAIR) and post-contrast T1 sequences. Detection of a tumor is based primarily on the presence of mass effect and signal alteration on these imaging sequences. The three main variables that differentiate tumors from normal tissue are: water content, regressive events and vascular architecture. Most brain tumors exhibit increased water content and, thus, appear hyperintense on T2-weighted and FLAIR images, and hypointense on T1-weighted images (Fig. 1.1 a,b, c and Fig. 1.2a,b, c). This hyperintensity is more pronounced in masses having a low nucleus/cytoplasm ratio (e.g., astrocytoma), than in masses with a high nucleus/cytoplasm ratio (e.g., medulloblastoma). The peritumoral hyperintensity on T2-weighted images is generally nonspecific and is thought to be due to tumor infiltration, vasogenic edema, or both.
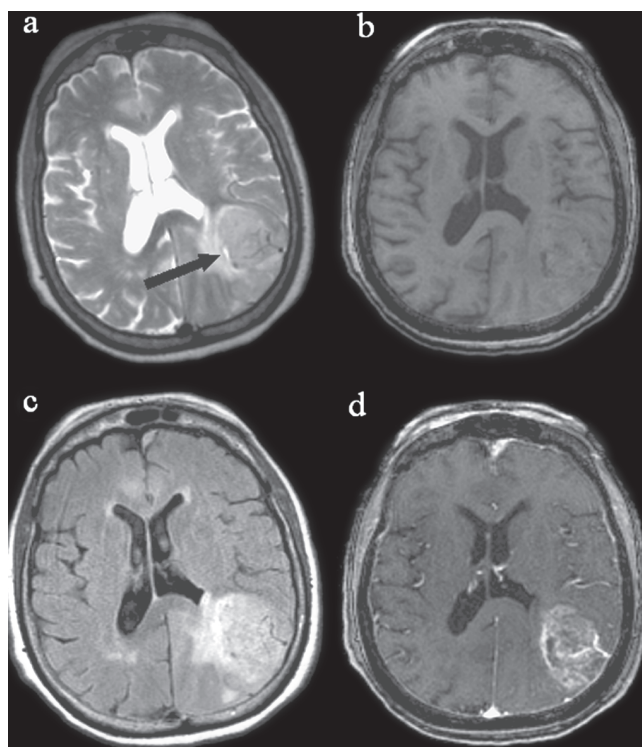

Fig. 1.1 High-grade glioma. Axial T2-weighted image (**a**) demonstrates an ill-defined, hyperintense (compared to gray matter), heterogeneous mass in the left parietal lobe along with vasogenic edema along the white matter tracts. Note the presence of necrotic foci (arrow) within the tumor. This mass appears as iso to hypointense on T1-weighted image (**b**) and hyperintense on FLAIR image (**c**). There is a heterogeneous contrast enhancement within the mass on the corresponding post contrast T1-weighted image (**d**)
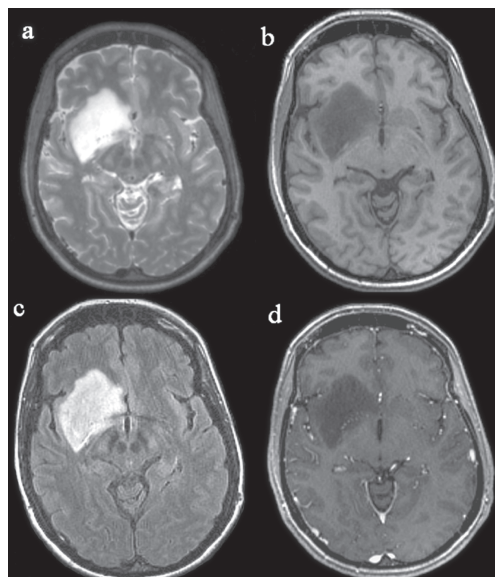
Fig. 1.2 Low-grade glioma. Axial T2-weighted image (**a**) demonstrates a homogenously hyperintense mass in the insular region extending into the right frontal lobe. This mass is well circumscribed with minimal mass effect and edema that appears hypointense on T1-weighted image (**b**) and hyperintense on FLAIR image (**c**). There is no evidence of abnormal contrast enhancement on the post contrast T1-weighted image (**d**)

Regressive events such as cyst formation, necrosis and hemorrhage, calcifications and fatty degenerative areas modulate the MRI appearance of brain tumors. Intratumoral cysts are secondary to focal mucoid degeneration and fluid transudation from cyst walls. Cysts can be filled with water, or contain considerable amounts of protein or other debris from prior hemorrhage. If the cyst contains water only, it has the same signal intensity as cerebrospinal fluid (CSF) on T2- and T1-weighted images. When the protein content increases, protons become bound in a hydration layer adjacent to the protein, significantly decreasing the T1 relaxation time of water, leading to an increase in the signal intensity on FLAIR and T1-weighted images. Necrotic areas result from ischaemic cell damage or intratumoral hemorrhagic events that result in the formation of pseudocystic areas. These areas typically appear hyperintense on T2 and hypointense on T1-weighted images, compared to normal brain parenchyma.

Certain primary intracranial neoplasms and metastatic tumors demonstrate hemorrhage and calcification [12]. Both chronic hemorrhage and calcifications appear hypointense on T2 and T2-weighted images, due to the induction of paramagnetic susceptibilities [13]. Recently, corrected gradient echo phase imaging has been used to differentiate hemorrhage and calcification [14, 15]. An abnormal vascular architecture is a feature that is generally observed in tumors. Stimulation of the formation of new capillaries (neo-vasculature) within the tumor tissue is facilitated

by hypoxia and endothelial growth factor receptors (EGFR). In malignant gliomas, formation of capillaries with fenestrated endothelia is stimulated, which leads to disruption of the blood-brain barrier (BBB) and contrast enhancement [16], as shown on Fig. 1-1d. On the other hand, in some tumors with a functioning BBB, these capillaries exhibit near-normal features, hence, these tumors do not enhance on contrast-enhanced T1-weighted images [16] as shown on Fig. 1.2d.

Metastatic tumors are characterized by the presence of typically leaky, non-central nervous system capillaries similar to their tissue of origin and, hence, exhibit intense enhancement. Extra-axial tumors, like meningiomas, arise from tissue whose capillaries lack tight junctions and, consequently, these tumors also exhibit contrast enhancement [16]. While the extent of a tumor in the brain can be evaluated by contrast enhancement, it is known that invasive tumor cells are also present beyond the enhancing portion of the tumor, particularly in gliomas. Since contrast enhancement on conventional MRI indicates disruption of BBB and not underlying regional vascularity, it cannot be used to predict histological grade [17]. However, Fayed, et al. [18] have reported a significant difference in the contrast-to-noise ratio (CNR) of gadolinium-enhancement between low- and high-grade gliomas. Using a CNR threshold of 35.86, these authors reported a sensitivity of 82.6 percent and a specificity of 91.7 percent for the prediction of malignancy.

Besides primary information on the size and location of the tumor, conventional MRI (T1, T2 and post-contrast T1 images) provides additional information about secondary phenomena such as mass effect, edema, hemorrhage, necrosis and signs of increased intracranial pressure.

General Features that Differentiate Intra-axial from Extra-axial Tumors

Differentiation between intra-axial and extra-axial masses is crucial as clinical management of these tumors is different [19]. This distinction has been made easier by multiplanar capabilities of MRI. Key features that help in identifying an intra-axial mass include gyral expansion, thinning or effacement of the adjacent extra-axial subarachnoid space and peripheral displacement of blood vessels along the pial surface of the brain (best seen on contrast-enhanced images) [19]. Imaging features more characteristic of extra-axial intradural masses include local bony changes such as hyperostosis, or widening of pre-existing foramina or canals; displacement of brain surface vessels away from bone and dura; white matter buckling, and widening of the subarachnoid space adjacent to the mass; central displacement of both the gray-white junction and presence of blood vessels along the pial surface. Extradural masses show similar behavior, but they usually displace the dural sheet centrally [19].

Common Brain Tumors Occurring in Adults

Intra-axial Tumors

The most common tumors of intra-axial location are gliomas and metastases. Gliomas derived from brain cells can, thus, be classified as true brain tumors,