Advanced Drug Delivery Reviews 76 (2014) 98–115

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Multimodal imaging of gliomas in the context of evolving cellular and molecular therapies ☆

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ARTICLE INFO

Available online 28 July 2014

Chemical compounds studied in this article:
Temozolomide (PubChem CID: 5394)
Gadolinium (PubChem CID: 23982)
^{11}C-methionine (PubChem CID: 15556483)
^{18}F-fluoroethyltyrosine (PubChem CID: 44439370)
^{18}F-fluorodeoxyglucose (PubChem CID: 450503)
^{18}F-fluorothymidine (PubChem CID: 450772)
^{18}F-fluoromisonidazole (PubChem CID: 450173)

Keywords:
Brain tumors
Neuroimaging
Magnetic resonance imaging
Positron emission tomography
Molecular imaging
Computer vision
Image analysis
Radiology information systems

ABSTRACT

The vast majority of malignant gliomas relapse after surgery and standard radio-chemotherapy. Novel molecular and cellular therapies are thus being developed, targeting specific aspects of tumor growth. While histopathology remains the gold standard for tumor classification, neuroimaging has over the years taken a central role in the diagnosis and treatment follow up of brain tumors. It is used to detect and localize lesions, define the target area for biopsies, plan surgical and radiation interventions and assess tumor progression and treatment outcome. In recent years the application of novel drugs including anti-angiogenic agents that affect the tumor vasculature, has drastically modulated the outcome of brain tumor imaging. To properly evaluate the effects of emerging experimental therapies and successfully support treatment decisions, neuroimaging will have to evolve. Multimodal imaging systems with existing and new contrast agents, molecular tracers, technological advances and advanced data analysis can all contribute to the establishment of disease relevant biomarkers that will improve disease management and patient care. In this review, we address the challenges of glioma imaging in the context of novel molecular and cellular therapies, and take a prospective look at emerging experimental and pre-clinical imaging techniques that bear the promise of meeting these challenges.

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☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Targeted Imaging".

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http://dx.doi.org/10.1016/j.addr.2014.07.010

Key points

- High grade gliomas are heterogeneous and infiltrative, causing them to relapse after conventional standard therapies. New treatment approaches such as molecular and cellular therapies offer the perspective of a better personalized treatment.
- To provide clinicians with the appropriate information needed to efficiently deal with the treatment of gliomas, neuroimaging would benefit from an evolution from non-specific contrast based protocols to protocols that are oriented toward disease relevant and treatment specific biomarkers.
- Technological advances and the combination of imaging modalities, new contrast mechanisms and advanced data processing techniques will assist in addressing the challenges of tumor imaging in the context of emerging treatment approaches.

1. Introduction

Gliomas are brain tumors that arise from abnormally proliferating glial cells, which normally provide support and protection of neurons in the central nervous system. Glioblastoma (GBM), the focus of the present review, represents the most malignant form of gliomas with a mean patient survival after diagnosis of about 14 months [1]. Despite standard treatment involving surgical resection, radiation therapy and chemotherapy, only very few patients survive more than 5 years [2]. GBMs are highly heterogeneous; when tumors in different patients are compared, they vary in mutation status [3], in putative glial cell lineage, in epigenetic profiles and in histological appearance. Similarly, within single tumors, cell clones with different genetic profiles and even different ploidies co-exist within a microenvironment made up of varying non-neoplastic stromal cells, immune cells and extracellular matrix components. This heterogeneity represents a key challenge in tumor characterization and for the development of effective therapies. Data from high throughput molecular analyses attempts to define subclasses of GBM that differ by their genetic and epigenetic alterations, gene expression profiles, clinical aggressiveness, prognosis and response to treatment [4,5]. Although there is some discrepancy in currently proposed subclasses, the most recent work combines methylation profiles with specific genetic mutations and patient age group, to propose a classification into 6 distinct subgroups for pediatric and adult GBM [6]. Yet, these molecular classifications have so far not led to a diversification in treatment [7].

Initial diagnosis of GBM is largely based on magnetic resonance imaging or computed tomography, indicating the importance of

Table 1
Molecular and cellular therapies for gliomas.

Therapy paradigm	Principle of action	Status of development
Inhibition of 'oncogenic' growth and proliferation signaling networks	Interference with the signaling associated with glioma development, such as inhibition of tyrosine kinase growth factor receptors (e.g. EGFR and its constitutively activated variant EGFRvIII [176]), or inhibition of their downstream cellular activity regulators (e.g. mTOR, Akt [177])	Very few of these molecules have demonstrated significant improvement in terms of time-to-progression or overall survival so far, whether given as monotherapy or in combination treatment [178], owing to the complexity of these signaling networks and the versatility of adaptation mechanisms available to tumor cells.
Angiogenesis inhibition	Interference with the formation of new blood vessels initiated by the tumor. Agents include monoclonal antibody against VEGF-A such as bevacizumab (Avastin), and tyrosine kinase inhibitors (TKIs) that target several pro-angiogenic molecules.	Avastin is approved by the FDA for recurrent GBMs. Despite improved patient condition, likely caused by reduced vessel permeability and edema, clinical trials in newly diagnosed GBM have not demonstrated benefit in overall survival, whether given as monotherapy or in combination with chemotherapy [179–181].
Stress response targeting	Strategies include e.g. the targeting of the adapted metabolism of tumor cells by glycolysis [182] or autophagy inhibitors [183], the targeting of DNA repair mechanisms to improve the efficiency of DNA alkylating agents or induce apoptosis [184].	Their use in clinical trials has only demonstrated limited effects so far, possibly due to lack of specificity and the possible activation of alternative pathways.
Immunotherapy	Immunotherapeutic strategies include passive immunotherapy, in which immune cells or antibodies are delivered to target tumor cells, and active immunotherapy whose purpose is to stimulate the response of the patient's native immune system.	Trials so far have provided mixed results [185]. Vaccines that generate EGFRvIII specific antibodies resulted in improved progression free and overall survival [186]. Dendritic cell vaccination provided good clinical response in early clinical trials [187].
Gene and viral therapies	Viruses are being engineered to insert genes that are cytotoxic, tackle the proliferation capacity or DNA repair mechanisms of tumor cells. Oncolytic viruses selectively replicate in tumors, with subsequent tumor cell lysis and dispersion within the tumor.	Clinical studies using gene therapy reported improvements in median survival [188]. Proof-of-concept oncolytic virotherapy studies in glioma patients have confirmed general safety and showed encouraging long term survival in some cases [189].
Local therapies	Strategies are also being developed for the local delivery of therapeutic agents, to circumvent the blood brain barrier and achieve greater efficacy of the administered compound while reducing toxicity.	Drug delivering polymers [190] and cell encapsulation devices [191] can be implanted during surgical resection. Diffusion of therapeutic agents can be facilitated by convection enhanced delivery [192], nanoparticles with high affinity for tumor cells [193], or temporal disruption of the blood–brain-barrier by microbubble-enhanced focused ultrasound [194].

neuroimaging right from the start. The clinical management of malignant gliomas typically starts with surgical resection or gross total removal, followed by radiochemotherapy. Although a complete resection of the tumor is usually not achievable because of the infiltrative nature of the disease, the surgical step is critical to reduce the elevated intracranial pressure and for the management of seizures. The neurosurgeon also collects the tissue for neuropathologists to establish the definitive diagnosis that will further determine the treatment. Conventional radiotherapy is administered as fractionated external photon beams, but newer particle therapies, using protons or carbon ions, are also being investigated for their ability to better target tumor tissue while sparing surrounding healthy tissue. Concomitant and adjuvant chemotherapy uses the DNA-alkylating agent Temozolomide. Dosage and schedule of delivery are based on a protocol developed by the landmark study of the EORTC-NCIC [1]. Nevertheless, since all GBMs eventually recur, the aim of the treatment is palliative at best.

Currently, many alternative experimental protocols for glioma treatment are being investigated. These include small molecule inhibitors that interfere with aberrant signaling events associated with glioma growth or its adapted metabolism. Angiogenesis inhibitors, immunotherapies, gene and viral therapies, as well as strategies for local delivery of therapeutic compounds are also under development or at different stages of clinical use. These novel therapies were recently reviewed in a special issue of *The Cancer Journal* [8], and are summarized in Table 1, together with results from recent clinical trials. It is currently unclear if and when these approaches will be implemented in clinical practice, but the focus is to adopt a more personalized approach and tailor the therapy according to the molecular features of the individual tumor.

2. Imaging of gliomas in the clinic

Neuroimaging has, over the years, become invaluable in the management of gliomas. MRI is the preferred modality for glioma imaging, owing to the variety of soft tissue contrasts available, and its ability to provide morphological, physiological and metabolic information about the tumor. MRI is used at all stages of glioma management, from the detection and localization of the tumor, to the planning of neurosurgery and radiotherapy and the assessment of treatment efficacy [9]. Positron emission tomography (PET) can complement MRI by providing access to molecular targets with high sensitivity. Tracers of proliferation and metabolic activity are increasingly being used in pre-therapy assessment and in the monitoring of treatment response [10]. CT often provides the anatomical context in PET studies but can also be used to detect tumors (after injection of contrast) and in perfusion studies [11,12]. Other modalities less frequently used include single photon emission computed tomography (SPECT), an alternative nuclear imaging technique to PET that uses longer half-life isotopes, which are easier and cheaper to produce, but provides images of lower spatial resolution. The use of ultrasound in brain tumor imaging is hindered by the presence of the skull, limiting its use to specialized applications such as pediatric brain tumors [13] or the assessment of tumor boundaries during surgery [14]. Table 2 provides an overview of some of the most important features of the different modalities used for the imaging of gliomas. The remainder of this chapter presents the MRI and PET protocols that are most commonly used in the clinic and the challenges faced when imaging gliomas.

2.1. MRI

A standard MRI study for GBM patients comprises several anatomical series (Fig. 1A–C): T1 weighted sequences, after the intravenous injection of a gadolinium (Gd) based contrast agent, typically show tumor as a hyperintense signal as contrast leaks out of impaired blood vessels and accumulates into tumor tissue (Fig. 1A). T2 weighted sequences (Fig. 1B) can possibly detect non-enhancing tumors since the prolonged T2 relaxation time of tumor tissue makes them appear hyperintense in comparison to normal tissue. T2 weighted fluid attenuated inversion recovery (FLAIR) sequences (Fig. 1C), in which the signal from the cerebrospinal fluid has been suppressed, can also be used to delineate tumors in the vicinity of ventricles or to further highlight areas of non-enhancing tumor, in particular infiltration zones and edema.

Perfusion weighted imaging (PWI) after bolus injection of contrast (Fig. 1D) complements these anatomical series by providing access to

Table 2
Features of modalities used for glioma imaging.

Modality	Key features
Magnetic resonance imaging (MRI)	• Based on the magnetic properties of hydrogen nuclei placed in a high magnetic field (non-ionizing radiations) • Versatile modality with wide variety of soft tissue contrasts available • High spatial resolution (0.2–1 mm) and fair sensitivity (10^{-3}–10^{-5} mol/l) • Provide anatomical, functional and metabolic information
Positron emission tomography (PET)	• Nuclear imaging technique that uses positron emitting radionuclides with short half-life isotopes such as carbon-11 (20′), oxygen-15 (2′) or fluorine-18 (110′) • High sensitivity (10^{-11}–10^{-12} mol/l) and limited spatial resolution (5–10 mm) • Production of radiolabeled isotopes is expensive and requires the proximity of a cyclotron • Molecular imaging of targets such as receptors, enzymes or protein sites • Biodistribution of tracers may depend on blood–brain barrier, trapping of enzyme substrates, cell surface internalization, protein binding and metabolism
Single-photon emission computed tomography (SPECT)	• Alternative nuclear imaging technique that uses the direct gamma radiations emitted by longer half-life radioisotopes such as technetium-99 m (6 h) or iodine-123 (13 h) • Well established, widely available and cheaper than PET • Good sensitivity (10^{-10}–10^{-11} mol/l) and limited spatial resolution (7–15 mm) • Simultaneously image several radionuclides (differentiated by their energy)
Computed tomography (CT)	• Fast, effective and high resolution technique based on X-ray attenuation in tissues • Often used to provide the anatomical context in PET or SPECT studies
Ultrasound (US)	• High temporal resolution technique based on the reflection of sound waves that allows real-time imaging, although its use in brain malignancies is impaired by the presence of the skull.

physiological parameters such as blood volume, blood flow and possibly blood vessel permeability. Blood volume positively correlates with tumor grade [15,16] and has been used to assess treatment efficacy [17] or differentiate recurrence from post-treatment radiation effect [18]. Diffusion weighted imaging (DWI) (Fig. 1E), may help in separating edema from infiltrative tumor cells or distinguish neoplastic regions from abscesses [19]. Longitudinal changes in the mobility of water molecules has been proposed as an early marker of treatment response [20,21], correlating with time-to-progression and overall survival [22]. Finally, chemical shift imaging (CSI), a magnetic resonance spectroscopy technique, provides access to the spatial distribution of a limited number of abundant metabolites in vivo (Fig. 1F). Ratios such as Choline/N-acetylaspartate and lactate/lipids levels can help to distinguish tumor types and grades [23], predict survival [24], or separate tumor recurrence from radiation necrosis [25,26].

2.2. PET

In some clinical centers, MRI is complemented by PET imaging to visualize molecular processes in gliomas (Fig. 2). PET tracers of cell proliferation based on amino acid metabolism, such as ^{11}C-methionine (^{11}C-MET) (Fig. 2A) and ^{18}F-fluor-ethyl-tyrosine (^{18}FET) (Fig. 2B), are the most commonly applied. For the imaging of gliomas they are more useful than ^{18}F-fluorodeoxyglucose (^{18}F-FDG) (Fig. 2A), which produces a high background signal in the brain (because of high glucose consumption) and has limited sensitivity in detecting brain tumors [27–29]. ^{11}C-MET and ^{18}FET are superior for the detection of gliomas and the planning of radio-therapy, including in regions of infiltrative tumor cells not detected by MRI [30].

For example, it has been shown that radiotherapy planning using ^{18}FET data may lead to larger treatment volumes with more precise delineation of active tumor tissue and potentially less “out of field” recurrences [31,32]. Moreover dynamic analysis of the tracer uptake provides more accurate information about the “aggressiveness” of the tumor as reflected by the WHO grading [33]. It has been suggested that with dynamic ^{18}FET tracing, tumors with unfavorable prognosis can be distinguished even within the same WHO grade [34], and anaplastic foci can be identified in otherwise low grade gliomas [35]. ^{18}FET also appears to be a powerful tool to distinguish tumor recurrence from radiotherapy induced changes [36].

Nucleic acid tracers such as ^{18}F-fluorothymidine (^{18}F-FLT) have also been proposed as markers of proliferation (Fig. 2C). In clinical trials, they have proved to be superior to ^{18}F-FDG and MRI in differentiating low-grade from high-grade gliomas, providing a good correlation with histological proliferation markers [37]. Reduced uptake of ^{11}C-MET, ^{18}FET and ^{18}F-FLT are all promising markers of response to treatment and predictors of favorable clinical outcome [38–41].

PET also allows the monitoring of tumor hypoxia, an important feature of high grade gliomas. Hypoxia may induce resistance to radio- and chemo-therapy through several mechanisms, including reduced radiation induced DNA damage, poor drug delivery from blood vessels, slow-down of proliferation, and gene expression changes that enable cellular rescue from severe damage. PET tracers such as ^{18}F-fluoromisonidazole (^{18}F-FMISO) are thus increasingly being considered to plan and assess the efficacy of radio- and chemotherapy treatment (Fig. 2D) [42,43].

Neuroimaging is increasingly being used for the planning of surgical procedures. Anatomical MRI series can be loaded in neuronavigation systems to establish surgical routes and guide the neurosurgeon during the procedure (Fig. 3A). If available, additional sequences that provide information about the physiological and metabolic state of the tumor can also be included. Advanced sequences such as Diffusion Tensor Imaging tractography can be used to visualize the displacement of white matter tracts that results from the presence of tumors (Fig. 3B), and functional MRI is used to locate eloquent areas in the brain (Fig. 3C). Metabolic imaging with PET tracers may help to locate tumor hot spots that should be targeted by the biopsy (Fig. 3D).

2.3. Challenges

There are a number of challenges associated with brain tumor imaging in the clinic today. Conventional MRI protocols are mostly nonspecific and don't directly differentiate tumor cells from healthy tissue. This makes it difficult to characterize brain lesions and establish prognosis [44], and limits the detection of the infiltrative compartment of the tumor. Criteria most commonly used in the clinic to assess the treatment efficacy in gliomas were originally established by Mac Donald and colleagues in 1990 [45]. They are mainly based on the changes in tumor size over time, assessed from MRI or CT sequences. Imaging based on T1-weighted sequences acquired after injection of Gadolinium-based contrast agents suffers, however, from the problems of pseudo-progression, that is radiation induced necrosis confounding with recurrent tumors [46], and pseudo-response, that is reduction of contrast uptake, such as after anti-angiogenic therapy, despite tumor progression [47]. These difficulties have prompted a group of experts known as the Response Assessment in Neuro-Oncology (RANO) working group to propose revised criteria in 2010. The new recommendations distinguish contrast enhancement within and outside the area of radiation, and introduce T2 weighted FLAIR to assess edema and tumor infiltration [48]. Still, imaging of this infiltrative compartment remains a challenge for current imaging modalities, and new techniques

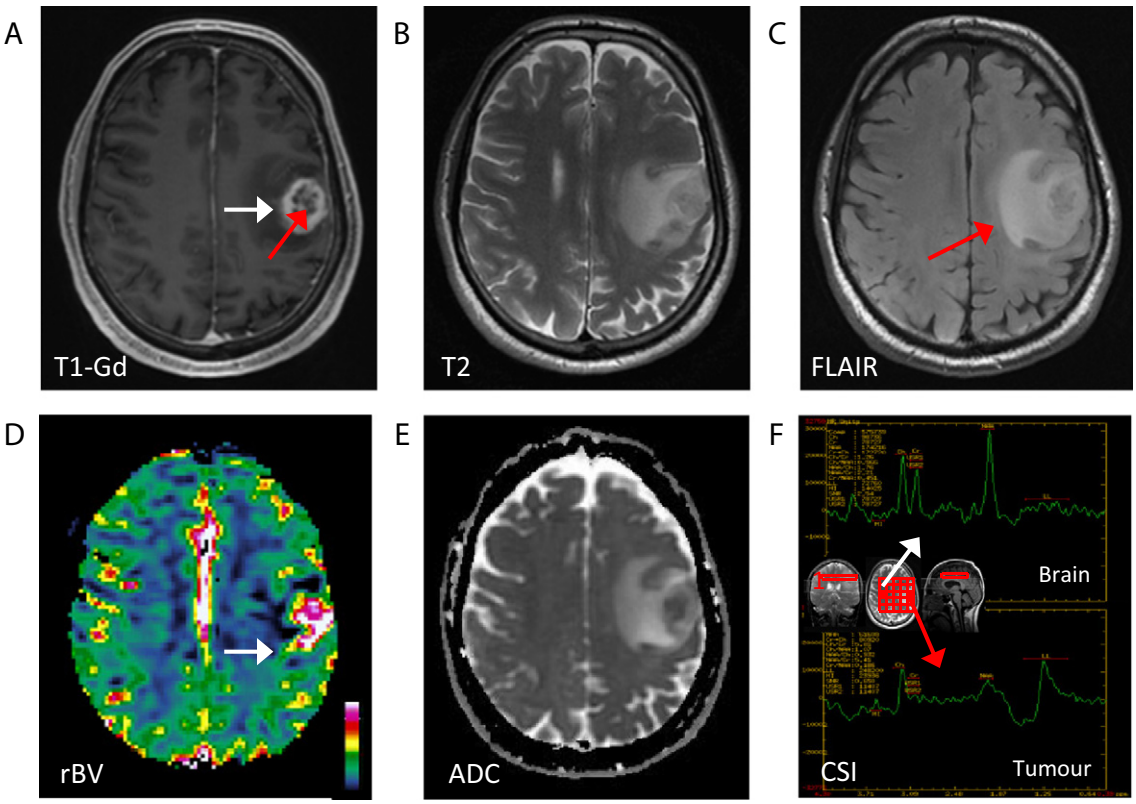

Fig. 1. Multiparametric assessment of brain tumors with MRI. Multiparametric MRI provides morphological, physiological and metabolic data on the tumor. In the present case, for a patient diagnosed with GBM: (A) T1 sequence after injection of Gd contrast showing a necrotic tumor core (red arrow) surrounded by a hyperintense ring of contrast enhancement (white arrow) caused by a leaky tumor vasculature. (B) T2 sequence showing a large abnormal signal with a hyperintense core. (C) T2-FLAIR sequence providing insight into the extent of edema (red arrow). (D) rCBV map showing active tumor cells at the periphery of the tumor (white arrow). (E) ADC map showing area of abnormal water molecule diffusion which may be caused by a combination of factors including necrosis, edema and hypercellularity. (F) CSI spectroscopy showing the position of the grid of analyzed voxels, spectra corresponding to voxels corresponding to healthy brain (white arrow) and tumor tissue (red arrow). Images in panels A–F, courtesy of M Lund-Johansen and R Grüner, Bergen. Gd: gadolinium, ADC: apparent diffusion coefficient, rCBV: relative cerebral blood volume, FLAIR: fluid attenuated inversion recovery, CSI: chemical shift imaging.

for the in situ detection of infiltrating tumor cells in surgical settings may partially address this issue in the future [49,50].

In the context of novel molecular and cellular therapies to come, the treatment of glioma patients would greatly benefit from a better insight into the molecular processes that cause the disease, determining how these molecular processes are affected by a given therapy, and how the putative molecular changes can be detected by MRI and PET. Precise information on general treatment paradigms such as proliferation, angiogenesis, inflammation, infiltration, as well as on specific disease characteristics, such as the presence of receptors, transport proteins or point mutations, would be useful at crucial decision times during treatment. In the following sections, we will describe key imaging technologies, currently in experimental and pre-clinical development, that could assist in addressing these challenges.

3. Experimental approaches to the imaging of gliomas

3.1. MRI contrast strategies

Basic contrast in MRI comes from differences in local water content, which can be modulated by regional differences in the longitudinal (T1) and transversal (T2) relaxation times of the tissues. Although the intrinsic contrast achieved can be sufficient to distinguish anatomical regions and some tissue pathologies, it is often necessary to improve the sensitivity and specificity of diagnosis by the use of exogenous contrast agents or endogenous contrast mechanisms. MRI is a very versatile modality in this regard and the mechanisms through which contrast can be achieved are described in common MRI text books [51]. These include techniques as diverse as those based on inversion recovery, magnetization transfer, spin tagging, chemical shift, iron-induced susceptibility changes, perfusion and water molecule diffusion. In the following paragraphs, we describe how these techniques are being applied to the study of gliomas. Fig. 4 provides recent examples of such techniques.

3.1.1. Exogenous contrast agents

Intravenous administration with subsequent accumulation of low molecular weight contrast agents (<1000 Da) in brain tumors with impaired blood–brain-barrier has represented the cornerstone of brain tumor detection in recent decades. Contrast agents reduce the T1 of tissues in which they accumulate, providing a hyperintense signal in T1-weighted sequences. Their influence on the T2 and T2* of blood in which they circulate is also exploited in perfusion applications via the dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) technique. However, concerns with Gadolinium-based contrast agents are that they are non-specific and can lead to a rare but serious complication in patients with renal diseases, known as nephrogenic systemic fibrosis [52].

Next generation contrast agents, including higher molecular weight agents (>30,000 Da) are thus being investigated to address these challenges. They are usually based on nanoparticles with an iron oxide core with a biostable inert polymer coating that improves contrast in T2- or T2*-weighted sequences by disrupting local magnetic fields. They are often referred to as superparamagnetic iron oxide nanoparticles (SPIO) or ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) depending on their size. They can be used in perfusion and

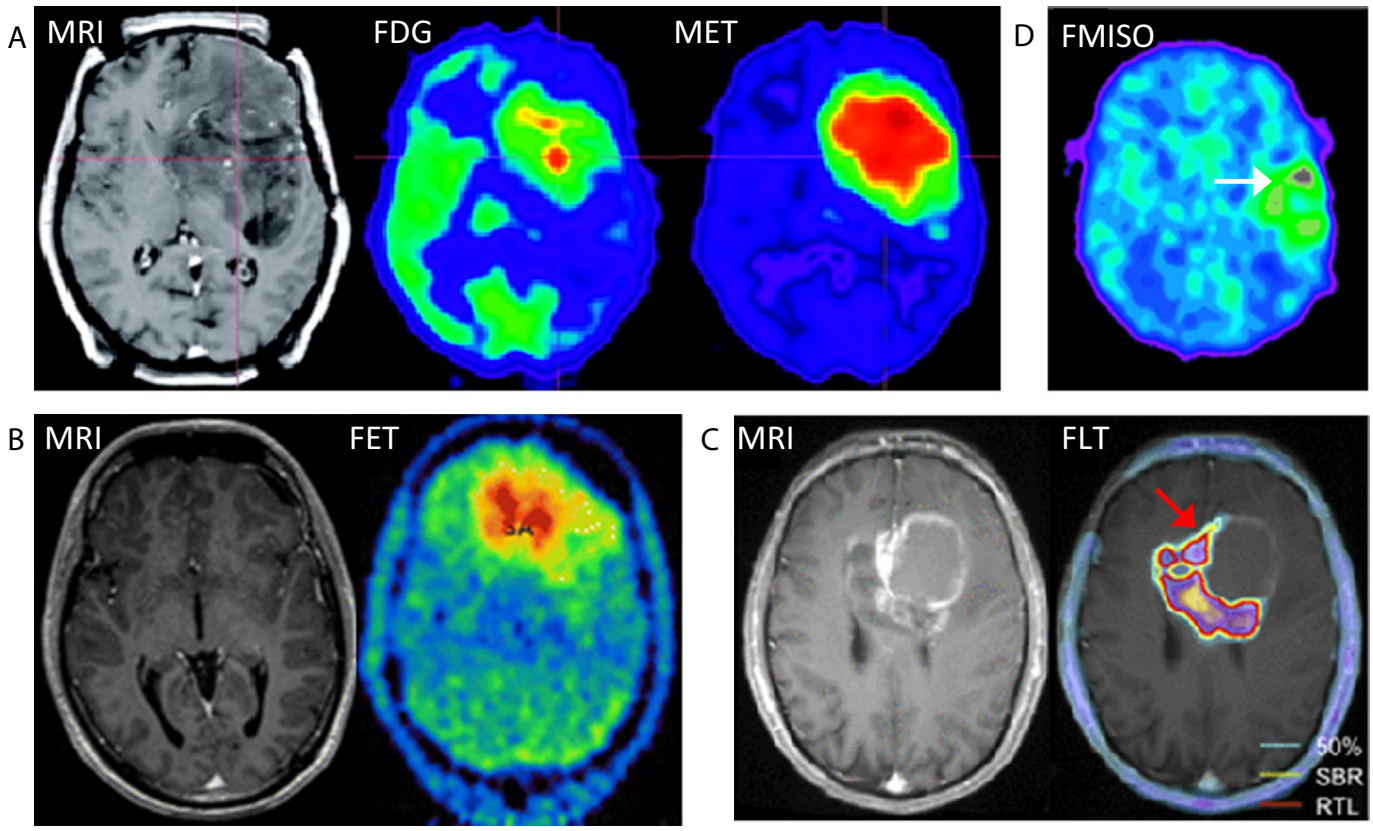

Fig. 2. Molecular imaging of brain tumors with PET. Typical PET tracers used for molecular imaging of gliomas in the clinic (highest PET activity shown in red): (A) Metabolic imaging of an infiltrating anaplastic astrocytoma patient. Uptake of ^{18}F-FDG is higher in the tumor than in the surrounding gray matter. Uptake of ^{11}C-MET is also higher in the tumor and extends beyond the area of high FDG uptake. (B) ^{18}FET–PET of a second glioma patient treated with antiangiogenic therapy, showing high tracer uptake despite the absence of contrast enhancement in MRI. (C) ^{18}F-FLT overlaid on MRI for a third GBM patient, showing high uptake values indicative of high tumor cell proliferation in the tumor compartment infiltrating through the corpus callosum (red arrow). 50%, SBR and RTL lines denote different segmentation methods (see ref [208] for details) (D) ^{18}F-FMISO scan of a fourth patient with a GBM in the left temporal lobe, showing the accumulation of the tracer in hypoxic regions of the tumor (white arrow). Information in panels A, B, C, D reproduced and adapted with authorization from [208,237–239], © by the Society of Nuclear Medicine And Molecular Imaging, Inc. ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, ^{11}C-MET: ^{11}C-methionine, ^{18}FET: ^{18}F-fluor-ethyl-tyrosine, ^{18}F-FLT: ^{18}F-fluorothymidine, ^{18}F-FMISO: ^{18}F-fluoromisonidazole.

angiography applications where the contrast agent is expected to remain in the vascular compartment, hence being also referred to as blood pool contrast agents. Such nanoparticles can also be engineered for the imaging of molecular targets, where the homing to the target is achieved by attaching molecules such as standard antibodies or derivatives to the nanoparticle body (Fig. 4A). In pre-clinical models, this principle has for instance been applied to the detection and quantification of receptors strongly modulated in GBMs such as the epidermal growth factor receptor EGFR [53], the vascular endothelial growth factor receptor 2 VEGFR-2 [54] or the cell adhesion receptor integrin $\alpha_v\beta_3$ [55]. Nanoparticles can also be engineered for combined diagnosis and therapy [56,57].

3.1.2. Magnetization transfer

With chemical exchange saturation transfer (CEST), endogenous diamagnetic agents such as proteins, glycogens or glucosaminoglycans can be used to image their own presence, the presence of other compounds or environmental factors such as pH or temperature. For example, magnetization transfer of the amide protons (Fig. 4B), has been proposed to detect brain tumors even in the absence of impaired blood vessels [58] or to differentiate tumor recurrence from radiation necrosis [59]. Exogenous paramagnetic agents consisting of lanthanide complexes, termed paramagnetic CEST agents (PARA-CEST), are also being developed that allow a more selective activation of ligand protons and a more pronounced CEST effect. The possibility to design agents that detect and quantify nearly any biologically important metabolite or that respond to changes in environmental conditions, as well as the possibility to monitor several targets simultaneously, make these agents attractive [60]. Technical challenges associated with elevated energy absorption and toxicity however have to be addressed before such agents can be used in clinical application [61].

3.1.3. Spin tagging

Arterial spin labeling (ASL) is used to obtain 3D blood flow maps of the brain in a short time (Fig. 4C), without the need for exogenous contrast agent injection [62]. Technical advances in high magnetic fields and new sequences could also provide access to permeability parameters within ASL experiments in the future [63]. Blood flow values calculated with ASL correlate with those obtained by perfusion MRI techniques that use exogenous contrast such as dynamic susceptibility contrast MRI (DSC) [64]. Therefore, despite the inherently much lower contrast-to-noise ratio of the ASL technique, many of the DSC applications for brain tumors should also be possible using ASL. Clinical studies have started to show that this technique can be used to differentiate high grade from low grade gliomas and other malignancies [65,66], or to distinguish tumor recurrence from radiation necrosis [67].

3.1.4. Functional MRI

Blood-oxygenation level-dependent (BOLD) MRI has been used in functional brain imaging studies for a number of years. The technique has now been proposed to image hypoxia [68,69] or to assess vascular

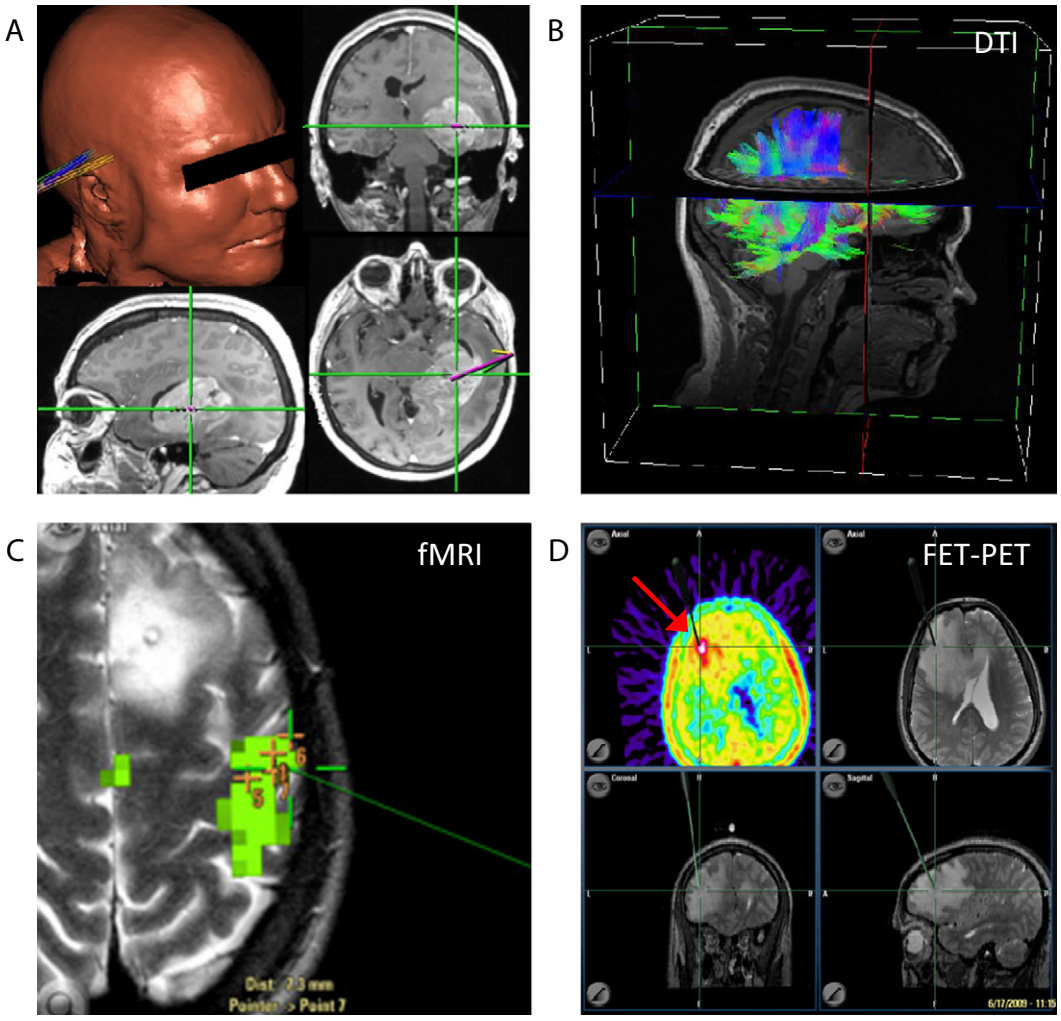

Fig. 3. Pre-operative MRI and neuronavigation. (A) 3D anatomic MRI series are used in neuronavigation systems to plan the surgical resection route or to select target biopsy spots in brain tumor patients. (B) DTI-based tractography shows the displacement of white matter tracts caused by a tumor located in the frontal lobe. (C) Integration of fMRI detects relevant areas of the motor cortex (overlaid in green), located in the vicinity of a low grade glioma. (D) Integration of ^{18}FET–PET imaging selectively detects anaplastic glioma tissue presenting as 'hot-spot' target for biopsy (red arrow). Images in panels A and B, courtesy of M Lund-Johansen and R Grüner, Bergen. Images in panels C and D, courtesy of JC Tonn, Munich. DTI: diffusion tensor imaging, fMRI: functional magnetic resonance imaging, ^{18}FET: ^{18}F-fluor-ethyl-tyrosine.

maturity, angiogenesis and response to treatment in mixed oxygen–carbogen challenges [70,71].

3.1.5. Susceptibility weighted imaging

Susceptibility weighted imaging (SWI) provides contrast based on the susceptibility differences between blood and tissues. Phase images are used to detect these differences and enhance the contrast of magnitude images, rendering them highly sensitive to venous blood, hemorrhages and iron storage (Fig. 4D). SWI has been used to characterize the angiogenic behavior of tumors [72], micro-hemorrhages after radiotherapy [73], to grade intracranial gliomas [74], and to assess responses to therapy [75].

3.1.6. Angiography

Time resolved magnetic resonance angiography (MRA) performed during contrast-agent injection (Fig. 4E) provides additional information for routine examination of brain tumors, such as vascular anomalies and relationship between lesions and vessels [76].

3.1.7. Specific tissue signal suppression

Double inversion recovery (DIR) sequences nullify the signal associated with the CSF and the white matter simultaneously, allowing better differentiation between tumor and normal brain tissue in comparison to FLAIR sequences [77].

3.1.8. Elastography

Access to tissue viscoelastic constants (tumor stiffness) using magnetic resonance elastography (MRE) may provide a predictive marker of tumor malignancy and contribute to the early non-invasive assessment of suspicious cerebral lesions [78].

3.2. Advances in physiological imaging

3.2.1. Perfusion

Dynamic susceptibility contrast MRI (DSC-MRI) is the most commonly used method for perfusion imaging in the clinic, due to its ease of implementation, short duration and readily accessible biomarkers such as blood volume, blood flow and transit time. It is based on changes in T2 or T2* relaxivity, induced by the first pass of a contrast agent bolus injection. High-speed acquisitions are needed to maintain a good temporal resolution, which can only be achieved at the expense of reduced spatial resolution and signal-to-noise ratio. The accumulation of the contrast agent in tissues at the end of the perfusion series can be exploited afterwards to acquire high-resolution anatomical images. By

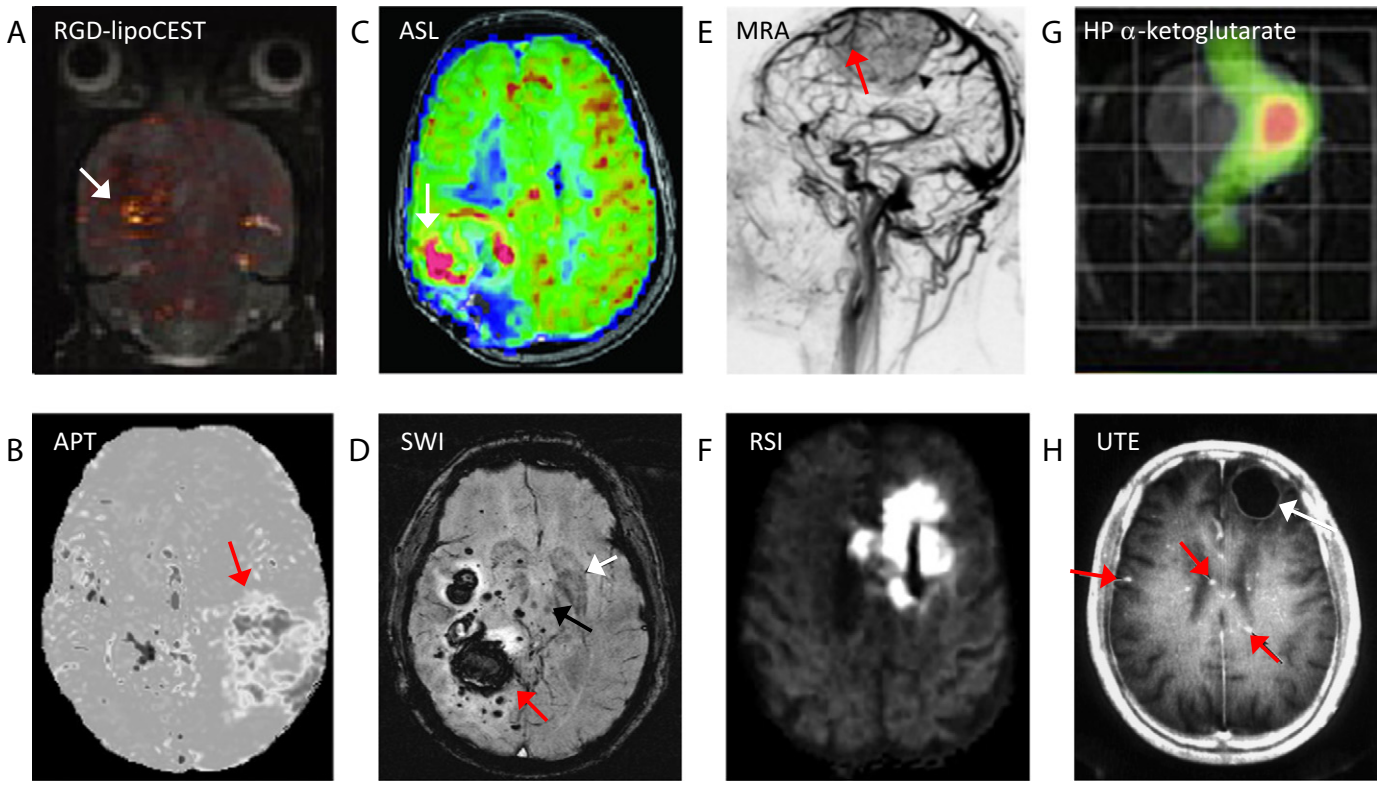

Fig. 4. Advanced MR contrast mechanisms. Examples of clinical and preclinical sequences making use of new MR contrast mechanisms: (A) Accumulation of RGD-lipoCEST nanoparticles in cells expressing integrin $\alpha_v\beta_3$ receptors (white arrow), for a mouse bearing a U87MG induced intracerebral tumor. (B) APT of a diffuse glioma showing high intensity in the tumor (red arrow) compared to normal brain tissue. (C) ASL blood flow map of a recurrent GBM patient displaying elevated blood flow at the tumor periphery (white arrow). (D) SWI of astrocytoma grade II postsurgery, showing blood products in both tumor and surrounding tissue (red arrow) which may be postsurgical or tumor-induced, as well as iron rich structures such as basal ganglia (white arrow) and red nuclei (black arrow). (E) TOF-MRA of a case of angioma performed during contrast agent injection displaying tumor vasculature (red arrow) (F) RSI of a GBM showing histopathologically confirmed bevacizumab-induced coagulative necrosis. (G) Accumulation of 2-HG in a glioma bearing mouse after injection of hyperpolarized a-ketoglutarate, reflecting the presence of IDH mutation, an important prognosis factor. (H) UTE showing multiple angiomas (white spots, red arrows) and possibly gliosis (white arrow) in the rim surrounding cavity after glioma resection. Information in panels A, B, C, D, E, F, G, and H adapted from references [240], [235], [241], [242], [76], [243], [105], [149], respectively, with permission. RGD: arginylglycylaspartic acid, CEST: chemical exchange saturation transfer, APT: amide proton transfer, ASL: arterial spin labeling, SWI: susceptibility weighted imaging, TOF-MRA: time of flight-magnetic resonance angiography, RSI: restriction spectrum imaging, 2-HG: 2-hydroxyglutarate, IDH: isocitrate dehydrogenase, UTE: ultrashort echo time.

using dynamic contrast enhanced MRI (DCE-MRI), an alternative method based on changes in T1 relaxivity induced by multiple passages of a contrast agent, it is possible to obtain additional parameters related to blood vessel permeability [79]. This however requires longer scan time and more complex pharmacokinetic modeling. The additional parameters obtained can, for example, be used to investigate the vascular changes induced by anti-angiogenic therapies [80]. Recent developments have focused on integrating both methods in dual echo sequences [81,82] and on optimizing the models used to derive quantifiable perfusion parameters [83,84].

3.2.2. Diffusion

Diffusion weighted imaging (DWI) suffers from confounding factors in that increased cellularity (due to tumor cell infiltration) reduces water-molecule diffusion, while vasogenic edema and necrosis increase it. It has therefore been proposed that by using a multidiffusion time acquisition sequence, a technique called Restriction Spectrum Imaging (Fig. 4F), the separation of hindered and less restricted water compartments is possible. This makes it easier to visualize the infiltrative tumor cell compartment [85], interpret tumor response following anti-angiogenic therapy [86], and improve the reconstruction of white matter tracts in regions of peritumoral FLAIR hyperintensity [87].

Also, conventional MRI methods used to assess the apparent diffusion coefficient (ADC) employ relatively long diffusion times and are thus sensitive to diffusion restrictions at the length scale of cellular dimension. Using oscillating gradient diffusion techniques at moderate frequency, it is possible to detect diffusion restrictions at lower length scales, smaller than the diameter of a single cell, resulting in greater sensitivity to sub-cellular structures. Application of this technique to assess the chemotherapeutic-treatment response in animal models of gliomas suggests that early changes in microstructures, such as the reduction in mean nuclear size, can induce diffusion changes that can be detected much earlier than changes in cellular density [88]. Clinical applications have so far been limited to optimizing the technique, and demonstrating its ability to visualize microstructures within the brain [89].

3.3. Advances in magnetic resonance spectroscopy

Single voxel magnetic resonance spectroscopy (MRS) and chemical shift imaging (CSI) are spectroscopy techniques used to detect the presence of metabolites in vivo. In comparison to nuclear magnetic resonance (NMR) of metabolites in solution, proton MRS on conventional clinical systems suffers from high background noise and shimming challenges, which limits the spectral resolution and the sensitivity of detection to a small number of abundant metabolites. Advanced spectroscopy techniques are thus being introduced to address these challenges.

3.3.1. Spectral editing

To improve the separation of overlapping resonances, techniques that have long been used in NMR, such as spectral editing and 2D NMR, are now being investigated in vivo as well. This has for instance been used for the detection of lactate and other metabolites in

astrocytomas [90], and for the detection of 2-hydroxyglutarate in isocitrate dehydrogenase (IDH) mutated gliomas [91].

3.3.2. Multinuclear spectroscopy

Non-proton spectroscopy can also be used to supplement the metabolic information provided by proton spectra. ^{31}P-MRS has for instance been used to assess pH and analyze intracellular energy storage in malignant gliomas [92], and to evaluate response to therapies [93]. The tracing of ^{13}C-labeled molecules and their metabolites is finding applications in preclinical and clinical studies of glucose metabolism [94] and drug biodistribution [95]. Additional hardware, such as coils tuned for multinuclear spectroscopy, is required although typically not included as part of the standard configuration of clinical MR imaging systems.

3.3.3. Hyperpolarization

Hyperpolarization, a magnetic labeling technique used to enhance the signal of exogenous compounds for detection by MRI, currently does not have the sensitivity and the wide range of metabolic tracers that PET has. Yet, it benefits from a number of features that are appealing for the future of metabolic imaging in the clinic. These include the simultaneous detection of a precursor and its metabolites, the absence of radiation, and fast acquisitions that open new avenues to real-time metabolic imaging [96]. Some of the metabolic processes currently under investigation include the conversion of pyruvate to lactate and alanine to assess glycolysis and response to therapy [97–99], or the conversion of fumarate to malate proposed as a marker of cell necrosis [100]. Hyperpolarized compounds for the analysis of extra- and intracellular pH [101], redox state [102], glutaminolysis [103], choline kinase activity [104] and more recently IDH status [105] have also been introduced in experimental settings (Fig. 4G). The simultaneous hyperpolarization of several compounds is possible, enabling for instance the assessment of metabolism, pH, necrosis and perfusion in a single acquisition [106]. However, technical challenges have to be met before hyperpolarized compounds can be deployed in the clinic. The short half-life of the hyperpolarized compounds currently limits their use to fast occurring processes, and specialized sequences and standardized data analysis tools are required to facilitate the implementation of this technology.

3.4. Advances in molecular imaging

In Section 2.2, we have introduced PET tracers that are used in the clinic today. While proliferation and metabolic activity are often the first subject of investigation, other molecular features of glioma that are relevant for their treatment can also be imaged. PET remains the most popular modality for molecular imaging, owing to its very high sensitivity and the large number of tracers available. In comparison, SPECT tracers have typically suffered from poor spatial resolution that renders quantification difficult. Nevertheless, new technical advances in data reconstruction techniques that allow improved spatial resolution and quantification, associated with the lower cost and longer half-life of SPECT tracers, as well as the possibility to use several tracers simultaneously, could herald a rebirth of this technology. MRI tracers that use nanoparticles are also gaining acceptance because of their non-invasive profile and the prospect of combining molecular imaging with anatomical and physiological imaging in a single modality. In this section, we review key molecular features that are important for the treatment of gliomas and describe some of the approaches that are being developed for their imaging in vivo.

3.4.1. Proliferation and metabolic activity

In addition to the tracers described in Section 2.2, other radiolabeled amino acid tracers are actively being investigated. For example, Fluorodopa (^{18}F-FDOPA), a PET amino acid tracer to detect intracerebral dopamine, appears to be superior to ^{18}F-FDG PET and MRI in detecting recurrence especially in low grade glioma [107–109], and in predicting survival in recurrent glioma treated with bevacizumab [110]. SPECT tracers, such as 131-iodine-alpha-methyl tyrosine (^{131}I-IMT), also an amino acid based agent, and 99mTc-glucoheptonate (^{99m}Tc-GHA), a glucose analog, have been investigated to plan radiotherapy treatment and differentiate tumor recurrence from radiation induced necrosis [30,111–113].

3.4.2. Cellular death

PET molecular tracers have also been used for the selective detection of apoptosis in vivo. They include radiolabeled derivatives of Annexin V, a naturally occurring ligand specific for the membrane protein phosphatidylserine expressed by apoptotic cells, as well as molecules targeting caspases, the proteolytic enzymes activated in apoptosis to cleave intracellular proteins [114,115].

3.4.3. Tumor vasculature

Various strategies have been developed for the imaging of the deregulated vasculature of tumors. These include the imaging of the VEGF/VEGFR signaling pathway, which plays a pivotal role in regulating angiogenesis [116], and the imaging of integrins, the transmembrane receptors involved in regulating the attachment of cells to the extracellular matrix. Integrin $\alpha_v\beta_3$ is up-regulated in the tumor vasculature but not by quiescent endothelial cells [117] and its expression correlates with tumor aggressiveness [118], making it a natural target for drug delivery and imaging by nanoparticles labeled for PET or MRI [119–121]. Other peptides and monoclonal antibodies targeting receptors involved in the signaling associated with angiogenesis have also been radiolabeled for PET or SPECT imaging. They have been used to assess the expression of targets such as Ephrin, c-Met and PDGFR in pre-clinical studies on gliomas [122–124]. Changes in transverse relaxivity after injection of blood-pool contrast agents have also been used to determine indexes of vessel size and changes in vascular morphology caused by tumor angiogenesis [125–127].

3.4.4. Immune response

Evidence points at a role of microglia/macrophages in the immunosuppression and promotion of glioma growth [128]. Translocator protein, an outer mitochondrial membrane protein, has been used as a marker of microglial activation. The radiolabeling of its ligand for PET imaging bears potential as a cancer biomarker, correlating with disease progression and survival [129]. MR imaging of phagocytosis, mainly mediated by microglia and brain macrophages, may also be possible following an intravenous injection of iron oxide nanoparticles [130].

3.4.5. Molecular targets and pathways

PET tracers for a number of receptor tyrosine kinases and major downstream signaling components relevant for glioma development, such as endothelial growth factor receptor (EGFR), Akt, p53, and hypoxia inducible factor-1 (HIF-1), are also being tested in preclinical settings. They may have a role in the stratification of patients and the assessment of treatment efficacy in future clinical applications [131].

3.4.6. Drug delivery

New combinatorial formulations are being developed to improve the biodistribution of systemically administered therapeutic agents. Examples include liposomes, polymers, micelles, nanoparticles and antibody systems carrying therapeutic loads, which can be supplemented by contrast agents for imaging the homing of the drug to the tumor [132]. The (pre)clinically most relevant applications of these techniques relate to the validation and optimization of drug delivery and the prescreening of patients on the basis of predicted treatment efficacy [133]. Examples of techniques for labeling therapeutic drugs to trace their biodistribution in vivo, include the radiolabeling of Temozolomide for PET detection [134] or its labeling with ^{13}C for detection by MRS [95].

3.4.7. Other molecular imaging approaches

Although nuclear medicine, and to some extent nanoparticles engineered for MRI detection, are at the forefront of molecular imaging, other techniques based on sound and light waves are being investigated for specific applications. Despite not having the sensitivity, tomographic capacity, and depth of penetration of PET and MRI, they provide the benefits of cost and time efficiency, without the need for ionizing radiation. Optical imaging and ultrasonography have, for example, been applied to pediatric tumor imaging [13], intra-operative delineation of tumor margins [14], postoperative detection of residual tumors [135], and the assessment of tumor perfusion [136]. Photoacoustic and thermoacoustic imaging are also being investigated for the functional or molecular characterization of cancer tissue, with potential applications in cancer detection, diagnosis and treatment guidance [137].

While some of these imaging markers are still under development, others are making their way to clinical trials and routine practice. Table 3 provides an overview of the PET/SPECT tracers and MRI protocols most commonly investigated in clinical trials to provide novel molecular and metabolic insight.

4. Technological advances

Recent advances in hardware and data analysis techniques are likely to contribute to the advancement of neuroimaging. Imaging features such as resolution, speed of acquisition, contrast and specificity of tracers will continuously improve, and the combination of multiple information sources should enable the establishment of composite markers that will provide better insight into aspects of the disease that are relevant for its treatment.

4.1. Next generation imaging modalities

4.1.1. High field magnets

In MRI, the strength of the magnetic field determines the amplitude of the net magnetization and the maximum signal strength that can be achieved and used for either improved image quality or reduced scan time. However, higher field magnets come with a higher price and are subject to some limitations. Field homogeneity is difficult to achieve, causing more pronounced susceptibility artifacts and distortions in fast imaging techniques. Sequences have to be re-designed to achieve the same contrast as with lower field magnets and to limit the radiofrequency power deposition in patients. Nevertheless, the improved image quality obtained at these higher fields using diffusion and perfusion techniques appears to enable better diagnostic accuracy in brain tumors [138]. Improved susceptibility weighted imaging may also prove useful to predict responses to anti-angiogenic therapy [139]. Arterial spin labeling (ASL) perfusion imaging may benefit from an increase in signal-to-noise ratio and blood T1 relaxation time available at these higher fields, although counterbalancing effects of increased field inhomogeneity and reduced T2 will have to be considered as well [140]. The physiological effect of a higher field on patients and staff will have to be properly accounted for too.

4.1.2. Parallel imaging

Parallel imaging, using phased array coils and multiple transmitter and receiver channels, has become an integral part of modern clinical MRI. Sequences have been adapted to integrate spatial encoding using an increasing number of read-out channels, allowing for a reduction of scan time and/or an increase in image resolution and quality [141]. With parallel imaging, anatomical series can benefit from a reduction of scan time and associated patient discomfort. Alternatively parallel imaging can provide increased spatial resolution that allows for the detection of smaller lesions, better characterization of larger tumor content (calcification, blood products, cysts) and better delineation of tumor boundaries, important for differential diagnosis and treatment planning [142]. Physiological series, especially those based on fast

Table 3
Molecular and physiological imaging of glioma.

	Tumor detection	Diagnosis	Prognosis	Surgery guidance	Radiotherapy planning	Response to treatment	Pseudoprogression	Proliferation	Metabolic activity	Cellular death	Angiogenesis	Hypoxia	References
PET/SPECT													
^{11}C-MET	√	√	√	√	√	√	√	√					[39,195–197]
^{18}FET	√	√	√	√	√	√	√	√					[36,41,198–200]
^{18}F-FDOPA	√	√	√	√	√	√	√	√					[109,201,202]
^{131}I-IMT	√		√		√	√	√	√					[111,203–206]
^{18}F-FLT	√	√	√			√	√	√					[37,40,207–210]
^{18}F-FDG	√	√	√	√	√	√	√		√				[211–216]
^{18}F-Choline	√	√	√		√			√					[217–219]
^{18}F-FMISO		√	√		√							√	[42,43,220–222]
MRI													
DSC/DCE	√	√	√	√		√	√				√		[16–18,20,223]
DWI/DTI	√	√	√	√		√	√			√			[22,224–226]
MRS/CSI		√	√	√	√	√			√	√			[23–26,227]
ASL		√	√			√							[67,228–230]
BOLD				√							√	√	[69,70,231]
SWI	√	√		√		√							[72,73,232,233]
MRA											√		[76,234]
APT/CEST	√	√											[58,235,236]
Other modalities													
Optical				√									[49]

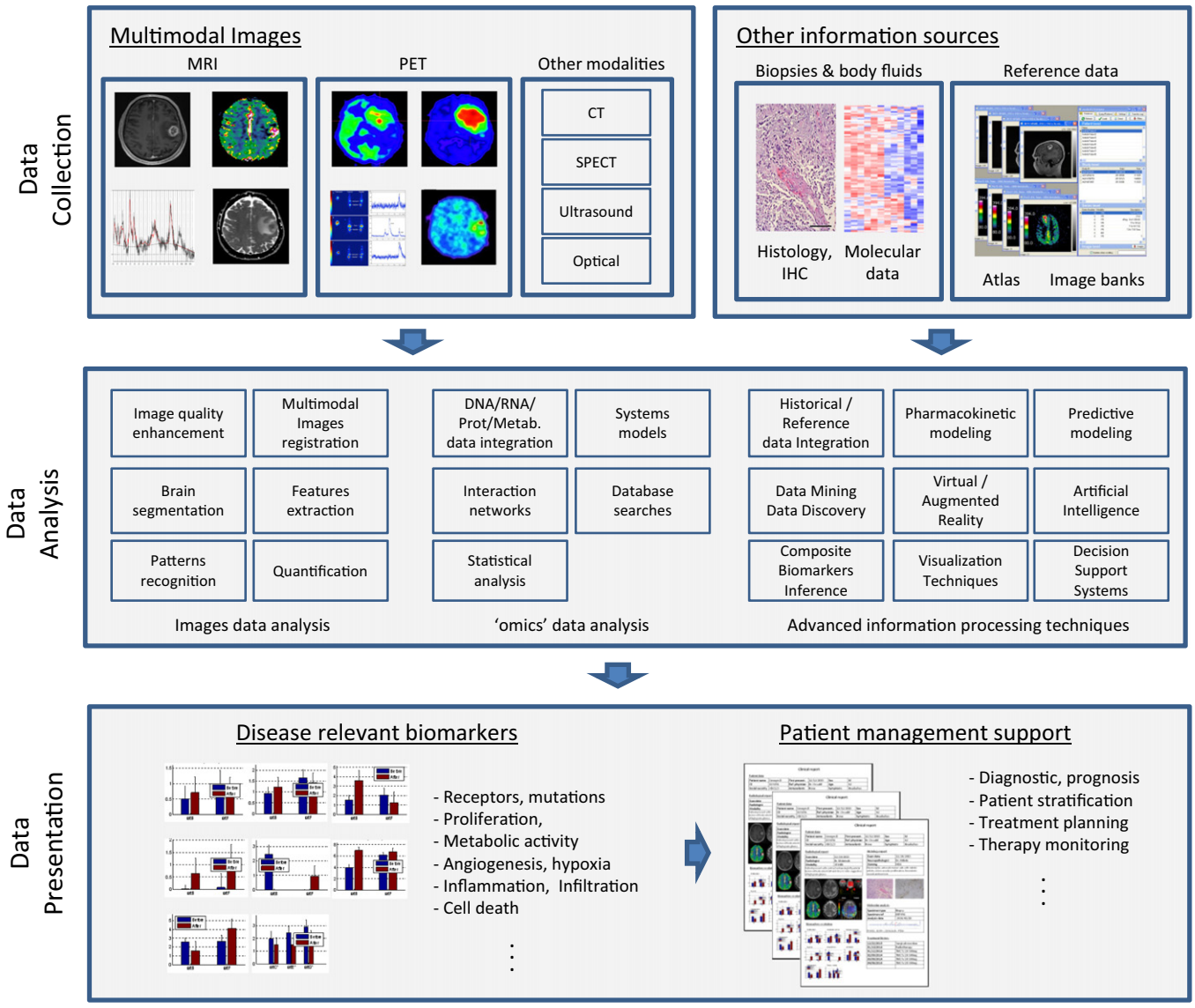

Fig. 5. Conceptual framework for brain tumor data management. The use of imaging and non-imaging data to support the management of brain tumors can be envisaged as a multi-step process. First, anatomical images of the brain obtained by MRI are completed by images that represent the spatial distribution of physiological parameters related to perfusion, metabolic activity or the level of molecular targets, assessed by MRI, PET and possibly other imaging modalities. The second step is the combination of this multi-parametric data with non-imaging data coming from the histological and molecular analysis of biopsies and body fluids, possibly compared to historical and external reference data when available. Advanced information processing techniques used at this stage may include image features extraction, biological network analysis, pharmacokinetic and tumor growth modeling, advanced data discovery and presentation techniques. The ultimate goal of the analysis is to provide the physician dealing with the patient a set of validated disease relevant biomarkers, that will be used when key decisions are to be taken, such as to establish diagnosis and prognosis, to stratify patients to therapy, to plan treatment and monitor its efficacy.

acquisition techniques such as Echo Planar Imaging, also benefit from the improved speed of acquisition, image quality and resolution. These include perfusion MRI [143,144], fMRI and DTI [145,146] and spectroscopic imaging [147,148].

4.1.3. Fast imaging protocols

New sequences are being developed that allow faster acquisitions and new contrast establishment. Ultrashort echo time sequences (Fig. 4H), for example, using non-conventional k-space sampling strategies, make it possible to image structures with very short T2 relaxation times, such as gliosis, hemorrhage, angiomas, and the loss of short T2 components in the white matter surrounding gliomas [149]. Compressed sensing techniques accelerate acquisitions by randomly undersampling k-space data to exploit the sparsity in MR images [150].

4.1.4. Hybrid systems

Hybrid PET/CT systems have become an integral part of the imaging of non-cranial tumors. Whole body ^{18}F-FDG PET/CT has, for instance, proven to be an invaluable tool for the detection of metastatic lesions. In the context of the brain, with MRI being the preferred modality over CT, it is expected that the recently introduced PET/MRI hybrid systems will also play a major role in the future. Immediate benefits for the patient include increased comfort and convenience (by performing MRI and PET exams in a single session) and reduced exposure to radiation in comparison to PET/CT. The simultaneous acquisition of PET and MRI also provides advantages such as improved reconstruction of PET data using anatomical information and motion correction and improved arterial input function characterization (obtained from MRI) for PET kinetic modeling [151]. Improved delineation of tumor extent, by adding FET–PET or MET–PET to MRI physiological imaging, will benefit

treatment planning and assessment of tumor recurrence [152,153]. The combination of blood flow, vessel permeability, diffusion and metabolite data provided by MRI/MRS with PET tracers for hypoxia, proliferation and necrosis, as well as the development of bimodal tracers, would also enable a more complete assessment of tumor status and an earlier assessment of response to treatment. These unique applications, when clinical experience is established, are expected to drive the wider acceptance of hybrid systems in the future.

4.2. Advances in data analysis

New developments in computer hardware and software promise to continue revolutionizing the field of medical imaging. The same advances in high throughput calculations that have made possible computed tomography of X-ray based scanners and the reconstruction of MR images from signals acquired in k-space, can also be used for the post-processing of acquired raw data and the computation of derived biomarkers that can assist clinicians in the management of gliomas.

4.2.1. Quantitative biomarkers

Clinical standards such as T1-weighted, T2-weighted or FLAIR protocols provide images of tissue contrast that are used for the qualitative assessment of brain tumors. Yet, a quantitative assessment of tumor morphological and physiological parameters could lead to more accurate tumor grading, by avoiding the sampling error that can result from biopsy tissue selection processes. A precise quantitative assessment of tumor spread would also benefit radiotherapy planning and the assessment of the efficacy of treatment [44].

Tissue contrast, in commonly used anatomical scans, depends on the tracer used, the acquisition parameters of the protocol, the hardware used, and the ability of the contrast agent to reach targeted sites, making the delineation of borders of infiltrative tumors challenging in gliomas. Biomarkers derived from physiological scans can be of assistance in this respect, such as those derived from perfusion and water molecule diffusion sequences, absolute concentrations of abundant metabolites and standard uptake values of PET tracers, which are quantitative in nature [154]. Biomarker determination often requires offline processing of the acquired raw data, possibly using complex pharmacokinetic models to account for exchange of tracers between vascular and extra-vascular compartments [155]. Standardization of the mathematical models and algorithms used will be needed to enable inter-institution comparisons of quantitative biomarkers and end points derived from such studies.

4.2.2. Composite biomarkers

As MRI protocols based on new contrast mechanisms are implemented and complemented with information from other imaging modalities, a growing number of parameters will be made available that can be combined to increase our ability to image relevant features of brain tumors and assess critical treatment information. Computer-based image analysis of such multi-parametric datasets can be used to classify brain tumors by type and grade [156], predict survival [157], detect early progression [158] or identify infiltrated tissue likely to result from tumor recurrence after resection [159]. Computational methods used may include machine learning, multi-parametric segmentation and biophysical modeling of tumors [160].

4.2.3. Computer-assisted decision making

Expert systems are information systems that make decisions based on a complex set of information and rules. They can assist in establishing diagnosis based on symptoms. Neural networks systems, for example, create interaction models that reproduce the type of connections that occur in the brain. After a training period during which parameters that describe the connections are established, new cases are presented to the model for classification. Such techniques have often proven to be superior to conventional manual approaches for the analysis of multi-parametric MR images, in applications such as the classification of brain neoplasms [161,162], glioma cell population discrimination [163], prediction of survival [157], distinction of pseudoprogression from tumor recurrence [164] or assessment of responses to anti-angiogenic therapy [165].

4.2.4. Tumor growth modeling

During the last two decades, a number of mathematical models have been developed to simulate tumor growth. These models may be useful to plan and predict the efficacy of treatment and to develop and test hypotheses that can lead to a better understanding of the biological process involved in tumor development [166,167]. Acquired MRI series can be registered to a brain atlas to help identify abnormal signals in these sequences, or to serve as a basis for growth simulation accounting for cell proliferation and tissue deformations [168].

4.2.5. Visualization

Visualization refers to the rendering of measurements for human interpretation, with the goal to generate insight and develop knowledge beyond the simple display of raw data. In this context, data might take the form of spatially distributed single scalars (such as pixel intensity, blood volume, amino acid uptake …), vectors or tensors (water molecule diffusion anisotropy), spectroscopic measurements or even biological 'omics' data such as gene expression, signaling pathways, protein interaction networks, etc.

The pathway from data to insight involves several technologies, including computer graphics and display technologies (2D/3D/4D, representations of colors, multimodality image fusion) as well as human vision and perception (viewing angle, image luminance, glare, reflection, ambient light) that can all affect diagnostic accuracy [169]. A number of features of visualization pipelines are important to facilitate the navigation through the data, and the search, qualification and quantification of relevant features. They include pre-processing steps for de-noising and elimination of artifacts, registration of images acquired on different modalities and/or at different time points, segmentation and the classification of tissue types for emphasis of relevant objects. Transfer functions can then be used to map data to visualization parameters such as gray value or opacity. Other visualization techniques include surface and volume rendering, data manipulation for multiplanar slice selection, rotation and scaling of 3D volumes, clipping and virtual resection functions (to interactively remove subvolumes from subsequent visualizations), and illumination to enhance the ability of humans to distinguish objects and their properties.

The most common of these features are available in commercial software provided by imaging modality manufacturers, while some of the most advanced ones exist only in specialized software and have been used in other areas of medical imaging [170]. In the context of brain tumor imaging, applications of these visualization techniques could include diagnosis, treatment planning and education [171].

4.2.6. Virtual and augmented reality

Virtual reality is a computer-based technique used to simulate real-world environments. The simulated graphical environment can be rendered on a computer screen or through stereoscopic displays to enhance the visual experience. The technique is for instance used for the training of neurosurgeons [172]. Augmented reality extends this concept by superimposing computer-generated graphics to real world images in real time. Its use in the operating room is appealing as it could provide the neurosurgeon with an interactive atlas of the patient brain, reconstructed from pre-operative images [173]. This could be used to locate in situ tumor infiltrated tissue as well as eloquent areas of the brain that have to be spared during surgery.

4.2.7. 'Omics' data enrichment

Omics data, such as DNA, RNA, proteins and metabolite data, generated through high throughput analysis of body fluids and tissue extracts, provides insight into the molecular changes induced in a

given tumor phenotype or by a specific treatment. Although such techniques typically provide limited information on the spatial distribution of these molecules, they complement and enrich the image biomarkers by providing novel genetic classification tools and important molecular biomarkers such as 1p/19q co-deletion, MGMT methylation and IDH mutation, which have clinical relevance in diagnosis, prognosis and establishment of treatment strategies [174,175].

Altogether, these technical advances in data management and image processing techniques could be used in a data management framework designed to provide physicians with the information needed to support the decision process during the course of glioma management (Fig. 5).

5. Perspectives

Given the large volume of ongoing cancer research, one may hope for a better outlook for glioma patients in the near future. New treatment approaches may target the specific features of individual tumors, and this requires neuroimaging to evolve, in particular, by making use of multi-modal imaging techniques, molecular probes and quantitative biomarkers of the disease. MRI is expected to remain the modality of choice because of the versatility in providing soft tissue contrasts. PET and possibly SPECT will also continue to contribute due to their functional and molecular imaging capabilities, and superior sensitivity.

The integration of data coming from different imaging modalities and the use of novel and improved contrast by labeling endogenous and exogenous molecules will provide access to consolidated disease-relevant biomarkers. The combination of PET tracers targeting amino acids and cell metabolism with MRI techniques, such as diffusion, perfusion, spectroscopy, and hyperpolarization techniques, could, for instance, be used to provide an integrated view of cellular proliferation and metabolic activity of the tumor. The same imaging markers would also be used for a precise delineation of the tumor extent prior to treatment, or for the identification of the most relevant targets for biopsies.

Water molecule diffusion, changes in vascular structures, metabolite ratios, protein content detected by magnetization transfer, and nanoparticles homing to infiltrating cells, could all contribute to the assessment of tumor cell invasion in the future. Molecular imaging techniques, using PET tracers or nanoparticles loaded with MR reporters, could be used to probe pathologically modulated levels of receptors, cytokines, growth factors and related signaling pathways. Together with histology, immunohistochemistry and molecular 'omics' analyses of tumor biopsies and body fluids, this would help stratify patients to the treatment providing the best prognosis. The availability of disease relevant biomarkers such as proliferation, efficiency of drug delivery, cell death, changes in microenvironment, tumor cell invasion, and immune system responses, would make the global assessment of treatment efficiency more precise than with the non-specific contrast protocols used today.

Some of the markers described in this review have been in clinical use for a number of years, but others will require further (pre)clinical validation before being adopted in routine practice. How many of these will be used depend on finding the right balance between several factors, including completeness of information, scan time, patient discomfort and overall cost. Given the growing number of information sources and the need to integrate them, advanced computerized data analysis and presentation techniques will be required, ultimately providing physicians with a set of validated imaging and non-imaging markers, needed to make properly informed decisions during the course of the disease.

Acknowledgments

This work was funded by the *Centre de Recherche Public de la Santé* (CRP-Santé) of Luxembourg, the University of Bergen and the Haukeland Hospital of Bergen, Norway.

References

[1] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R.O. Mirimanoff, R. European Organisation for, T. Treatment of Cancer Brain, G. Radiotherapy, G. National Cancer Institute of Canada Clinical Trials, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. 352 (2005) 987–996.

[2] R. Stupp, M.E. Hegi, W.P. Mason, M.J. van den Bent, M.J. Taphoorn, R.C. Janzer, S.K. Ludwin, A. Allgeier, B. Fisher, K. Belanger, P. Hau, A.A. Brandes, J. Gijtenbeek, C. Marosi, C.J. Vecht, K. Mokhtari, P. Wesseling, S. Villa, E. Eisenhauer, T. Gorlia, M. Weller, D. Lacombe, J.G. Cairncross, R.O. Mirimanoff, R. European Organisation for, T. Treatment of Cancer Brain, G. Radiation Oncology, G. National Cancer Institute of Canada Clinical Trials, Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial, Lancet Oncol. 10 (2009) 459–466.

[3] N. Cancer Genome Atlas Research, Comprehensive genomic characterization defines human glioblastoma genes and core pathways, Nature 455 (2008) 1061–1068.

[4] H.S. Phillips, S. Kharbanda, R. Chen, W.F. Forrest, R.H. Soriano, T.D. Wu, A. Misra, J.M. Nigro, H. Colman, L. Soroceanu, P.M. Williams, Z. Modrusan, B.G. Feuerstein, K. Aldape, Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis, Cancer Cell 9 (2006) 157–173.

[5] R.G. Verhaak, K.A. Hoadley, E. Purdom, V. Wang, Y. Qi, M.D. Wilkerson, C.R. Miller, L. Ding, T. Golub, J.P. Mesirov, G. Alexe, M. Lawrence, M. O'Kelly, P. Tamayo, B.A. Weir, S. Gabriel, W. Winckler, S. Gupta, L. Jakkula, H.S. Feiler, J.G. Hodgson, C.D. James, J.N. Sarkaria, C. Brennan, A. Kahn, P.T. Spellman, R.K. Wilson, T.P. Speed, J. W. Gray, M. Meyerson, G. Getz, C.M. Perou, D.N. Hayes, N. Cancer Genome Atlas Research, Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1, Cancer Cell 17 (2010) 98–110.

[6] D. Sturm, S. Bender, D.T. Jones, P. Lichter, J. Grill, O. Becher, C. Hawkins, J. Majewski, C. Jones, J.F. Costello, A. Iavarone, K. Aldape, C.W. Brennan, N. Jabado, S.M. Pfister, Paediatric and adult glioblastoma: multiform (epi)genomic culprits emerge, Nat. Rev. Cancer 14 (2014) 92–107.

[7] M. Weller, R. Stupp, M. Hegi, W. Wick, Individualized targeted therapy for glioblastoma: fact or fiction? Cancer J. 18 (2012) 40–44.

[8] J.M. Baehring, Glioblastoma multiforme—new approaches to therapy, Cancer J. 18 (2012) 11.

[9] N. Upadhyay, A.D. Waldman, Conventional MRI evaluation of gliomas, Br. J. Radiol. 84 (Spec No 2) (2011) S107–S111.

[10] T. Nihashi, I.J. Dahabreh, T. Terasawa, PET in the clinical management of glioma: evidence map, AJR Am. J. Roentgenol. 200 (2013) W654–W660.

[11] R. Jain, Perfusion CT imaging of brain tumors: an overview, AJNR Am. J. Neuroradiol. 32 (2011) 1570–1577.

[12] S.K. Ellika, R. Jain, S.C. Patel, L. Scarpace, L.R. Schultz, J.P. Rock, T. Mikkelsen, Role of perfusion CT in glioma grading and comparison with conventional MR imaging features, AJNR Am. J. Neuroradiol. 28 (2007) 1981–1987.

[13] D.C. Harwood-Nash, Neuroimaging and pediatrics, Current Opinion in Neurology and Neurosurgery, 41991. 858–863.

[14] G. Unsgard, O. Solheim, F. Lindseth, T. Selbekk, Intra-operative imaging with 3D ultrasound in neurosurgery, Acta Neurochir. Suppl. 109 (2011) 181–186.

[15] H.J. Aronen, I.E. Gazit, D.N. Louis, B.R. Buchbinder, F.S. Pardo, R.M. Weisskoff, G.R. Harsh, G. R. Cosgrove, E.F. Halpern, F.H. Hochberg, et al., Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings, Radiology 191 (1994) 41–51.

[16] M. Law, S. Yang, H. Wang, J.S. Babb, G. Johnson, S. Cha, E.A. Knopp, D. Zagzag, Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging, AJNR Am. J. Neuroradiol. 24 (2003) 1989–1998.

[17] S. Cha, E.A. Knopp, G. Johnson, A. Litt, J. Glass, M.L. Gruber, S. Lu, D. Zagzag, Dynamic contrast-enhanced T2-weighted MR imaging of recurrent malignant gliomas treated with thalidomide and carboplatin, AJNR Am. J. Neuroradiol. 21 (2000) 881–890.

[18] L.S. Hu, L.C. Baxter, K.A. Smith, B.G. Feuerstein, J.P. Karis, J.M. Eschbacher, S.W. Coons, P. Nakaji, R.F. Yeh, J. Debbins, J.E. Heiserman, Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements, AJNR Am. J. Neuroradiol. 30 (2009) 552–558.

[19] M.S. Alam, Z. Sajjad, M. Azeemuddin, Z.A. Khan, F. Mubarak, W. Akhtar, Diffusion weighted MR imaging of ring enhancing brain lesions, J. Coll. Physicians Surg. Pak. : JCPSP 22 (2012) 428–431.

[20] C.J. Galban, T.L. Chenevert, C.R. Meyer, C. Tsien, T.S. Lawrence, D.A. Hamstra, L. Junck, P.C. Sundgren, T.D. Johnson, S. Galban, J.S. Sebolt-Leopold, A. Rehemtulla, B.D. Ross, Prospective analysis of parametric response map-derived MRI biomarkers: identification of early and distinct glioma response patterns not predicted by standard radiographic assessment, Clin. Cancer Res. : Off. J. Am. Assoc. Cancer Res. 17 (2011) 4751–4760.

[21] B.A. Moffat, T.L. Chenevert, T.S. Lawrence, C.R. Meyer, T.D. Johnson, Q. Dong, C. Tsien, S. Mukherji, D.J. Quint, S.S. Gebarski, P.L. Robertson, L.R. Junck, A. Rehemtulla, B.D. Ross, Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 5524–5529.

[22] D.A. Hamstra, T.L. Chenevert, B.A. Moffat, T.D. Johnson, C.R. Meyer, S.K. Mukherji, D. J. Quint, S.S. Gebarski, X. Fan, C.I. Tsien, T.S. Lawrence, L. Junck, A. Rehemtulla, B.D. Ross, Evaluation of the functional diffusion map as an early biomarker of time-to-

progression and overall survival in high-grade glioma, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 16759–16764.
[23] W. Moller-Hartmann, S. Herminghaus, T. Krings, G. Marquardt, H. Lanfermann, U. Pilatus, F.E. Zanella, Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions, Neuroradiology 44 (2002) 371–381.
[24] Y. Li, J.M. Lupo, R. Parvataneni, K.R. Lamborn, S. Cha, S.M. Chang, S.J. Nelson, Survival analysis in patients with newly diagnosed glioblastoma using pre- and postradiotherapy MR spectroscopic imaging, Neuro Oncol. 15 (2013) 607–617.
[25] J.P. Rock, D. Hearshen, L. Scarpace, D. Croteau, J. Gutierrez, J.L. Fisher, M.L. Rosenblum, T. Mikkelsen, Correlations between magnetic resonance spectroscopy and image-guided histopathology, with special attention to radiation necrosis, Neurosurgery 51 (2002) 912–919 (discussion 919-920).
[26] E.E. Graves, S.J. Nelson, D.B. Vigneron, L. Verhey, M. McDermott, D. Larson, S. Chang, M.D. Prados, W.P. Dillon, Serial proton MR spectroscopic imaging of recurrent malignant gliomas after gamma knife radiosurgery, AJNR Am. J. Neuroradiol. 22 (2001) 613–624.
[27] B. Gulyas, C. Halldin, New PET radiopharmaceuticals beyond FDG for brain tumor imaging, Q. J. Nucl. Med. Mol. Imaging : Off. Publ. Ital. Assoc. Nucl. Med. 56 (2012) 173–190.
[28] H. Zhuang, J.Q. Yu, A. Alavi, Applications of fluorodeoxyglucose-PET imaging in the detection of infection and inflammation and other benign disorders, Radiol. Clin. North Am. 43 (2005) 121–134.
[29] M.E. Phelps, J.C. Mazziotta, Positron emission tomography: human brain function and biochemistry, Science 228 (1985) 799–809.
[30] L. Gotz, T.S. Spehl, W.A. Weber, A.L. Grosu, PET and SPECT for radiation treatment planning, Q. J. Nucl. Med. Mol. Imaging : Off. Publ. Ital. Assoc. Nucl. Med. 56 (2012) 163–172.
[31] M. Niyazi, J. Geisler, A. Siefert, S.B. Schwarz, U. Ganswindt, S. Garny, O. Schnell, B. Suchorska, F.W. Kreth, J.C. Tonn, P. Bartenstein, C. la Fougere, C. Belka, FET-PET for malignant glioma treatment planning, Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol. 99 (2011) 44–48.
[32] M. Niyazi, O. Schnell, B. Suchorska, S.B. Schwarz, U. Ganswindt, J. Geisler, P. Bartenstein, F.W. Kreth, J.C. Tonn, S. Eigenbrod, C. Belka, C. la Fougere, FET-PET assessed recurrence pattern after radio-chemotherapy in newly diagnosed patients with glioblastoma is influenced by MGMT methylation status, Radiother. Oncol. : J. Eur. Soc. Ther. Radiol. Oncol. 104 (2012) 78–82.
[33] N.L. Jansen, V. Graute, L. Armbruster, B. Suchorska, J. Lutz, S. Eigenbrod, P. Cumming, P. Bartenstein, J.C. Tonn, F.W. Kreth, C. la Fougere, MRI-suspected low-grade glioma: is there a need to perform dynamic FET PET? Eur. J. Nucl. Med. Mol. Imaging 39 (2012) 1021–1029.
[34] N.L. Jansen, B. Suchorska, V. Wenter, S. Eigenbrod, C. Schmid-Tannwald, A. Zwergal, M. Niyazi, M. Drexler, P. Bartenstein, O. Schnell, J.C. Tonn, N. Thon, F.W. Kreth, C. la Fougere, Dynamic ^{18}F-FET PET in newly diagnosed astrocytic low-grade glioma identifies high-risk patients, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 55 (2014) 198–203.
[35] M. Kunz, N. Thon, S. Eigenbrod, C. Hartmann, R. Egensperger, J. Herms, J. Geisler, C. la Fougere, J. Lutz, J. Linn, S. Kreth, A. von Deimling, J.C. Tonn, H.A. Kretzschmar, G. Popperl, F.W. Kreth, Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas, Neuro Oncol. 13 (2011) 307–316.
[36] W. Rachinger, C. Goetz, G. Popperl, F.J. Gildehaus, F.W. Kreth, M. Holtmannspotter, J. Herms, W. Koch, K. Tatsch, J.C. Tonn, Positron emission tomography with O-(2-[^{18}F]fluoroethyl)-l-tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas, Neurosurgery 57 (2005) 505–511 (discussion 505-511).
[37] K. Miyake, A. Shinomiya, M. Okada, T. Hatakeyama, N. Kawai, T. Tamiya, Usefulness of FDG, MET and FLT-PET studies for the management of human gliomas, J. Biomed. Biotechnol. 2012 (2012) 205818.
[38] W. Chen, S. Delaloye, D.H. Silverman, C. Geist, J. Czernin, J. Sayre, N. Satyamurthy, W. Pope, A. Lai, M.E. Phelps, T. Cloughesy, Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [^{18}F] fluorothymidine positron emission tomography: a pilot study, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 25 (2007) 4714–4721.
[39] N. Galldiks, L.W. Kracht, L. Burghaus, A. Thomas, A.H. Jacobs, W.D. Heiss, K. Herholz, Use of 11C-methionine PET to monitor the effects of temozolomide chemotherapy in malignant gliomas, Eur. J. Nucl. Med. Mol. Imaging 33 (2006) 516–524.
[40] J. Schwarzenberg, J. Czernin, T.F. Cloughesy, B.M. Ellingson, W.B. Pope, C. Geist, M. Dahlbom, D.H. Silverman, N. Satyamurthy, M.E. Phelps, W. Chen, 3'-deoxy-3'-^{18}F-fluorothymidine PET and MRI for early survival predictions in patients with recurrent malignant glioma treated with bevacizumab, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 53 (2012) 29–36.
[41] N. Galldiks, K.J. Langen, R. Holy, M. Pinkawa, G. Stoffels, K.W. Nolte, H.J. Kaiser, C.P. Filss, G.R. Fink, H.H. Coenen, M.J. Eble, M.D. Piroth, Assessment of treatment response in patients with glioblastoma using O-(2-^{18}F-fluoroethyl)-L-tyrosine PET in comparison to MRI, J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 53 (2012) 1048–1057.
[42] I. Mendichovszky, A. Jackson, Imaging hypoxia in gliomas, Br. J. Radiol. 84 (Spec No 2) (2011) S145–S158.
[43] L.M. Cher, C. Murone, N. Lawrentschuk, S. Ramdave, A. Papenfuss, A. Hannah, G.J. O'Keefe, J.I. Sachinidis, S.U. Berlangieri, G. Fabinyi, A.M. Scott, Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using ^{18}F-fluoromisonidazole, ^{18}F-FDG PET, and immunohistochemical studies, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 47 (2006) 410–418.
[44] A.D. Waldman, A. Jackson, S.J. Price, C.A. Clark, T.C. Booth, D.P. Auer, P.S. Tofts, D.J. Collins, M.O. Leach, J.H. Rees, S. National Cancer Research Institute Brain Tumour Imaging, Quantitative imaging biomarkers in neuro-oncology, Nature reviews, Clin. Oncol. 6 (2009) 445–454.
[45] D.R. Macdonald, T.L. Cascino, S.C. Schold Jr., J.G. Cairncross, Response criteria for phase II studies of supratentorial malignant glioma, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 8 (1990) 1277–1280.
[46] D. Brandsma, L. Stalpers, W. Taal, P. Sminia, M.J. van den Bent, Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas, Lancet Oncol. 9 (2008) 453–461.
[47] J.L. Clarke, S. Chang, Pseudoprogression and pseudoresponse: challenges in brain tumor imaging, Curr. Neurol. Neurosci. Rep. 9 (2009) 241–246.
[48] P.Y. Wen, D.R. Macdonald, D.A. Reardon, T.F. Cloughesy, A.G. Sorensen, E. Galanis, J. Degroot, W. Wick, M.R. Gilbert, A.B. Lassman, C. Tsien, T. Mikkelsen, E.T. Wong, M. C. Chamberlain, R. Stupp, K.R. Lamborn, M.A. Vogelbaum, M.J. van den Bent, S.M. Chang, Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 28 (2010) 1963–1972.
[49] W. Stummer, U. Pichlmeier, T. Meinel, O.D. Wiestler, F. Zanella, H.J. Reulen, A.L.-G.S. Group, Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial, Lancet Oncol. 7 (2006) 392–401.
[50] M. Ji, D. Orringer, C. Freudiger, S. Ramkissoon, X. Liu, D. Lau, A. Golby, I. Norton, M. Hayashi, N. Agar, G. Young, C. Spino, S. Santagata, S. Camelo-Piragua, K. Ligon, O. Sagher, X. Xie, Rapid, label-free detection of brain tumors with stimulated Raman scattering microscopy, Sci. Transl. Med. 5 (2013) 201ra119.
[51] M. Brown, R. Semelka, Mri: Basic Principles and Applications, Fourth edition, 2010.
[52] M.R. Prince, H. Zhang, M. Morris, J.L. MacGregor, M.E. Grossman, J. Silberzweig, R.L. DeLapaz, H.J. Lee, C.M. Magro, A.M. Valeri, Incidence of nephrogenic systemic fibrosis at two large medical centers, Radiology 248 (2008) 807–816.
[53] M.S. Shazeeb, C.H. Sotak, M. DeLeo III, A. Bogdanov Jr., Targeted signal-amplifying enzymes enhance MRI of EGFR expression in an orthotopic model of human glioma, Cancer Res. 71 (2011) 2230–2239.
[54] T. He, N. Smith, D. Saunders, S. Doblas, Y. Watanabe, J. Hoyle, R. Silasi-Mansat, F. Lupu, M. Lerner, D.J. Brackett, R.A. Towner, Molecular MRI assessment of vascular endothelial growth factor receptor-2 in rat C6 gliomas, J. Cell. Mol. Med. 15 (2011) 837–849.
[55] Y. Liu, Y. Yang, C. Zhang, A concise review of magnetic resonance molecular imaging of tumor angiogenesis by targeting integrin alphavbeta3 with magnetic probes, Int. J. Nanomedicine 8 (2013) 1083–1093.
[56] Y.E. Koo, G.R. Reddy, M. Bhojani, R. Schneider, M.A. Philbert, A. Rehemtulla, B.D. Ross, R. Kopelman, Brain cancer diagnosis and therapy with nanoplatforms, Adv. Drug Deliv. Rev. 58 (2006) 1556–1577.
[57] I. Brigger, C. Dubernet, P. Couvreur, Nanoparticles in cancer therapy and diagnosis, Adv. Drug Deliv. Rev. 54 (2002) 631–651.
[58] C.K. Jones, M.J. Schlosser, P.C. van Zijl, M.G. Pomper, X. Golay, J. Zhou, Amide proton transfer imaging of human brain tumors at 3T, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 56 (2006) 585–592.
[59] J. Zhou, E. Tryggestad, Z. Wen, B. Lal, T. Zhou, R. Grossman, S. Wang, K. Yan, D.X. Fu, E. Ford, B. Tyler, J. Blakeley, J. Laterra, P.C. van Zijl, Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides, Nat. Med. 17 (2011) 130–134.
[60] M. Woods, D.E. Woessner, A.D. Sherry, Paramagnetic lanthanide complexes as PARACEST agents for medical imaging, Chem. Soc. Rev. 35 (2006) 500–511.
[61] I. Hancu, W.T. Dixon, M. Woods, E. Vinogradov, A.D. Sherry, R.E. Lenkinski, CEST and PARACEST MR contrast agents, Acta Radiol. 51 (2010) 910–923.
[62] M.A. Fernandez-Seara, B.L. Edlow, A. Hoang, J. Wang, D.A. Feinberg, J.A. Detre, Minimizing acquisition time of arterial spin labeling at 3T, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 59 (2008) 1467–1471.
[63] J. Wang, M.A. Fernandez-Seara, S. Wang, K.S. St Lawrence, When perfusion meets diffusion: in vivo measurement of water permeability in human brain, J. Cereb. Blood Flow Metab. : Off. J. Int. Soc. Cereb. Blood Flow Metab. 27 (2007) 839–849.
[64] C. Warmuth, M. Gunther, C. Zimmer, Quantification of blood flow in brain tumors: comparison of arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging, Radiology 228 (2003) 523–532.
[65] R.L. Wolf, J. Wang, S. Wang, E.R. Melhem, D.M. O'Rourke, K.D. Judy, J.A. Detre, Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla, J. Magn. Reson. Imaging : JMRI 22 (2005) 475–482.
[66] M.A. Weber, S. Zoubaa, M. Schlieter, E. Juttler, H.B. Huttner, K. Geletneky, C. Ittrich, M.P. Lichy, A. Kroll, J. Debus, F.L. Giesel, M. Hartmann, M. Essig, Diagnostic performance of spectroscopic and perfusion MRI for distinction of brain tumors, Neurology 66 (2006) 1899–1906.
[67] Y. Ozsunar, M.E. Mullins, K. Kwong, F.H. Hochberg, C. Ament, P.W. Schaefer, R.G. Gonzalez, M.H. Lev, Glioma recurrence versus radiation necrosis? A pilot comparison of arterial spin-labeled, dynamic susceptibility contrast enhanced MRI, and FDG-PET imaging, Acad. Radiol. 17 (2010) 282–290.
[68] S.P. Robinson, F.A. Howe, L.M. Rodrigues, M. Stubbs, J.R. Griffiths, Magnetic resonance imaging techniques for monitoring changes in tumor oxygenation and blood flow, Semin. Radiat. Oncol. 8 (1998) 197–207.
[69] N.J. Taylor, H. Baddeley, K.A. Goodchild, M.E. Powell, M. Thoumine, L.A. Culver, J.J. Stirling, M.I. Saunders, P.J. Hoskin, H. Phillips, A.R. Padhani, J.R. Griffiths, BOLD MRI of human tumor oxygenation during carbogen breathing, J. Magn. Reson. Imaging : JMRI 14 (2001) 156–163.
[70] D. Ben Bashat, M. Artzi, H. Ben Ami, O. Aizenstein, D.T. Blumenthal, F. Bokstein, B. W. Corn, Z. Ram, A.A. Kanner, B. Lifschitz-Mercer, I. Solar, T. Kolatt, M. Palmon, Y. Edrei, R. Abramovitch, Hemodynamic response imaging: a potential tool for the assessment of angiogenesis in brain tumors, PLoS One 7 (2012) e49416.
[71] R. Mazurchuk, R. Zhou, R.M. Straubinger, R.I. Chau, Z. Grossman, Functional magnetic resonance (fMR) imaging of a rat brain tumor model: implications for evaluation of tumor microvasculature and therapeutic response, Magn. Reson. Imaging 17 (1999) 537–548.
[72] G. Grabner, I. Nobauer, K. Elandt, C. Kronnerwetter, A. Woehrer, C. Marosi, D. Prayer, S. Trattnig, M. Preusser, Longitudinal brain imaging of five malignant

glioma patients treated with bevacizumab using susceptibility-weighted magnetic resonance imaging at 7T, Magn. Reson. Imaging 30 (2012) 139–147.
[73] J.M. Lupo, C.F. Chuang, S.M. Chang, I.J. Barani, B. Jimenez, C.P. Hess, S.J. Nelson, 7-Tesla susceptibility-weighted imaging to assess the effects of radiotherapy on normal-appearing brain in patients with glioma, Int. J. Radiat. Oncol. Biol. Phys. 82 (2012) e493–e500.
[74] W. Mohammed, H. Xunning, S. Haibin, M. Jingzhi, Clinical applications of susceptibility-weighted imaging in detecting and grading intracranial gliomas: a review, Cancer Imaging : Off. Publ. Int. Cancer Imaging Soc. 13 (2013) 186–195.
[75] J.M. Lupo, E. Essock-Burns, A.M. Molinaro, S. Cha, S.M. Chang, N. Butowski, S.J. Nelson, Using susceptibility-weighted imaging to determine response to combined anti-angiogenic, cytotoxic, and radiation therapy in patients with glioblastoma multiforme, Neuro Oncol. 15 (2013) 480–489.
[76] Z. Zou, L. Ma, L. Cheng, Y. Cai, X. Meng, Time-resolved contrast-enhanced MR angiography of intracranial lesions, J. Magn. Reson. Imaging : JMRI 27 (2008) 692–699.
[77] R.J. Harris, T.F. Cloughesy, W.B. Pope, S. Godinez, Y. Natsuaki, P.L. Nghiemphu, H. Meyer, D. Paul, Y. Behbahanian, A. Lai, B.M. Ellingson, Pre- and post-contrast three-dimensional double inversion-recovery MRI in human glioblastoma, J. Neuro-Oncol. 112 (2013) 257–266.
[78] M. Simon, J. Guo, S. Papazoglou, H. Scholand-Engler, C. Erdmann, U. Melchert, M. Bonsanto, J. Braun, D. Petersen, I. Sack, J. Wuerfel, Non-invasive characterization of intracranial tumors by magnetic resonance elastography, New J. Phys. 15 (2013).
[79] J.S. Taylor, W.E. Reddick, Evolution from empirical dynamic contrast-enhanced magnetic resonance imaging to pharmacokinetic MRI, Adv. Drug Deliv. Rev. 41 (2000) 91–110.
[80] O. Keunen, M. Johansson, A. Oudin, M. Sanzey, S.A. Rahim, F. Fack, F. Thorsen, T. Taxt, M. Bartos, R. Jirik, H. Miletic, J. Wang, D. Stieber, L. Stuhr, I. Moen, C.B. Rygh, R. Bjerkvig, S.P. Niclou, Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 3749–3754.
[81] S. Sourbron, M. Heilmann, A. Biffar, C. Walczak, J. Vautier, A. Volk, M. Peller, Bolus-tracking MRI with a simultaneous T1- and T2*-measurement, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 62 (2009) 672–681.
[82] C.C. Quarles, J.C. Gore, L. Xu, T.E. Yankeelov, Comparison of dual-echo DSC-MRI- and DCE-MRI-derived contrast agent kinetic parameters, Magn. Reson. Imaging 30 (2012) 944–953.
[83] A. Bjornerud, K.E. Emblem, A fully automated method for quantitative cerebral hemodynamic analysis using DSC-MRI, J. Cereb. Blood Flow Metab. : Off. J. Int. Soc. Cereb Blood Flow Metab. 30 (2010) 1066–1078.
[84] T. Taxt, R. Jirik, C.B. Rygh, R. Gruner, M. Bartos, E. Andersen, F.R. Curry, R.K. Reed, Single-channel blind estimation of arterial input function and tissue impulse response in DCE-MRI, IEEE Trans. Biomed. Eng. 59 (2012) 1012–1021.
[85] N.S. White, C.R. McDonald, N. Farid, J.M. Kuperman, S. Kesari, A.M. Dale, Improved conspicuity and delineation of high-grade primary and metastatic brain tumors using "restriction spectrum imaging": quantitative comparison with high B-value DWI and ADC, AJNR Am. J. Neuroradiol. 34 (2013) 958–964 (S951).
[86] P.D. Kothari, N.S. White, N. Farid, R. Chung, J.M. Kuperman, H.M. Girard, A. Shankaranarayanan, S. Kesari, C.R. McDonald, A.M. Dale, Longitudinal restriction spectrum imaging is resistant to pseudoresponse in patients with high-grade gliomas treated with bevacizumab, AJNR Am. J. Neuroradiol. 34 (2013) 1752–1757.
[87] C.R. McDonald, N.S. White, N. Farid, G. Lai, J.M. Kuperman, H. Bartsch, D.J. Hagler, S. Kesari, B.S. Carter, C.C. Chen, A.M. Dale, Recovery of white matter tracts in regions of peritumoral FLAIR hyperintensity with use of restriction spectrum imaging, AJNR Am. J. Neuroradiol. 34 (2013) 1157–1163.
[88] D.C. Colvin, M.E. Loveless, M.D. Does, Z. Yue, T.E. Yankeelov, J.C. Gore, Earlier detection of tumor treatment response using magnetic resonance diffusion imaging with oscillating gradients, Magn. Reson. Imaging 29 (2011) 315–323.
[89] A.T. Van, S.J. Holdsworth, R. Bammer, In vivo investigation of restricted diffusion in the human brain with optimized oscillating diffusion gradient encoding, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 71 (2014) 83–94.
[90] M.A. McLean, A. Sun, T.E. Bradstreet, A.K. Schaeffer, H. Liu, R. Iannone, G. Herman, R. A. Railkar, I. Joubert, J.H. Gillard, S.J. Price, J.R. Griffiths, Repeatability of edited lactate and other metabolites in astrocytoma at 3T, J. Magn. Reson. Imaging : JMRI 36 (2012) 468–475.
[91] O.C. Andronesi, G.S. Kim, E. Gerstner, T. Batchelor, A.A. Tzika, V.R. Fantin, M.G. Vander Heiden, A.G. Sorensen, Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy, Sci. Transl. Med. 4 (2012) 116ra114.
[92] D. Maintz, W. Heindel, H. Kugel, R. Jaeger, K.J. Lackner, Phosphorus-31 MR spectroscopy of normal adult human brain and brain tumours, NMR Biomed. 15 (2002) 18–27.
[93] H.S. Venkatesh, M.M. Chaumeil, C.S. Ward, D.A. Haas-Kogan, C.D. James, S.M. Ronen, Reduced phosphocholine and hyperpolarized lactate provide magnetic resonance biomarkers of PI3K/Akt/mTOR inhibition in glioblastoma, Neuro Oncol. 14 (2012) 315–325.
[94] E.A. Maher, I. Marin-Valencia, R.M. Bachoo, T. Mashimo, J. Raisanen, K.J. Hatanpaa, A. Jindal, F.M. Jeffrey, C. Choi, C. Madden, D. Mathews, J.M. Pascual, B.E. Mickey, C.R. Malloy, R.J. Deberardinis, Metabolism of [U-(13) C]glucose in human brain tumors in vivo, NMR Biomed. 25 (2012) 1234–1244.
[95] Y. Kato, D.A. Holm, B. Okollie, D. Artemov, Noninvasive detection of temozolomide in brain tumor xenografts by magnetic resonance spectroscopy, Neuro Oncol. 12 (2010) 71–79.
[96] K. Golman, R. in 't Zandt, M. Thaning, Real-time metabolic imaging, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 11270–11275.
[97] I. Park, R. Bok, T. Ozawa, J.J. Phillips, C.D. James, D.B. Vigneron, S.M. Ronen, S.J. Nelson, Detection of early response to temozolomide treatment in brain tumors using hyperpolarized 13C MR metabolic imaging, J. Magn. Reson. Imaging : JMRI 33 (2011) 1284–1290.
[98] M.M. Chaumeil, T. Ozawa, I. Park, K. Scott, C.D. James, S.J. Nelson, S.M. Ronen, Hyperpolarized 13C MR spectroscopic imaging can be used to monitor Everolimus treatment in vivo in an orthotopic rodent model of glioblastoma, Neuroimage 59 (2012) 193–201.
[99] S.J. Nelson, J. Kurhanewicz, D.B. Vigneron, P.E. Larson, A.L. Harzstark, M. Ferrone, M. van Criekinge, J.W. Chang, R. Bok, I. Park, G. Reed, L. Carvajal, E.J. Small, P. Munster, V.K. Weinberg, J.H. Ardenkjaer-Larsen, A.P. Chen, R.E. Hurd, L.I. Odegardstuen, F.J. Robb, J. Tropp, J.A. Murray, Metabolic imaging of patients with prostate cancer using hyperpolarized [1-(1)(3)C]pyruvate, Sci. Transl. Med. 5 (2013) 198ra108.
[100] F.A. Gallagher, M.I. Kettunen, D.E. Hu, P.R. Jensen, R.I. Zandt, M. Karlsson, A. Gisselsson, S.K. Nelson, T.H. Witney, S.E. Bohndiek, G. Hansson, T. Peitersen, M.H. Lerche, K.M. Brindle, Production of hyperpolarized [1,4-13C2]malate from [1,4-13C2]fumarate is a marker of cell necrosis and treatment response in tumors, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 19801–19806.
[101] F.A. Gallagher, M.I. Kettunen, K.M. Brindle, Imaging pH with hyperpolarized 13C, NMR Biomed. 24 (2011) 1006–1015.
[102] S.E. Bohndiek, M.I. Kettunen, D.E. Hu, B.W. Kennedy, J. Boren, F.A. Gallagher, K.M. Brindle, Hyperpolarized [1-13C]-ascorbic and dehydroascorbic acid: vitamin C as a probe for imaging redox status in vivo, J. Am. Chem. Soc. 133 (2011) 11795–11801.
[103] F.A. Gallagher, M.I. Kettunen, S.E. Day, D.E. Hu, M. Karlsson, A. Gisselsson, M.H. Lerche, K.M. Brindle, Detection of tumor glutamate metabolism in vivo using (13)C magnetic resonance spectroscopy and hyperpolarized [1-(13)C]glutamate, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 66 (2011) 18–23.
[104] C. Gabellieri, S. Reynolds, A. Lavie, G.S. Payne, M.O. Leach, T.R. Eykyn, Therapeutic target metabolism observed using hyperpolarized 15N choline, J. Am. Chem. Soc. 130 (2008) 4598–4599.
[105] M.M. Chaumeil, P.E. Larson, H.A. Yoshihara, O.M. Danforth, D.B. Vigneron, S.J. Nelson, R.O. Pieper, J.J. Phillips, S.M. Ronen, Non-invasive in vivo assessment of IDH1 mutational status in glioma, Nat. Commun. 4 (2013) 2429.
[106] D.M. Wilson, K.R. Keshari, P.E. Larson, A.P. Chen, S. Hu, M. Van Criekinge, R. Bok, S.J. Nelson, J.M. Macdonald, D.B. Vigneron, J. Kurhanewicz, Multi-compound polarization by DNP allows simultaneous assessment of multiple enzymatic activities in vivo, J. Magn. Reson. 205 (2010) 141–147.
[107] S. Karunanithi, P. Sharma, A. Kumar, B.C. Khangembam, G.P. Bandopadhyaya, R. Kumar, A. Goenka, D.K. Gupta, A. Malhotra, C. Bal, Comparative diagnostic accuracy of contrast-enhanced MRI and (18)F-FDOPA PET-CT in recurrent glioma, Eur. Radiol. 23 (2013) 2628–2635.
[108] S. Karunanithi, P. Sharma, A. Kumar, B.C. Khangembam, G.P. Bandopadhyaya, R. Kumar, D.K. Gupta, A. Malhotra, C. Bal, ^{18}F-FDOPA PET/CT for detection of recurrence in patients with glioma: prospective comparison with ^{18}F-FDG PET/CT, Eur. J. Nucl. Med. Mol. Imaging 40 (2013) 1025–1035.
[109] W. Chen, D.H. Silverman, S. Delaloye, J. Czernin, N. Kamdar, W. Pope, N. Satyamurthy, C. Schiepers, T. Cloughesy, ^{18}F-FDOPA PET imaging of brain tumors: comparison study with ^{18}F-FDG PET and evaluation of diagnostic accuracy, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 47 (2006) 904–911.
[110] R.J. Harris, T.F. Cloughesy, W.B. Pope, P.L. Nghiemphu, A. Lai, T. Zaw, J. Czernin, M.E. Phelps, W. Chen, B.M. Ellingson, ^{18}F-FDOPA and ^{18}F-FLT positron emission tomography parametric response maps predict response in recurrent malignant gliomas treated with bevacizumab, Neuro Oncol. 14 (2012) 1079–1089.
[111] S. Samnick, J.B. Bader, D. Hellwig, J.R. Moringlane, C. Alexander, B.F. Romeike, W. Feiden, C.M. Kirsch, Clinical value of iodine-123-alpha-methyl-L-tyrosine single-photon emission tomography in the differential diagnosis of recurrent brain tumor in patients pretreated for glioma at follow-up, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 20 (2002) 396–404.
[112] A. Santra, R. Kumar, P. Sharma, C. Bal, P.K. Julka, A. Malhotra, Detection of recurrence in glioma: a comparative prospective study between Tc-99 m GHA SPECT and F-18 FDG PET/CT, Clin. Nucl. Med. 36 (2011) 650–655.
[113] A. Santra, P. Sharma, R. Kumar, C. Bal, A. Kumar, P.K. Julka, A. Malhotra, Comparison of glucoheptonate single photon emission computed tomography and contrast-enhanced MRI in detection of recurrent glioma, Nucl. Med. Commun. 32 (2011) 206–211.
[114] F.G. Blankenberg, In vivo detection of apoptosis, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 49 (Suppl. 2) (2008) 81S–95S.
[115] A.M. Spence, D.A. Mankoff, M. Muzi, Positron emission tomography imaging of brain tumors, Neuroimaging Clin. N. Am. 13 (2003) 717–739.
[116] W. Cai, X. Chen, Multimodality imaging of vascular endothelial growth factor and vascular endothelial growth factor receptor expression, Front. Biosci. : J. Virtual Libr. 12 (2007) 4267–4279.
[117] J.D. Hood, D.A. Cheresh, Role of integrins in cell invasion and migration, Nat. Rev. Cancer 2 (2002) 91–100.
[118] R.A. Cairns, R. Khokha, R.P. Hill, Molecular mechanisms of tumor invasion and metastasis: an integrated view, Curr. Mol. Med. 3 (2003) 659–671.
[119] R. Haubner, W.A. Weber, A.J. Beer, E. Vabuliene, D. Reim, M. Sarbia, K.F. Becker, M. Goebel, R. Hein, H.J. Wester, H. Kessler, M. Schwaiger, Noninvasive visualization of the activated alphavbeta3 integrin in cancer patients by positron emission tomography and [^{18}F]Galacto-RGD, PLoS Med. 2 (2005) e70.
[120] O. Schnell, B. Krebs, J. Carlsen, I. Miederer, C. Goetz, R.H. Goldbrunner, H.J. Wester, R. Haubner, G. Popperl, M. Holtmannspotter, H.A. Kretzschmar, H. Kessler, J.C. Tonn, M. Schwaiger, A.J. Beer, Imaging of integrin alpha(v)beta(3) expression in

patients with malignant glioma by [18F] Galacto-RGD positron emission tomography, Neuro Oncol. 11 (2009) 861–870.
[121] D.A. Sipkins, D.A. Cheresh, M.R. Kazemi, L.M. Nevin, M.D. Bednarski, K.C. Li, Detection of tumor angiogenesis in vivo by alphaVbeta3-targeted magnetic resonance imaging, Nat. Med. 4 (1998) 623–626.
[122] M. Huang, C. Xiong, W. Lu, R. Zhang, M. Zhou, Q. Huang, J. Weinberg, C. Li, Dual-modality micro-positron emission tomography/computed tomography and near-infrared fluorescence imaging of EphB4 in orthotopic glioblastoma xenograft models, Mol. Imaging Biol. : MIB : Off. Publ. Acad. Mol. Imaging 16 (2014) 74–84.
[123] E.M. Kim, E.H. Park, S.J. Cheong, C.M. Lee, D.W. Kim, H.J. Jeong, S.T. Lim, M.H. Sohn, K. Kim, J. Chung, Characterization, biodistribution and small-animal SPECT of I-125-labeled c-Met binding peptide in mice bearing c-Met receptor tyrosine kinase-positive tumor xenografts, Nucl. Med. Biol. 36 (2009) 371–378.
[124] M. Benezra, D. Hambardzumyan, O. Penate-Medina, D.R. Veach, N. Pillarsetty, P. Smith-Jones, E. Phillips, T. Ozawa, P.B. Zanzonico, V. Longo, E.C. Holland, S.M. Larson, M.S. Bradbury, Fluorine-labeled dasatinib nanoformulations as targeted molecular imaging probes in a PDGFB-driven murine glioblastoma model, Neoplasia 14 (2012) 1132–1143.
[125] J. Dennie, J.B. Mandeville, J.L. Boxerman, S.D. Packard, B.R. Rosen, R.M. Weisskoff, NMR imaging of changes in vascular morphology due to tumor angiogenesis, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 40 (1998) 793–799.
[126] J.H. Jensen, R. Chandra, MR imaging of microvasculature, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 44 (2000) 224–230.
[127] R.T. Ullrich, J.F. Jikeli, M. Diedenhofen, P. Bohm-Sturm, M. Unruh, S. Vollmar, M. Hoehn, In-vivo visualization of tumor microvessel density and response to anti-angiogenic treatment by high resolution MRI in mice, PLoS One 6 (2011) e19592.
[128] G. Kaur, S.J. Han, I. Yang, C. Crane, Microglia and central nervous system immunity, Neurosurg. Clin. N. Am. 21 (2010) 43–51.
[129] D.R. Owen, P.M. Matthews, Imaging brain microglial activation using positron emission tomography and translocator protein-specific radioligands, Int. Rev. Neurobiol. 101 (2011) 19–39.
[130] S. Venneti, B.J. Lopresti, C.A. Wiley, Molecular imaging of microglia/macrophages in the brain, Glia 61 (2013) 10–23.
[131] Y. Waerzeggers, P. Monfared, T. Viel, A. Faust, K. Kopka, M. Schafers, B. Tavitian, A. Winkeler, A. Jacobs, Specific biomarkers of receptors, pathways of inhibition and targeted therapies: pre-clinical developments, Br. J. Radiol. 84 (Spec No 2) (2011) S168–S178.
[132] A. Bhatnagar, R. Hustinx, A. Alavi, Nuclear imaging methods for non-invasive drug monitoring, Adv. Drug Deliv. Rev. 41 (2000) 41–54.
[133] T. Lammers, S. Aime, W.E. Hennink, G. Storm, F. Kiessling, Theranostic nanomedicine, Acc. Chem. Res. 44 (2011) 1029–1038.
[134] L. Rosso, C.S. Brock, J.M. Gallo, A. Saleem, P.M. Price, F.E. Turkheimer, E.O. Aboagye, A new model for prediction of drug distribution in tumor and normal tissues: pharmacokinetics of temozolomide in glioma patients, Cancer Res. 69 (2009) 120–127.
[135] M. Maurer, G. Becker, R. Wagner, M. Woydt, E. Hofmann, I. Puls, A. Lindner, A. Krone, Early postoperative transcranial sonography (TCS), CT, and MRI after resection of high grade glioma: evaluation of residual tumour and its influence on prognosis, Acta Neurochir. 142 (2000) 1089–1097.
[136] E. Vicenzini, R. Delfini, F. Magri, F. Puccinelli, M. Altieri, A. Santoro, M.F. Giannoni, L. Bozzao, V. Di Piero, G.L. Lenzi, Semiquantitative human cerebral perfusion assessment with ultrasound in brain space-occupying lesions: preliminary data, J. Ultrasound Med. : Off. J. Am. Inst. Ultrasound. Med. 27 (2008) 685–692.
[137] S. Mallidi, G.P. Luke, S. Emelianov, Photoacoustic imaging in cancer detection, diagnosis, and treatment guidance, Trends Biotechnol. 29 (2011) 213–221.
[138] S.K. Lee, Diffusion tensor and perfusion imaging of brain tumors in high-field MR imaging, Neuroimaging Clin. N. Am. 22 (2012) 123–134 (ix).
[139] A. Di Ieva, C. Matula, F. Grizzi, G. Grabner, S. Trattnig, M. Tschabitscher, Fractal analysis of the susceptibility weighted imaging patterns in malignant brain tumors during antiangiogenic treatment: technical report on four cases serially imaged by 7 T magnetic resonance during a period of four weeks, World Neurosurg. 77 (2012) (785 e711-721).
[140] X. Golay, E.T. Petersen, Arterial spin labeling: benefits and pitfalls of high magnetic field, Neuroimaging Clin. N. Am. 16 (2006) 259–268 (x).
[141] A. Deshmane, V. Gulani, M.A. Griswold, N. Seiberlich, Parallel MR imaging, J. Magn. Reson. Imaging : JMRI 36 (2012) 55–72.
[142] S. Schoenberg, O. Dietrich, M. Reiser (Eds.), Parallel Imaging in Clinical MR Applications, 2007.
[143] R. Stollberger, F. Fazekas, Improved perfusion and tracer kinetic imaging using parallel imaging, Top. Magn. Reson. Imaging : TMRI 15 (2004) 245–254.
[144] R.M. Lebel, J. Jones, J.C. Ferre, M. Law, K.S. Nayak, Highly accelerated dynamic contrast enhanced imaging, Magn. Reson. Med. 71 (2014) 635–644.
[145] D.A. Feinberg, K. Setsompop, Ultra-fast MRI of the human brain with simultaneous multi-slice imaging, J. Magn. Reson. 229 (2013) 90–100.
[146] X. Shi, X. Ma, W. Wu, F. Huang, C. Yuan, H. Guo, Parallel imaging and compressed sensing combined framework for accelerating high-resolution diffusion tensor imaging using inter-image correlation, Magn. Reson. Med. 71 (2014), http://dx.doi.org/10.1002/mrm.25290 May 13. [Epub ahead of print].
[147] S.J. Nelson, E. Ozhinsky, Y. Li, I. Park, J. Crane, Strategies for rapid in vivo 1H and hyperpolarized 13C MR spectroscopic imaging, J. Magn. Reson. 229 (2013) 187–197.
[148] E. Ozturk-Isik, A.P. Chen, J.C. Crane, W. Bian, D. Xu, E.T. Han, S.M. Chang, D.B. Vigneron, S.J. Nelson, 3D sensitivity encoded ellipsoidal MR spectroscopic imaging of gliomas at 3 T, Magn. Reson. Imaging 27 (2009) 1249–1257.
[149] P.D. Gatehouse, G.M. Bydder, Magnetic resonance imaging of short T2 components in tissue, Clin. Radiol. 58 (2003) 1–19.
[150] M. Lustig, D. Donoho, J.M. Pauly, Sparse MRI: The application of compressed sensing for rapid MR imaging, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 58 (2007) 1182–1195.
[151] T.E. Yankeelov, T.E. Peterson, R.G. Abramson, D. Garcia-Izquierdo, L.R. Arlinghaus, X. Li, N.C. Atuegwu, C. Catana, H.C. Manning, Z.A. Fayad, J.C. Gore, Simultaneous PET-MRI in oncology: a solution looking for a problem? Magn. Reson. Imaging 30 (2012) 1342–1356.
[152] I. Neuner, J.B. Kaffanke, K.J. Langen, E.R. Kops, L. Tellmann, G. Stoffels, C. Weirich, C. Filss, J. Scheins, H. Herzog, N.J. Shah, Multimodal imaging utilising integrated MR-PET for human brain tumour assessment, Eur. Radiol. 22 (2012) 2568–2580.
[153] B. Pirotte, S. Goldman, O. Dewitte, N. Massager, D. Wikler, F. Lefranc, N.O. Ben Taib, S. Rorive, P. David, J. Brotchi, M. Levivier, Integrated positron emission tomography and magnetic resonance imaging-guided resection of brain tumors: a report of 103 consecutive procedures, J. Neurosurg. 104 (2006) 238–253.
[154] J. Arbizu, S. Tejada, J.M. Marti-Climent, R. Diez-Valle, E. Prieto, G. Quincoces, C. Vigil, M.A. Idoate, J.L. Zubieta, I. Penuelas, J.A. Richter, Quantitative volumetric analysis of gliomas with sequential MRI and (1)(1)C-methionine PET assessment: patterns of integration in therapy planning, Eur. J. Nucl. Med. Mol. Imaging 39 (2012) 771–781.
[155] P.S. Tofts, Quantitative MRI if the Brain: Measuring Changes Caused by Disease, 2005.
[156] E.I. Zacharaki, S. Wang, S. Chawla, D. Soo Yoo, R. Wolf, E.R. Melhem, C. Davatzikos, Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 62 (2009) 1609–1618.
[157] E.I. Zacharaki, N. Morita, P. Bhatt, D.M. O'Rourke, E.R. Melhem, C. Davatzikos, Survival analysis of patients with high-grade gliomas based on data mining of imaging variables, AJNR Am. J. Neuroradiol. 33 (2012) 1065–1071.
[158] J. Patriarche, B. Erickson, Part 2. Automated change detection and characterization applied to serial MR of brain tumors may detect progression earlier than human experts, J. Digit. Imaging 20 (2007) 321–328.
[159] R. Verma, E.I. Zacharaki, Y. Ou, H. Cai, S. Chawla, S.K. Lee, E.R. Melhem, R. Wolf, C. Davatzikos, Multiparametric tissue characterization of brain neoplasms and their recurrence using pattern classification of MR images, Acad. Radiol. 15 (2008) 966–977.
[160] C. Davatzikos, E.I. Zacharaki, A. Gooya, V. Clark, Multi-parametric analysis and registration of brain tumors: constructing statistical atlases and diagnostic tools of predictive value, Conference proceedings : … Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2011, pp. 6979–6981.
[161] M.C. Preul, Z. Caramanos, D.L. Collins, J.G. Villemure, R. Leblanc, A. Olivier, R. Pokrupa, D.L. Arnold, Accurate, noninvasive diagnosis of human brain tumors by using proton magnetic resonance spectroscopy, Nat. Med. 2 (1996) 323–325.
[162] E.I. Zacharaki, V.G. Kanas, C. Davatzikos, Investigating machine learning techniques for MRI-based classification of brain neoplasms, Int. J. Comput. Assist. Radiol. Surg. 6 (2011) 821–828.
[163] Y. Li, D.M. Sima, S. Van Cauter, U. Himmelreich, A.R. Croitor Sava, Y. Pi, Y. Liu, S. Van Huffel, Unsupervised nosologic imaging for glioma diagnosis, IEEE Trans. Biomed. Eng. 60 (2013) 1760–1763.
[164] X. Hu, K.K. Wong, G.S. Young, L. Guo, S.T. Wong, Support vector machine multiparametric MRI identification of pseudoprogression from tumor recurrence in patients with resected glioblastoma, J. Magn. Reson. Imaging : JMRI 33 (2011) 296–305.
[165] G. Liberman, Y. Louzoun, O. Aizenstein, D.T. Blumenthal, F. Bokstein, M. Palmon, B. W. Corn, D. Ben Bashat, Automatic multi-modal MR tissue classification for the assessment of response to bevacizumab in patients with glioblastoma, Eur. J. Radiol. 82 (2013) e87–e94.
[166] K.R. Swanson, C. Bridge, J.D. Murray, E.C. Alvord Jr., Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion, J. Neurol. Sci. 216 (2003) 1–10.
[167] T.S. Deisboeck, L. Zhang, J. Yoon, J. Costa, In silico cancer modeling: is it ready for prime time? Nat. Clin. Pract. Oncol. 6 (2009) 34–42.
[168] S. Bauer, C. May, D. Dionysiou, G. Stamatakos, P. Buchler, M. Reyes, Multiscale modeling for image analysis of brain tumor studies, IEEE Trans. Biomed. Eng. 59 (2012) 25–29.
[169] R. Weissleder, B.D. Ross, A. Rehemtulla, S.S. Gambhir, Molecular Imaging - Principles and Practice, People's Medical Publishing House, USA, 2010.
[170] C. Lundstrom, A. Persson, S. Ross, P. Ljung, S. Lindholm, F. Gyllensvard, A. Ynnerman, State-of-the-art of visualization in post-mortem imaging, APMIS : Acta Pathol. Microbiol. Immunol. Scand. 120 (2012) 316–326.
[171] B. Preim, Visualization in Medicine: Theory, Algorithms, and Applications, 2007.
[172] A. Alaraj, M.G. Lemole, J.H. Finkle, R. Yudkowsky, A. Wallace, C. Luciano, P.P. Banerjee, S.H. Rizzi, F.T. Charbel, Virtual reality training in neurosurgery: Review of current status and future applications, Surg. Neurol. Int. 2 (2011) 52.
[173] J.H. Shuhaiber, Augmented reality in surgery, Arch. Surg. 139 (2004) 170–174.
[174] L. Thomas, A.L. Di Stefano, F. Ducray, Predictive biomarkers in adult gliomas: the present and the future, Curr. Opin. Oncol. 25 (2013) 689–694.
[175] M. Assem, Z. Sibenaller, S. Agarwal, M.S. Al-Keilani, M.A. Alqudah, T.C. Ryken, Enhancing diagnosis, prognosis, and therapeutic outcome prediction of gliomas using genomics, Omics : J. Integr. Biol. 16 (2012) 113–122.
[176] H.W. Lo, EGFR-targeted therapy in malignant glioma: novel aspects and mechanisms of drug resistance, Curr. Mol. Pharmacol. 3 (2010) 37–52.
[177] E. Galanis, J.C. Buckner, M.J. Maurer, J.I. Kreisberg, K. Ballman, J. Boni, J.M. Peralba, R. B. Jenkins, S.R. Dakhil, R.F. Morton, K.A. Jaeckle, B.W. Scheithauer, J. Dancey, M. Hidalgo, D.J. Walsh, G. North Central Cancer Treatment, Phase II trial of

temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 23 (2005) 5294–5304.
[178] P.C. De Witt Hamer, Small molecule kinase inhibitors in glioblastoma: a systematic review of clinical studies, Neuro Oncol. 12 (2010) 304–316.
[179] T.T. Batchelor, D.G. Duda, E. di Tomaso, M. Ancukiewicz, S.R. Plotkin, E. Gerstner, A. F. Eichler, J. Drappatz, F.H. Hochberg, T. Benner, D.N. Louis, K.S. Cohen, H. Chea, A. Exarhopoulos, J.S. Loeffler, M.A. Moses, P. Ivy, A.G. Sorensen, P.Y. Wen, R.K. Jain, Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 28 (2010) 2817–2823.
[180] O.L. Chinot, W. Wick, W. Mason, R. Henriksson, F. Saran, R. Nishikawa, A.F. Carpentier, K. Hoang-Xuan, P. Kavan, D. Cernea, A.A. Brandes, M. Hilton, L. Abrey, T. Cloughesy, Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (2014) 709–722.
[181] M.R. Gilbert, J.J. Dignam, T.S. Armstrong, J.S. Wefel, D.T. Blumenthal, M.A. Vogelbaum, H. Colman, A. Chakravarti, S. Pugh, M. Won, R. Jeraj, P.D. Brown, K.A. Jaeckle, D. Schiff, V.W. Stieber, D.G. Brachman, M. Werner-Wasik, I.W. Tremont-Lukats, E.P. Sulman, K.D. Aldape, W.J. Curran Jr., M.P. Mehta, A randomized trial of bevacizumab for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (2014) 699–708.
[182] E.D. Michelakis, G. Sutendra, P. Dromparis, L. Webster, A. Haromy, E. Niven, C. Maguire, T.L. Gammer, J.R. Mackey, D. Fulton, B. Abdulkarim, M.S. McMurtry, K.C. Petruk, Metabolic modulation of glioblastoma with dichloroacetate, Sci. Transl. Med. 2 (2010) 31ra34.
[183] J. Sotelo, E. Briceno, M.A. Lopez-Gonzalez, Adding chloroquine to conventional treatment for glioblastoma multiforme: a randomized, double-blind, placebo-controlled trial, Ann. Intern. Med. 144 (2006) 337–343.
[184] M.E. Hegi, L. Liu, J.G. Herman, R. Stupp, W. Wick, M. Weller, M.P. Mehta, M.R. Gilbert, Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 26 (2008) 4189–4199.
[185] A.A. Thomas, M.S. Ernstoff, C.E. Fadul, Immunotherapy for the treatment of glioblastoma, Cancer J. 18 (2012) 59–68.
[186] J.H. Sampson, A.B. Heimberger, G.E. Archer, K.D. Aldape, A.H. Friedman, H.S. Friedman, M.R. Gilbert, J.E. Herndon II, R.E. McLendon, D.A. Mitchell, D.A. Reardon, R. Sawaya, R.J. Schmittling, W. Shi, J.J. Vredenburgh, D.D. Bigner, Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 28 (2010) 4722–4729.
[187] R. Yamanaka, J. Homma, N. Yajima, N. Tsuchiya, M. Sano, T. Kobayashi, S. Yoshida, T. Abe, M. Narita, M. Takahashi, R. Tanaka, Clinical evaluation of dendritic cell vaccination for patients with recurrent glioma: results of a clinical phase I/II trial, Clin. Cancer Res. : Off. J. Am. Assoc. Cancer Res. 11 (2005) 4160–4167.
[188] A. Immonen, M. Vapalahti, K. Tyynela, H. Hurskainen, A. Sandmair, R. Vanninen, G. Langford, N. Murray, S. Yla-Herttuala, AdvHSV-tk gene therapy with intravenous ganciclovir improves survival in human malignant glioma: a randomised, controlled study, Mol. Ther. : J. Am. Soc. Gene Ther. 10 (2004) 967–972.
[189] G. Wollmann, K. Ozduman, A.N. van den Pol, Oncolytic virus therapy for glioblastoma multiforme: concepts and candidates, Cancer J. 18 (2012) 69–81.
[190] M. Westphal, D.C. Hilt, E. Bortey, P. Delavault, R. Olivares, P.C. Warnke, I.R. Whittle, J. Jaaskelainen, Z. Ram, A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma, Neuro Oncol. 5 (2003) 79–88.
[191] S.V. Bhujbal, P. de Vos, S.P. Niclou, Drug and cell encapsulation: alternative delivery options for the treatment of malignant brain tumors, Adv. Drug Deliv. Rev. 67–68 (2014) 142–153.
[192] R.H. Bobo, D.W. Laske, A. Akbasak, P.F. Morrison, R.L. Dedrick, E.H. Oldfield, Convection-enhanced delivery of macromolecules in the brain, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 2076–2080.
[193] E. Allard, C. Passirani, J.P. Benoit, Convection-enhanced delivery of nanocarriers for the treatment of brain tumors, Biomaterials 30 (2009) 2302–2318.
[194] K.C. Wei, P.C. Chu, H.Y. Wang, C.Y. Huang, P.Y. Chen, H.C. Tsai, Y.J. Lu, P.Y. Lee, I.C. Tseng, L.Y. Feng, P.W. Hsu, T.C. Yen, H.L. Liu, Focused ultrasound-induced blood-brain barrier opening to enhance temozolomide delivery for glioblastoma treatment: a preclinical study, PLoS One 8 (2013) e58995.
[195] T. Nariai, Y. Tanaka, H. Wakimoto, M. Aoyagi, M. Tamaki, K. Ishiwata, M. Senda, K. Ishii, K. Hirakawa, K. Ohno, Usefulness of L-[methyl-11C] methionine-positron emission tomography as a biological monitoring tool in the treatment of glioma, J. Neurosurg. 103 (2005) 498–507.
[196] A.W. Glaudemans, R.H. Enting, M.A. Heesters, R.A. Dierckx, R.W. van Rheenen, A.M. Walenkamp, R.H. Slart, Value of 11C-methionine PET in imaging brain tumours and metastases, Eur. J. Nucl. Med. Mol. Imaging 40 (2013) 615–635.
[197] T. Singhal, T.K. Narayanan, V. Jain, J. Mukherjee, J. Mantil, 11C-L-methionine positron emission tomography in the clinical management of cerebral gliomas, Mol. Imaging Biol. : MIB : Off. Publ. Acad. Mol. Imaging 10 (2008) 1–18.
[198] V. Dunet, C. Rossier, A. Buck, R. Stupp, J.O. Prior, Performance of ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) PET for the differential diagnosis of primary brain tumor: a systematic review and Metaanalysis, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 53 (2012) 207–214.
[199] N. Galldiks, G. Stoffels, M.I. Ruge, M. Rapp, M. Sabel, G. Reifenberger, Z. Erdem, N.J. Shah, G.R. Fink, H.H. Coenen, K.J. Langen, Role of O-(2-^{18}F-fluoroethyl)-L-tyrosine PET as a diagnostic tool for detection of malignant progression in patients with low-grade glioma, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 54 (2013) 2046–2054.
[200] H. Vees, S. Senthamizhchelvan, R. Miralbell, D.C. Weber, O. Ratib, H. Zaidi, Assessment of various strategies for ^{18}F-FET PET-guided delineation of target volumes in high-grade glioma patients, Eur. J. Nucl. Med. Mol. Imaging 36 (2009) 182–193.
[201] J. Schwarzenberg, J. Czernin, T.F. Cloughesy, B.M. Ellingson, W.B. Pope, T. Grogan, D. Elashoff, C. Geist, D.H. Silverman, M.E. Phelps, W. Chen, Treatment Response Evaluation Using ^{18}F-FDOPA PET in Patients with Recurrent Malignant Glioma on Bevacizumab Therapy, Clin. Cancer Res. : Off. J. Am. Assoc. Cancer Res. 20 (2014) 3550–3559.
[202] D.H. Pafundi, N.N. Laack, R.S. Youland, I.F. Parney, V.J. Lowe, C. Giannini, B.J. Kemp, M.P. Grams, J.M. Morris, J.M. Hoover, L.S. Hu, J.N. Sarkaria, D.H. Brinkmann, Biopsy validation of ^{18}F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study, Neuro Oncol. 15 (2013) 1058–1067.
[203] W. Weber, P. Bartenstein, M.W. Gross, D. Kinzel, H. Daschner, H.J. Feldmann, G. Reidel, S.I. Ziegler, C. Lumenta, M. Molls, M. Schwaiger, Fluorine-18-FDG PET and iodine-123-IMT SPECT in the evaluation of brain tumors, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 38 (1997) 802–808.
[204] D. Schmidt, U. Gottwald, K.J. Langen, F. Weber, A. Hertel, F. Floeth, J. Felsberg, G. Reifenberger, H.H. Coenen, H.W. Muller-Gartner, 3-[123I]Iodo-alpha-methyl-L-tyrosine uptake in cerebral gliomas: relationship to histological grading and prognosis, Eur. J. Nucl. Med. 28 (2001) 855–861.
[205] W.A. Weber, S. Dick, G. Reidl, B. Dzewas, R. Busch, H.J. Feldmann, M. Molls, C.B. Lumenta, M. Schwaiger, A.L. Grosu, Correlation between postoperative 3-[(123)I] iodo-L-alpha-methyltyrosine uptake and survival in patients with gliomas, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 42 (2001) 1144–1150.
[206] A.L. Grosu, H. Feldmann, S. Dick, B. Dzewas, C. Nieder, H. Gumprecht, A. Frank, M. Schwaiger, M. Molls, W.A. Weber, Implications of IMT-SPECT for postoperative radiotherapy planning in patients with gliomas, Int. J. Radiat. Oncol. Biol. Phys. 54 (2002) 842–854.
[207] Y. Yamamoto, Y. Ono, F. Aga, N. Kawai, N. Kudomi, Y. Nishiyama, Correlation of ^{18}F-FLT uptake with tumor grade and Ki-67 immunohistochemistry in patients with newly diagnosed and recurrent gliomas, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 53 (2012) 1911–1915.
[208] A.J. Idema, A.L. Hoffmann, H.D. Boogaarts, E.G. Troost, P. Wesseling, A. Heerschap, W.T. van der Graaf, J.A. Grotenhuis, W.J. Oyen, 3'-Deoxy-3'-^{18}F-fluorothymidine PET-derived proliferative volume predicts overall survival in high-grade glioma patients, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 53 (2012) 1904–1910.
[209] H. Shishido, N. Kawai, K. Miyake, Y. Yamamoto, Y. Nishiyama, T. Tamiya, Diagnostic Value of 11C-Methionine (MET) and 18F-Fluorothymidine (FLT) Positron Emission Tomography in Recurrent High-Grade Gliomas; Differentiation from Treatment-Induced Tissue Necrosis, Cancers 4 (2012) 244–256.
[210] F. Zhao, Y. Cui, M. Li, Z. Fu, Z. Chen, L. Kong, G. Yang, J. Yu, Prognostic value of 3'-Deoxy-3'-^{18}F-Fluorothymidine ([F] FLT PET) in patients with recurrent malignant gliomas, Nucl. Med. Biol. 41 (2014) 710–715.
[211] M.V. Padma, S. Said, M. Jacobs, D.R. Hwang, K. Dunigan, M. Satter, B. Christian, J. Ruppert, T. Bernstein, G. Kraus, J.C. Mantil, Prediction of pathology and survival by FDG PET in gliomas, J. Neuro-Oncol. 64 (2003) 227–237.
[212] A.M. Spence, M. Muzi, D.A. Mankoff, S.F. O'Sullivan, J.M. Link, T.K. Lewellen, B. Lewellen, P. Pham, S. Minoshima, K. Swanson, K.A. Krohn, ^{18}F-FDG PET of gliomas at delayed intervals: improved distinction between tumor and normal gray matter, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 45 (2004) 1653–1659.
[213] G. Di Chiro, E. Oldfield, D.C. Wright, D. De Michele, D.A. Katz, N.J. Patronas, J.L. Doppman, S.M. Larson, M. Ito, C.V. Kufta, Cerebral necrosis after radiotherapy and/or intraarterial chemotherapy for brain tumors: PET and neuropathologic studies, AJR Am. J. Roentgenol. 150 (1988) 189–197.
[214] M. Levivier, S. Goldman, B. Pirotte, J.M. Brucher, D. Baleriaux, A. Luxen, J. Hildebrand, J. Brotchi, Diagnostic yield of stereotactic brain biopsy guided by positron emission tomography with [^{18}F]fluorodeoxyglucose, J. Neurosurg. 82 (1995) 445–452.
[215] K.S. Tralins, J.G. Douglas, K.J. Stelzer, D.A. Mankoff, D.L. Silbergeld, R.C. Rostomily, S. Hummel, J. Scharnhorst, K.A. Krohn, A.M. Spence, Volumetric analysis of ^{18}F-FDG PET in glioblastoma multiforme: prognostic information and possible role in definition of target volumes in radiation dose escalation, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 43 (2002) 1667–1673.
[216] J.K. Lee, R.S. Liu, H.R. Shiang, D.H. Pan, Usefulness of semiquantitative FDG-PET in the prediction of brain tumor treatment response to gamma knife radiosurgery, J. Comput. Assist. Tomogr. 27 (2003) 525–529.
[217] N. Shinoura, M. Nishijima, T. Hara, T. Haisa, H. Yamamoto, K. Fujii, I. Mitsui, N. Kosaka, T. Kondo, T. Hara, Brain tumors: detection with C-11 choline PET, Radiology 202 (1997) 497–503.
[218] M. Utriainen, M. Komu, V. Vuorinen, P. Lehikoinen, P. Sonninen, T. Kurki, T. Utriainen, A. Roivainen, H. Kalimo, H. Minn, Evaluation of brain tumor metabolism with [11C]choline PET and 1H-MRS, J. Neuro-Oncol. 62 (2003) 329–338.
[219] F.M. Li, Q. Nie, R.M. Wang, S.M. Chang, W.R. Zhao, Q. Zhu, Y.K. Liang, P. Yang, J. Zhang, H.W. Jia, H.H. Fang, 11C-CHO PET in optimization of target volume delineation and treatment regimens in postoperative radiotherapy for brain gliomas, Nucl. Med. Biol. 39 (2012) 437–442.
[220] N. Kawai, W. Lin, W.D. Cao, D. Ogawa, K. Miyake, R. Haba, Y. Maeda, Y. Yamamoto, Y. Nishiyama, T. Tamiya, Correlation between F-fluoromisonidazole PET and expression of HIF-1alpha and VEGF in newly diagnosed and recurrent malignant gliomas, Eur. J. Nucl. Med. Mol. Imaging (2014) Apr 30. [Epub ahead of print].
[221] Y. Yamamoto, Y. Maeda, N. Kawai, N. Kudomi, F. Aga, Y. Ono, Y. Nishiyama, Hypoxia assessed by ^{18}F-fluoromisonidazole positron emission tomography in newly diagnosed gliomas, Nucl. Med. Commun. 33 (2012) 621–625.
[222] A.M. Spence, M. Muzi, K.R. Swanson, F. O'Sullivan, J.K. Rockhill, J.G. Rajendran, T.C. Adamsen, J.M. Link, P.E. Swanson, K.J. Yagle, R.C. Rostomily, D.L. Silbergeld, K.A.

Krohn, Regional hypoxia in glioblastoma multiforme quantified with [^{18}F] fluoromisonidazole positron emission tomography before radiotherapy: correlation with time to progression and survival, Clin. Cancer Res. : Off. J. Am. Assoc. Cancer Res. 14 (2008) 2623–2630.
[223] R.F. Barajas Jr., J.S. Chang, M.R. Segal, A.T. Parsa, M.W. McDermott, M.S. Berger, S. Cha, Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging, Radiology 253 (2009) 486–496.
[224] S. Higano, X. Yun, T. Kumabe, M. Watanabe, S. Mugikura, A. Umetsu, A. Sato, T. Yamada, S. Takahashi, Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis, Radiology 241 (2006) 839–846.
[225] P.A. Hein, C.J. Eskey, J.F. Dunn, E.B. Hug, Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury, AJNR Am. J. Neuroradiol. 25 (2004) 201–209.
[226] J.S. Wu, L.F. Zhou, W.J. Tang, Y. Mao, J. Hu, Y.Y. Song, X.N. Hong, G.H. Du, Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: a prospective, controlled study in patients with gliomas involving pyramidal tracts, Neurosurgery 61 (2007) 935–948 (discussion 948-939).
[227] H.P. Schlemmer, P. Bachert, K.K. Herfarth, I. Zuna, J. Debus, G. van Kaick, Proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy, AJNR Am. J. Neuroradiol. 22 (2001) 1316–1324.
[228] B. Roy, R. Awasthi, A. Bindal, P. Sahoo, R. Kumar, S. Behari, B.K. Ojha, N. Husain, C.M. Pandey, R.K. Rathore, R.K. Gupta, Comparative evaluation of 3-dimensional pseudocontinuous arterial spin labeling with dynamic contrast-enhanced perfusion magnetic resonance imaging in grading of human glioma, J. Comput. Assist. Tomogr. 37 (2013) 321–326.
[229] J. Furtner, B. Bender, C. Braun, J. Schittenhelm, M. Skardelly, U. Ernemann, S. Bisdas, Prognostic value of blood flow measurements using arterial spin labeling in gliomas, PLoS One 9 (2014) e99616.
[230] T. Noguchi, T. Yoshiura, A. Hiwatashi, O. Togao, K. Yamashita, E. Nagao, T. Shono, M. Mizoguchi, S. Nagata, T. Sasaki, S.O. Suzuki, T. Iwaki, K. Kobayashi, F. Mihara, H. Honda, Perfusion imaging of brain tumors using arterial spin-labeling: correlation with histopathologic vascular density, AJNR Am. J. Neuroradiol. 29 (2008) 688–693.
[231] A. Haberg, K.A. Kvistad, G. Unsgard, O. Haraldseth, Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome, Neurosurgery 54 (2004) 902–914 (discussion 914-905).
[232] H.S. Kim, G.H. Jahng, C.W. Ryu, S.Y. Kim, Added value and diagnostic performance of intratumoral susceptibility signals in the differential diagnosis of solitary enhancing brain lesions: preliminary study, AJNR Am. J. Neuroradiol. 30 (2009) 1574–1579.
[233] H. Zhang, Y. Tan, X.C. Wang, J.B. Qing, L. Wang, X.F. Wu, L. Zhang, Q.W. Liu, Susceptibility-weighted imaging: the value in cerebral astrocytomas grading, Neurol. India 61 (2013) 389–395.
[234] T. Kadota, H. Nakagawa, C. Kuroda, Malignant glioma. Evaluation with 3D time-of-flight MR angiography, Acta Radiol. 39 (1998) 227–232.
[235] O. Togao, T. Yoshiura, J. Keupp, A. Hiwatashi, K. Yamashita, K. Kikuchi, Y. Suzuki, S. O. Suzuki, T. Iwaki, N. Hata, M. Mizoguchi, K. Yoshimoto, K. Sagiyama, M. Takahashi, H. Honda, Amide proton transfer imaging of adult diffuse gliomas: correlation with histopathological grades, Neuro Oncol. 16 (2014) 441–448.
[236] Z. Wen, S. Hu, F. Huang, X. Wang, L. Guo, X. Quan, S. Wang, J. Zhou, MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast, Neuroimage 51 (2010) 616–622.
[237] B. Pirotte, S. Goldman, N. Massager, P. David, D. Wikler, A. Vandesteene, I. Salmon, J. Brotchi, M. Levivier, Comparison of ^{18}F-FDG and 11C-methionine for PET-guided stereotactic brain biopsy of gliomas, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 45 (2004) 1293–1298.
[238] M. Hutterer, M. Nowosielski, D. Putzer, D. Waitz, G. Tinkhauser, H. Kostron, A. Muigg, I.J. Virgolini, W. Staffen, E. Trinka, T. Gotwald, A.H. Jacobs, G. Stockhammer, O-(2-^{18}F-fluoroethyl)-L-tyrosine PET predicts failure of antiangiogenic treatment in patients with recurrent high-grade glioma, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 52 (2011) 856–864.
[239] M. Bruehlmeier, U. Roelcke, P.A. Schubiger, S.M. Ametamey, Assessment of hypoxia and perfusion in human brain tumors using PET with ^{18}F-fluoromisonidazole and 15O-H2O, J. Nucl. Med. : Off. Publ. Soc. Nucl. Med. 45 (2004) 1851–1859.
[240] J. Flament, F. Geffroy, C. Medina, C. Robic, J.F. Mayer, S. Meriaux, J. Valette, P. Robert, M. Port, D. Le Bihan, F. Lethimonnier, F. Boumezbeur, In vivo CEST MR imaging of U87 mice brain tumor angiogenesis using targeted LipoCEST contrast agent at 7 T, Magn. Reson. Med. : Off. J. Soc. Magn. Reson. Med. / Soc. Magn. Reson. Med. 69 (2013) 179–187.
[241] C.M. White, W.B. Pope, T. Zaw, J. Qiao, K.M. Naeini, A. Lai, P.L. Nghiemphu, J.J. Wang, T.F. Cloughesy, B.M. Ellingson, Regional and voxel-wise comparisons of blood flow measurements between dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) and arterial spin labeling (ASL) in brain tumors, J. Neuroimaging : Off. J. Am. Soc. Neuroimaging 24 (2014) 23–30.
[242] V. Sehgal, Z. Delproposto, D. Haddar, E.M. Haacke, A.E. Sloan, L.J. Zamorano, G. Barger, J. Hu, Y. Xu, K.P. Prabhakaran, I.R. Elangovan, J. Neelavalli, J.R. Reichenbach, Susceptibility-weighted imaging to visualize blood products and improve tumor contrast in the study of brain masses, J. Magn. Reson. Imaging : JMRI 24 (2006) 41–51.
[243] N. Farid, D.B. Almeida-Freitas, N.S. White, C.R. McDonald, K.A. Muller, S.R. Vandenberg, S. Kesari, A.M. Dale, Restriction-Spectrum Imaging of Bevacizumab-Related Necrosis in a Patient with GBM, Front. Oncol. 3 (2013) 258.