Imaging in Neuro-Oncology

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5.1 Introduction

The 2016 central nervous system (CNS) World Health Organization (WHO) classification of brain neoplasms has completely changed the way brain tumors are now classified, integrating both genotypic and phenotypic parameters, incorporated into the newly updated classification schema. This classification is based on a combination of histology and molecular patterns by direct evaluation of the mutated DNA or by immunohistochemistry, which evaluates the effects of the mutated genes on proteins (and this technique is more widely used also because of lower costs). Since histologic grading is still used in clinical practice, potential relevant inconsistency between the two might appear. The knowledge of this new classification is essential for radiologist as well as for all neuroscientists. The modern approach of imaging in the assessment of brain tumors aims to identify some morphological or metabolic patterns that may have an impact on their classification. This is synthesized in the term radiogenomics.

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5.2 Radiogenomics

The molecular stratification of brain tumors is quickly becoming an integral part of their diagnosis, prognosis, and clinical decision-making. Several studies over the past two decades provided insights into the genetic basis of tumorigenesis, explaining why tumors assigned to the same histopathological entity can have broadly different therapy responses and highly divergent clinical outcomes. The new 2016 WHO classification of CNS tumors uses, for the first time, molecular parameters in addition to histology to define many tumor entities [1, 2], thus clearly indicating the utmost significance of genome-wide biomarkers in the molecular era.

The molecular stratification is essential for estimating the individual prognosis [3–5]. The more relevant molecular biomarkers are isocitrate dehydrogenase (IDH) 1/2 mutation status and chromosome 1p/19q loss of heterozygosity (LOH). They are complemented by alpha-thalassemia/mental retardation syndrome X-linked (ATRX), which is predictive for associated IDH or H3F3A hotspot mutations [6]. The ATRX status itself confers a prognostic potential in diffuse gliomas [7]. The loss of ATRX expression is mostly induced by truncating ATRX mutations, resulting in an alternative lengthening of telomeres (ALT) phenotype [8, 9]. Moreover, O6-methylguanine DNA methyltransferase (MGMT) can be regarded as an independent prognostic factor in diffuse gliomas [10, 11], and the epidermal growth factor receptor (EGFR) amplification and EGFR variant III (EGFRvIII) mutation are related to neo-angiogenesis evaluation and representation.

Understanding how these molecular phenotypes are reflected on imaging is thus becoming increasingly important to define novel magnetic resonance imaging (MRI) biomarkers that can be used as surrogates for tissue-based molecular subtyping required to predict prognosis, to develop individualized patient therapies, and to follow up patients.

Radiogenomics is a new field of study aiming at determining the association between imaging features and molecular markers. Hence, more accurate approaches are recommended to identify the specific biological and microstructural characteristics of the underlying tumor tissue.

To this end, more sophisticated quantitative imaging approaches such as the analysis of texture features (i.e., pattern of local variations in image intensity) can be applied on anatomical MR images, seeking for correlations between tissue microstructure and thus tumor biology. Recent studies focused their attention on post-contrast T1-weighted and T2/FLAIR images searching for a link with molecular markers representing gene, protein, or metabolite expression, in order to create radiogenomics map to associate image features with biologic processes and molecular subgroups [12].

More recently, advanced imaging features derived from physiological imaging techniques, such as dMRI, PWI, and magnetic resonance spectroscopy (MRS), have shown to be promising to increase the accuracy of molecular subtyping by MRI.

5.3 Conventional Imaging

For many years computed tomography (CT) with contrast enhancement has been the gold standard for the diagnosis of brain tumors due to its ability to ascertain the presence of a brain lesion, to define its dimension and relation with surrounding brain structures, to assess perilesional edema, and to define the presence of multiple brain lesions. CT is superior to MRI for detecting calcifications, skull lesions, and hyper acute hemorrhage and helps direct differential diagnosis as well as immediate patient management [13, 14]. Continuous developments in MRI provide new insights into the diagnosis, classification, and understanding of the biology of brain tumors. MRI studies are characterized by higher contrast resolution associated with multiplanar views. MRI is characterized by high sensitivity for structural alterations caused by tumoral growth, which can be further enhanced by the use of paramagnetic contrast agents. Standard T1- and T2-weighted MRI acquisitions display high sensitivity for brain tumors and give information on the size and localization of the tumor [15]. A normal contrast-enhanced MRI scan essentially rules out the possibility of a brain tumor, but the role of neuroimaging is no longer simply to evaluate structural abnormality and to identify tumor-related complications. Functional, hemodynamic, metabolic, cellular, and cytoarchitectural alterations can be assessed by means of modern MRI. Thereby the current state of neuroimaging has evolved into a comprehensive diagnostic tool that allows the characterization of morphological as well as biological alterations, to diagnose and grade brain tumors, and to monitor and assess treatment response and patient prognosis [16]. Among advanced techniques, MR spectroscopy, diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) with tractography, perfusion-weighted imaging, and functional MRI play a role in the transition of clinical MR imaging from a purely morphology-based discipline to one that combines structure with brain function.

Most IDH-mutant and non-mutant diffuse astrocytomas infiltrate the white matter (far behind the abnormal MR signal) sparing of the cortex with mild mass effect. They are typically hypointense on T1WI and hyperintense on T2/FLAIR, without enhancement following contrast administration (Fig. 5.1). Blooming T2* signal can be appreciated if calcifications are present. IDH-mutant anaplastic astrocytomas are hypointense on T1WI and hyperintense on T2/FLAIR as well. Contrast enhancement ranges from none to moderate, but 50–70% of lesions may show some degree of enhancement.

IDH-wild-type anaplastic astrocytoma shows a diffuse infiltrative pattern frequently involving more than three cerebral lobes. This feature was commonly described in the past as gliomatosis cerebri, a term that is no longer used in the pathologic report.

IDH-wild-type glioblastoma (GBM) shows T1WI hyposignal with poorly marginated margins; mixed signal indicating subacute hemorrhage can be seen. T2/FLAIR signal is heterogeneous as well with hyperintensity with indistinct tumor margins and vasogenic edema. Inside the neoplasm mixed signal can indicate necrosis, cysts, fluid and debris levels, and “flow voids” from neovascularization. Enhancement is strong and irregular and typically surrounds a central

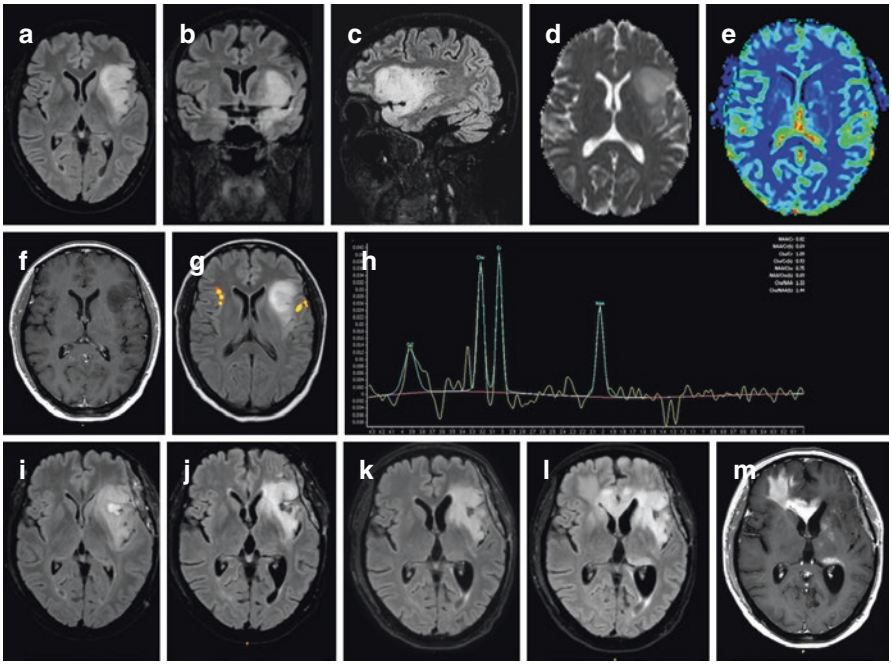

Fig. 5.1 A 52-year-old woman affected by recent epileptic episode. A hyperintense lesion on FLAIR images (**a–c**) is evident, with left fronto-temporal cortex involvement close to sylvian fissure. Low value of ADC (**d**) and relative CBV (**e**) with no enhancement after gadolinium injection (**f**) are visible. An area of BOLD signal changes close to the lesion after words recruitment task was interpreted as Broca's area (**g**). The spectroscopic evaluation reported a reduction of N-acetyl-aspartate into the lesion without significant increase of choline (**h**). After biopsy (**i**), a glioma was diagnosed, with lack of mutation of IDH1 (wild-type glioma) and methylation of MGMT. The follow-up examination (**j**, **k**) showed a stability of lesion extension. In the last follow-up (**l**, **m**) a significant progression of glioma with involvement of contralateral frontal lobe through genu of corpus callosum is appreciable with great enhancement after gadolinium injection. The patient died 13 months after diagnosis

non-enhancing core. Enhancement can be observed far from the central core of the neoplasm representing tumor extension into adjacent structures. This extension is microscopically evident even far from visible T2 signal alterations and areas of enhancement (Fig. 5.3).

IDH-mutant GBMs may appear non-enhancing, being somehow different from the classic large central necrotic core of IDH-wild-type GBMs.

Oligodendrogliomas (ODs) are glial neoplasms originated from oligodendrocytes that primarily affect supratentorial parenchyma (Fig. 5.2). Historically, co-deletion of whole chromosome arms 1p and 19q, namely 1p/19q co-deletion, has proved to be a diagnostic and prognostic biomarker of ODs. According to the 2016 WHO classification system, the "integrated diagnosis" of ODs requires histological classification, WHO grade, and molecular information (both IDH mutation and 1p/19q co-deletion). High-grade ODs are more prone to prominent edema and enhancement than low-grade ODs [17].

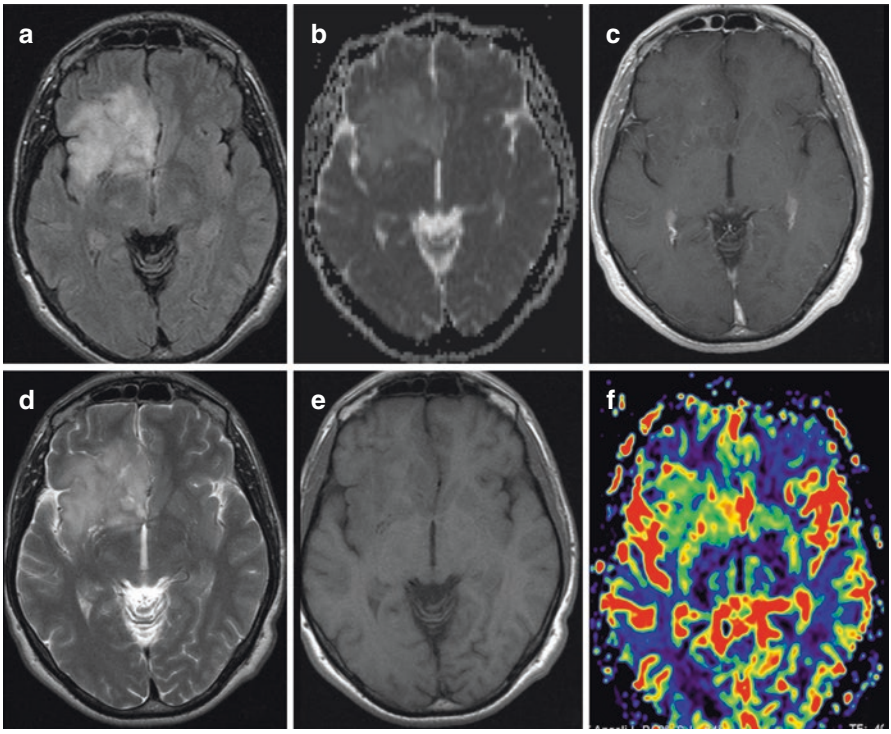

Fig. 5.2 Oligodendroglioma (both IDH1 mutation and 1p/19q co-deletion). Intra-axial lesion is evident in deep right fronto-basal region with T2-FLAIR hyperintensity (**a**, **d**), intermediate value of ADC (**b**), T1 iso-hypointensity (**e**), no enhancement after gadolinium injection (**c**), high values of CBV (**f**)

Some studies have tried to construct probabilistic radiographic atlases on anatomical magnetic resonance images of preoperative glioma locations, which may reflect the genetic profile of tumor precursor cells. IDH1 mutant tumors tended to be localized to the frontal lobe, whereas tumors with the methylation of the MGMT promoter occurred most frequently in the left temporal lobe, having a better prognosis than unmethylated tumors due to the higher sensitivity to chemotherapy [18].

A recent study assessed that tumor location was significantly different between MGMT promoter methylated and unmethylated groups, implying that the subventricular zone was more likely to be spared in patients with MGMT promoter methylation (Fig. 5.3). Besides, MGMT promoter methylation is prone to be associated with tumor necrosis. Other qualitative image features were not significantly different between these two groups, including multifocal, tumor cross midline, cyst, edema, enhancement, and side [19].

Some studies indicated that MGMT promoter methylation is poorly predicted with standard MRI features, such as T1-weighted images (T1WI), T2-weighted images (T2WI), and gadolinium (Gd)-enhanced T1WI.

Extracting additional information from medical imaging and relating it to a clinical variable of interest is broadly defined as radiomics. Radiomics is an emerging

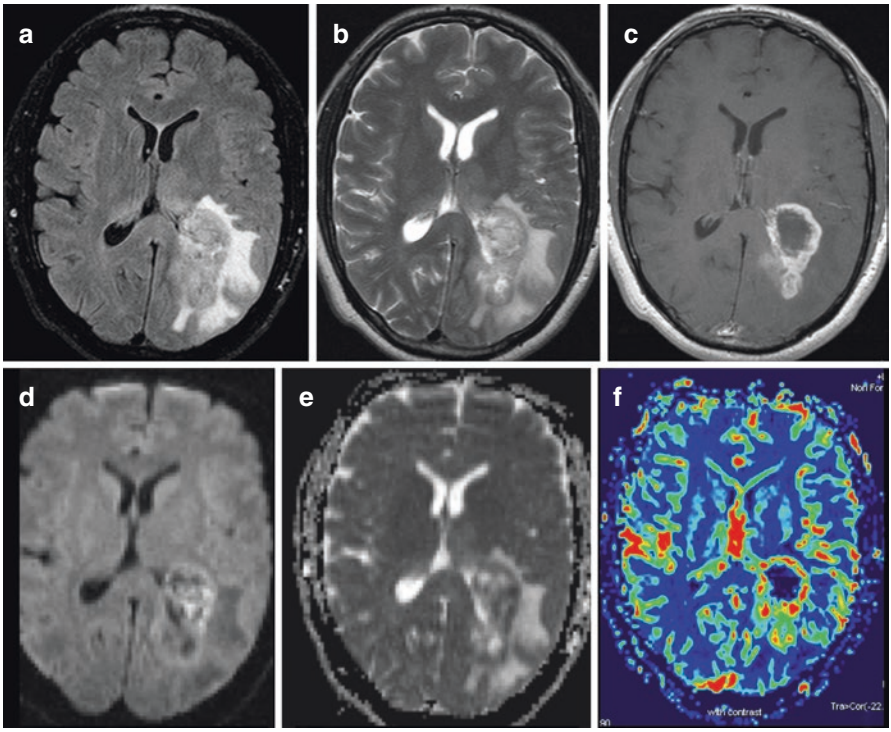

Fig. 5.3 Glioblastoma (wild-type glioma and unmethylated status). Left peritrigonal lesion characterized by un-homogeneous signal on FLAIR (**a**), T2 (**b**), peripheral enhancement after gadolinium (**c**), with restricted areas in DWI-ADC images (**d**, **e**), high values of CBV (**f**)

field that converts imaging data into a high-dimensional, mineable feature space using a large number of automatically extracted data characterization algorithms. Radiomics features include metrics such as spatial relationships, textural heterogeneity, and many other characteristics.

Radiomics features of GBM, especially the combination of enhanced T1W and T2W images, could reflect tumor molecular pathology indicators of MGMT methylation status. An association between imaging features and MGMT promoter methylation status in GBM could exist. MRI data could be applied to infer the molecular pathology of tumor target and may further guide clinical diagnosis and treatment [20].

Tumors with EGFR amplification and EGFRvIII mutation, which showed an increased angiogenesis, commonly occurred in the left temporal lobe anterior to the region identified by MGMT promoter methylation [2].

5.4 Advanced Techniques

5.4.1 Spectroscopy

The major clinical application of magnetic resonance spectroscopy for brain tumor patients has been its potential for non-invasive tumor grading [21–23]. These studies

have predominantly used MR spectroscopy techniques that detect a signal spectrum from a small region of interest (single-voxel MR spectroscopy). Higher mean choline and lower mean NAA levels in higher-grade tumors have been reported. However, most of the studies found large standard deviations in metabolite ratios and substantial overlap in individual values, which may restrict the accuracy of the technique. Studies using sophisticated data analysis techniques have shown a higher degree of accuracy for in vitro and in vivo spectroscopy studies [24]. A significant improvement in accuracy was obtained using a two-dimensional MRS imaging technique [23]. The combination of improved spatial resolution and increased number of voxels provides much more data about tumor heterogeneity and contributes in exploring the tumor margin. As a result, it is possible to measure the metabolite content of different areas of neoplasms and surrounding normal tissue. This is very useful for better characterizing glial tumors, in which very often coexist areas with different grading, and for a more accurate monitoring of possible malignant degeneration of benign tumors. In a serial proton MRS imaging study it was clearly demonstrated that an increased choline signal is associated with malignant progression of cerebral gliomas and that serial MRS imaging effectively and accurately differentiates between stable and progressive disease [25]. Moreover, sampling of several voxels inside tumors is very important in guiding biopsies, surgery, and radiotherapy. Color choline maps are indeed helpful in guiding stereotactic biopsy, thus improving diagnostic accuracy with decreased sampling error. Multi-voxel MRS techniques provide important information about tumor heterogeneity and allow targeting the region for biopsy to that of maximum spectral abnormality, resulting in an improvement of the diagnosis [26]. It was recently described that 3T MRS may show an elevated 2-hydroxyglutarate peak (2-HG) resonating at 2.25 ppm in IDH-mutant diffuse astrocytomas. Mutations in IDH1/2 confer a gain-of-function neomorphic enzymatic activity, resulting in the aberrant production and subsequent accumulation of 2-HG, which has been suggested to be an oncometabolite for this genetic mutation [27]. Magnetic resonance spectroscopy (MRS) has been identified as a tool in the diagnosis of IDH-mutant gliomas via the non-invasive detection of 2-HG. Although 2-HG represents an attractive marker for diagnosis and monitoring of disease progression, unambiguous detection via MRS has proven difficult to establish. Complex spectral overlap by a number of metabolites, such as glutamate, glutamine, and gamma-aminobutyric acid (GABA), found in abundance within healthy brain tissue, often confound the identification and detection of 2-HG as well as compromise accurate quantification of metabolite concentration. Several methods for detection of 2-HG in vivo have been proposed to optimize MRS for this application [27–31]. These encompass a range of acquisition and post-processing protocols designed to eliminate the confounding spectral overlap, and reliably quantify the 2-HG concentration in patients with IDH-mutant gliomas. The feasibility of detection of 2-HG in vivo at clinical strengths (3 T), using a standard single-voxel double echo point-resolved spectroscopy (PRESS) sequence with a TE of 30 ms, has been reported [31, 32].

Spectroscopy studies are also very useful in the assessment of response to therapy. The sensitivity of this technique in fact exceeds that of conventional MRI, with useful information being provided in lesions treated with chemotherapy or radiation therapy. There is general agreement that within high-dose regions that correspond to the radiation target, treatment response is reflected in reduction in the levels of choline, creatine, and NAA 2–3 months after treatment. In regions that are not

responsive to the radiation treatment, levels of choline may increase, corresponding to residual or recurrent tumor. This different behavior is of paramount importance in helping to differentiate between radio necrosis and recurrence, one of the most difficult topics in oncological neuroradiology. The possibility of monitoring the efficacy of new anti-tumoral compounds explains why MRS is included as a useful tool in many experimental protocols.

The high sensitivity of MRS is not matched by its specificity. Although several studies have reported that MRS makes possible the differentiation of diverse histological tumor types or abscesses or cystic lesions from neoplasms, the experience of routine daily practice has drawn attention to the risks related to the technique and warrants caution when considering differential diagnosis.

5.4.2 Diffusion Weighted Imaging and Diffusion Tensor Imaging

Diffusion-weighted MR has been widely used in the evaluation of brain tumors. With regard to extra-axial neoplasms, DWI can differentiate epidermoids from arachnoid cysts, both presenting similar signal intensity on T1- and T2-weighted images, while only epidermoids display very low ADC values [33, 34]. DWI has also been utilized in the differential diagnosis of malignant forms of meningiomas (grade WHO II–III) [35]. Primary cerebral lymphomas typically show signal hyperintensity in DWI with a low signal in the relative ADC maps, which is probably linked to the high cellularity of the tumor.

For intra-axial neoplasms it has been shown that pathological tissue has higher ADC values than healthy cerebral tissue and that the central necrotic component and the cystic component present greater diffusivity than the other components of neoplastic tissue [36]. Moreover, Brunberg et al. [37] demonstrated that edema and neoplastic tissue significantly differ in ADC values. Edema has a higher ADC value, which is probably linked to the preserved integrity of the myelin. Some studies have shown that water diffusibility is lower in high than in low-grade gliomas [38, 39], but a considerable overlap between ADCs has also been described [40]. DWI is commonly not restricted in IDH-mutant and non-mutant diffuse, anaplastic astrocytomas, and glioblastoma. ADC values obtained from standard clinical DWI are a highly significant predictor of non-enhancing glioma IDH status and may permit non-invasive molecular subtyping in accordance with the 2016 WHO classification. Low ADC values are associated with increased glioma cellularity and worse prognosis, supported by comparisons of diffusivity, histological specimens, and clinical data in multiple studies. Low diffusivity predicts poor astrocytoma survival independent from WHO grade and low ADC values are related to wild-type gliomas [41], as well as to high-grade ODs [17]. Older age, multifocality, brainstem involvement, lack of cystic change, and low ADC are independent predictors of IDH-wild-type grade II diffuse gliomas (DGs). Among these, ADC_{min} was most predictive with a threshold of $\leq 0.9 \times 10^{-3}$ mm^2/s conferring to it the greatest sensitivity (91%). Furthermore, while shorter progression free survival (PFS) and overall survival (OS) were seen in IDH-wild-type grade II DGs, combining IDH status and ADC_{min} better predicted PFS and OS than IDH status alone [42].

Some degree of DWI restriction is linked to other molecular characteristics of brain neoplasms such as MGMT methylation. MGMT promoter methylation is a strong predictor for response to alkylating agents and correlates with better survival. ADC was used as a potential surrogate biomarker for MGMT promoter methylation, however, with controversies [43–48]. In a study of Han et al. [19], the ADC value in GBMs with MGMT promoter methylation was higher than in those without MGMT promoter methylation. In accordance with several previous studies, ADC ratios or ADC minimum values are lower in tumors with unmethylated MGMT promoters than with methylated promoters [45, 46], and mean ADC had a positive relationship with the MGMT promoter methylation ratio [49] (Fig. 5.3). However, lower ADC value in MGMT promoter methylated GBMs was reported in a recent histogram analysis study [50]. Besides, no significant correlation between ADC values and MGMT promoter methylation status was also reported [48].

Diffusion tensor imaging is presently used to document the presence of white matter (WM) tracts and define their location with respect to the tumor (Fig. 5.4).

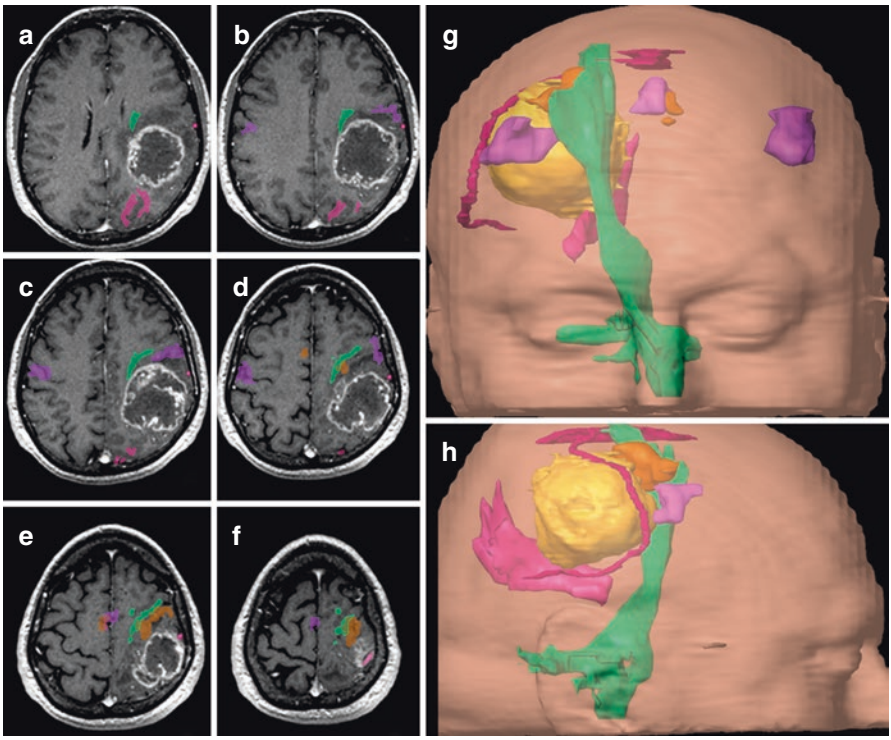

Fig. 5.4 Pre-surgical planning with tractographic reconstructions and motor area representation: axial (**a**–**f**) and volume rendering (**g**, **h**). Left fronto-parietal lesion (rolandic area) is evident (**a**–**f**). The lesion dislocated anteriorly the left cortico-spinal tract (green) (**a**–**f**), inferiorly the optic radiation (violet) (**g**, **h**). Motor areas of right hand (orange) (**d**–**f**) and right face (pink) (**b**–**d**) are dislocated anteriorly

Brain tumors may alter WM fibers in several ways: in particular, WM tracts may be displaced, infiltrated by tumor or edema, or destroyed [51]. Many studies have demonstrated that fractional anisotropy (FA), an index of fiber organization, decreases in the WM close to brain tumors [52, 53]. An increased ADC seems to play a major role in reducing the number of fibers, at least in symptomatic patients [54]. Diffusion tensor tractography (DTT), the main application of DTI, is the only imaging technique with the potential to generate realistic fiber-tract trajectories in the white matter (WM) of the brain in vivo [55]. DTI studies have demonstrated that edema, tissue compression, and degeneration may cause significant problems in the identification of trajectories compatible with WM tracts. Despite this, the combination of functional MRI (fMRI) and DTI is a useful tool for defining the seed region of interest for DTI-based tractography (DTT) and thus providing more comprehensive, functionally related, white matter mapping in preoperative assessment [56, 57]. Despite the high incidence of cases in which the lesion is responsible for changes that hinder the reconstruction of white matter tracts, the technique can change the surgical approach for corticotomy and define the extent of resection leading to change in the surgical procedure in 80% of cases [57, 58]. Combination of DTI-FT and intraoperative subcortical mapping makes possible the accurate identification of eloquent fiber tracts and enhances surgical performance and safety, while maintaining a high rate of functional preservation [58].

5.4.3 Perfusion Imaging

In the clinical setting, perfusion MRI has been proposed for tumor grading, identifying the best site for biopsy, for the differential diagnosis with non-neoplastic pathologies and to assess treatment response [59–61]. A cerebral blood volume ratio (rCBV) between the maximum value inside the tumor and the normal white matter higher than 1.75 was suggested as a threshold to distinguish between high- and low-grade gliomas [61].

In case of oligodendrogliomas (Fig. 5.2) these results are more debated since some studies demonstrated high rCBV even in low-grade tumors [62], whereas more recent studies demonstrated that perfusion MR is helpful in differentiating low-grade from anaplastic oligodendrogliomas [63]. In transforming low-grade gliomas, MR perfusion imaging demonstrated significant increases in rCBV up to 12 months before contrast enhancement was apparent on T1-weighted MR images, thus indicating the potential role of the technique in predicting malignant transformation [64]. As in high-grade gliomas, metastatic lesions show elevated rCBV. Lower rCBV values outside the enhancing component of the lesion might differentiate secondary from primary neoplasms, with a lower value in metastatic disease [65].

Moreover, $rCBV_{max}$ values are significantly associated with the IDH mutational status. Recent research showed that IDH mutation leads to 2HG accumulation, resulting in decreased hypoxia-inducible-factor 1-activation and downstream inhibition of angiogenesis-related signaling [66]. As demonstrated by Kickingereder et al. [67], IDH-mutant and wild-type tumors were both associated with distinct

imaging phenotypes and were predictable with rCBV imaging in a clinical setting (i.e., IDH-mutant tumors represented considerably lower rCBV). In a recent study, the $rCBV_{max}$ values in IDH-mutant tumors were significantly lower than in wild types [66]. Similar results are reported in a study of Lin et al. [17] on ODs, showing that rCBV values can differentiate low- and high-grade types.

The MGMT can be regarded as an independent prognostic factor in patients with primary GBM as MGMT promoter methylation increases responsiveness to temozolomide chemotherapy. The association between MGMT methylation and CBV results is debated. Ryoo et al. [68] found significantly higher rCBV values in GBMs with an unmethylated MGMT promoter than in those with a methylated MGMT; however, they did not take the IDH1/2 mutation status into account and analyzed only a small cohort of 25 patients. Conversely, in a study of Hempel et al. [3], rCBV values were significantly higher in IDH-wild-type GBMs with a methylated MGMT than in those with an unmethylated MGMT. These findings support the hypotheses of Chahal et al. [69], who found that MGMT-positive cells displayed higher levels of vascular endothelial growth factor receptor 1 (VEGFR-1) compared with MGMT unmethylated U87/EV cells leading to higher vascularization of GBM.

Perfusion MRI might help in the differential diagnosis with non-neoplastic disease. In demyelinating lesions and abscess rCBV is lower than in high-grade neoplasm and in cases of demyelinating disease even lower than in normal brain tissue [70].

The size of an enhancing lesion is commonly used as a feature of tumor behavior after therapy. Despite this, it has been demonstrated that rCBV and permeability (Ktrans) assessed with perfusion MR may decrease after therapy indicating success even without changes in tumor size. Consensus panels have published recommendations concerning the use of perfusion MR in monitoring the efficacy of therapy in intra-axial tumors [71].

Lastly, recurrent high-grade neoplasms are typically characterized by high rCBV, whereas tumor necrosis is generally associated with lack of rCBV elevation [72].

5.4.4 Functional MRI

In brain tumor patients, the aim of neurosurgery is to remove as much pathologic tissue as possible, thereby increasing survival time, while simultaneously minimizing the risk of postoperative neurological deficits [73]. Functional MR imaging is increasingly being used as part of the routine preoperative work-up of patients to establish the relationship of the lesion to eloquent areas, such as language or motor areas, and to evaluate hemispheric dominance. Identifying these areas purely on an anatomical basis is inexact, owing to considerable interindividual anatomical and functional variability, especially for language representation. Moreover, in the presence of a lesion, functional areas may be displaced due to mass effect, or function may have shifted to other areas in the brain due to plasticity [74] (Fig. 5.4). A preoperative functional MR imaging study of the main brain functions provides information on the feasibility of surgery and allows adequate assessment of the risk of postoperative neurologic deficits.

For optimal results, the relationship between the tumor margins and the functionally important brain areas needs to be established as accurately as possible [75].

The correlation between functional areas, as established with functional MR imaging versus intraoperative electrocortical stimulation, has been studied for both motor and, to a lesser extent, language representation brain areas. A high correlation has been shown for motor representation areas, but results from language representation studies are conflicting and disappointing.

Bizzi et al. [76] showed that the diagnostic performance of functional MR imaging may change according to the grade of the glioma: sensitivity is higher and specificity is lower in grade II and III gliomas than in glioblastoma multiforme, particularly for functional MR imaging of language. In patients with Rolando area tumors, the sensitivity and specificity of functional MR imaging are higher (88% and 87%, respectively) than in patients with a mass near language cortical areas (80% and 78%, respectively).

In conclusion, although functional MR imaging cannot yet replace intraoperative electrocortical stimulation in patients undergoing neurosurgery, it may be useful for guiding surgical planning and mapping, thereby reducing the extent and duration of craniotomy [77]. Moreover the combination of functional MRI and DTI-based tractography provides more complete preoperative cortical and subcortical mapping.

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