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Imaging and treatment of brain tumors through molecular targeting: Recent clinical advances

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ABSTRACT

Molecular imaging techniques have rapidly progressed over recent decades providing unprecedented *in vivo* characterization of metabolic pathways and molecular biomarkers. Many of these new techniques have been successfully applied in the field of neuro-oncological imaging to probe tumor biology. Targeting specific signaling or metabolic pathways could help to address several unmet clinical needs that hamper the management of patients with brain tumors. This review aims to provide an overview of the recent advances in brain tumor imaging using molecular targeting with positron emission tomography and magnetic resonance imaging, as well as the role in patient management and possible therapeutic implications.

1. Introduction

Molecular imaging is a rapidly evolving area with the development of many new molecular imaging techniques and applications, ranging from hardware, novel imaging agents, acquisition protocols, and advanced image analysis approaches. Despite significant advances in the oncological management of many brain tumors, many of these continue to have a very poor prognosis with more than two-thirds of adults diagnosed with glioblastoma dying within 2 years of diagnosis, which is partly due to the high degree of morphological, metabolic, and genetic heterogeneity observed both within and between tumors [1–4]. A better understanding of these mechanisms by using non-invasive methods of *in vivo* tissue characterization may contribute to this area of unmet need. Conventional imaging techniques demonstrate many aspects of tumor heterogeneity, but molecular imaging techniques can reveal and quantify this phenomenon in new ways, which can help to more accurately characterize these tumors and evaluate their response to therapy.

Cerebral metabolism is a highly regulated process, with a complex

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interplay between glial cells and neurons to meet the demand for adenosine triphosphate (ATP) production [5]. The main clinical tools to probe metabolic pathways include proton magnetic resonance spectroscopy (^{1}H MRS) and positron emission tomography (PET). PET is a very sensitive technique, providing a wide range of neurotracers to specifically image a range of metabolic pathways and provide quantitative measurement of metabolic parameters. Although MRS is less sensitive, it provides a non-invasive way of characterizing endogenous tumor metabolites, and allows for multiple metabolic pathways to be simultaneously explored without radiation exposure [6,7]. Magnetic resonance (MR) can be used to detect signal from several nuclei in addition to protons or ^{1}H, that can be used to explore tissue metabolism and cellular processes *in vivo*. For example, steady state distribution of tissue sodium (^{23}Na) can be used to probe biological compartments [8,9]. More recently, dynamic monitoring of hyperpolarized carbon-13 (^{13}C) labelled compounds has been used to probe both oxidative and reductive brain metabolism [10,11].

2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is a glucose analog which is transported by the transmembrane glucose transporters (GLUTs) and is phosphorylated by hexokinase in the first step of glycolysis. Owing to the physiologically high [^{18}F]FDG uptake in normal brain tissue, tumors may present with a relatively low tumor-to-background ratio, which may hinder detection especially in low-grade brain neoplasms [12]. There are several PET tracers that target metabolic pathways with a higher tumor-to-background ratio, such as protein synthesis, membrane lipid synthesis, and fatty acid synthesis [13,14]. The Response Assessment in Neuro-Oncology (RANO) working group has recommended amino acid tracers for glioma imaging, owing to their superiority over [^{18}F]FDG for several clinical indications, including differential diagnosis and grading of new brain lesions and assessment of tumor extension [15].

This review focuses on isotopic imaging of brain tumors using PET and MRI which could have a future role in neuro-oncology. It will also discuss the potential of combining molecular imaging with therapy in the form of theranostics, which is also likely to find an increasing role in future clinical practice.

2. Current role for imaging and unmet clinical needs in neuro-oncology

Gliomas are the most common primary brain tumors, accounting for nearly 70% of central nervous system (CNS) cancers, with glioblastoma (GBM) being the most frequent and malignant of the high grade gliomas (HGG)[16]. Maximal surgical resection is often the primary aim in the management of HGGs, although there is no consensus on the role of surgery for low-grade gliomas (LGGs) [17–19]. Therefore, an accurate assessment of tumor extent is mandatory to achieve gross total resection. However, as the tumor is very infiltrative, this can often be difficult to assess using conventional MRI protocols such as: T_2-weighted images (T_2WI), T_2 fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and T_1-weighted images (T_1WI) acquired pre- and post-gadolinium-based contrast agent administration (GBCA) [20–22]. DWI, based on the assumption of Brownian motion of water within tissues, can aid in assessing tumor infiltration within the *peri*-tumoral edema, but has limited specificity and sensitivity [23–27]. Advanced diffusion-based techniques such as diffusion kurtosis imaging (DKI) or the vascular, extracellular and restricted diffusion for cytometry in tumors (VERDICT) have emerged as novel potential tools to assess glioma microstructure, function, and heterogeneity which may improve the identification of tumour infiltration [28,29].

5-aminolevulinic acid (5-ALA), an endogenous precurser of heme, can be used intra-operatively for optical assessment of tumor infiltration. Exogenously administered 5-ALA leads to the accumulation of fluorescent protoporphyrin IX within malignant cells due to reduced ferrochelatase activity, which can be visualized at surgery [30,31]. The prolonged progression-free survival achieved by combining 5-ALA and MRI guidance for tumor detection and delineation, underlines the potential importance of targeting hybrid imaging techniques [32–34].

The delineation of tumor boundaries is also of key importance for radiotherapy planning, an integral component in the treatment of brain tumors both after the initial surgery/biopsy and at recurrence, as recommended by the American Society for Radiation Oncology (ASTRO) guidelines [35,36]. Image-guided identification and selection of the radiotherapy target can significantly reduce the dose delivered to normal tissues while maximizing treatment efficacy using novel techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) [37]. For example, tumor hypoxia is related to resistance of both radiation therapy and conventional chemotherapy and non-invasive assessment of tumor hypoxia can be used for "dose painting" or modulation of radiotherapy doses in areas of hypoxia as well as informing on the use of hypoxia-targeting drugs [38].

Non-invasive assessment of molecular biomarkers for *in vivo* phenotyping of gliomas is also a growing application for molecular imaging. Isocitrate dehydrogenase (IDH) has become one of the key biomarkers of underlying glioma biology and a cornerstone of the WHO brain tumor classification [39]. The discovery of the importance of IDH in tumorigenesis and aggressiveness led to *non-invasive* methods to detect the presence of the mutation using ^{1}H MRS. Specific mutations in IDH result in neomorphic enzyme function and the accumulation of the oncometabolite 2-hydroxglutarate (2HG). Detection of the oncometabolite 2HG *in vivo* indicates the presence of mutant IDH, which can be used not only to detect the mutation but also to predict therapy response earlier than morphological techniques [40–42].

Imaging also plays a significant role in treatment evaluation, which is currently based on the 2010 update of the RANO criteria [43]. According to those, both the T_1W post GBCA and the T_2W/FLAIR are used to assess interval change in size of the lesion. However, the updated RANO criteria still fall short of definitively distinguishing tumor progression, pseudoresponse (defined as decrease in contrast enhancement due to normalization of abnormally permeable tumor vessels), and pseudoprogression (defined as increased contrast enhancement after treatment which is not tumor related), resulting in uncertainties for up to 12 weeks after therapy [44]. Sensitive and specific methods to determine treatment evaluation are required to better define management at the earliest stage possible. Advanced imaging techniques that probe tumor biology could play a significant role in early therapy assessment and long-term follow-up in a routine clinical environment.

3. Developments in magnetic resonance imaging (MRI) for brain tumor imaging

MRI is the main imaging technique for assessment of patients with brain tumors. The current standard of practice in Europe is based on the recommendations of the RANO working group with significant limitations in therapy assessment within the first 3 months after treatment [43].

Several biological processes can be measured using proton MRS (^{1}H MRS), such as lactate concentration, membrane turnover, and cellular proliferation [45]. However, ^{1}H MRS requires interpretation by an experienced reader and clear thresholds for tumor grading are still a matter of debate [46]. Moreover, acquiring ^{1}H MRS across the brain using multi-voxel acquisition strategies leads to lengthy scan times and presents several technical challenges such as obtaining spectra close to the skull. A further challenge with clinical field strength ($\leq$3 T) MRS is the limited metabolic resolution leading to a restricted number of pathways that can be explored [47–49].

MRI can also be used to detect nuclei other than protons (or ^{1}H) to explore metabolic processes *in vivo*. However, the signal from nuclei such as ^{31}P, ^{23}Na, or ^{13}C is significantly reduced compared to protons due to lower *in vivo* concentrations, smaller gyromagnetic ratios, and relatively decreased nuclear polarizations. Therefore, until recently, multi-nuclei imaging with conventional MRI systems has been

challenging. With the more widespread availability of higher-field (≥3 T) magnets and the improvement in coil technology and acquisition sequences, these nuclei can now be successfully imaged within a clinically practical timescale. These techniques may provide useful data to complement conventional multi-parametric MRI protocols.

3.1. Phosphorus-31 magnetic resonance spectroscopy (^{31}P MRS)

Investigation of ^{31}P MRI to detect cerebral cellular energetics dates back to the 1980s. Initial experiments with ^{31}P MRS in preclinical models of glioma and neuroblastoma demonstrated high nucleoside triphosphate and phosphomonoesters with low peaks of phosphocreatine [50]. Necrosis is typically associated with decreased nucleoside triphosphate, decreased phosphomonoesters, and increased inorganic phosphate. Hirawaka *et al.* subsequently postulated that non-invasive assessment of ^{31}P could provide early assessment of therapy response before morphological changes, for instance through early increase in the inorganic phosphate concentration within the lesion [50].

Phospholipids (PL) are a key component of cellular membranes and probing PL provides information on cell replication and viability. Phosphomonoesters (PME) are precursors of PL while phosphodiesters (PDE) are products of PL catabolism. Both PME and PDE can be quantified with ^{31}P MRS and an increase in PME has been associated with cell proliferation, tumor progression and/or recurrence in GBM [51]. In contrast, low grade gliomas are characterized by low proliferative rates and have lower PME levels which can potentially be used in the differential diagnosis compared to higher grade tumors [51]. This distinction between HGG and LGG on ^{31}P MRS could be particularly useful for detecting areas of increased proliferation, as is present in in transforming gliomas.

Recently, the combination of higher filed strengths, improved coil design and acquisition sequences has permitted whole-brain spectroscopic imaging (^{31}P MRSI), paving the way for whole brain mapping of adenosine triphosphate (ATP) and phosphocreatine (PCr) [52]. It also offers the possibility of spatial mapping tissue pH within brain tumors [53]. HGGs typically show an acidified extracellular compartment which confers a survival benefit, facilitates infiltration by creating a hostile environment for normal tissue, and promotes malignancy through induction of cancer stem cells [54]. Some reports using single voxel MRS have shown mild intracellular alkalinization of astrocytomas, meningiomas and lymphomas compared to normal brain parenchyma [55–57]. A more recent report demonstrated a pH gradient from pseudonormal values within the leading edge to pronounced acidosis within the necrotic zone of a tumor [58]. The ability to image the spatial distribution of pH *in vivo* could provide valuable insights into glioma pathophysiology, identification of areas rich in cancer stem cells as a target for therapy, as well as the potential of monitoring response to therapy. A better insight into the role of pH in gliomas could also pave the way for new treatments, such as lysosome destabilizing drugs [59].

3.2. Sodium-23 magnetic resonance imaging (^{23}Na MRI)

In the 1980s, Maudsley and Hilal [8] postulated that sodium MRI would distinguish features of brain tumors that could not be detected on conventional proton imaging. Following on from this work, Feinberg [60] demonstrated the use of the technique in brain tumor patients. Subsequent research explored the use of ^{23}Na MRI in healthy brain and other neurological diseases, with promising results [61–63]. Recent developments in pulse sequence design and quantification have led to a renewed interest in this technique [64–68]. Imaging of the sodium ion is of significant interest for brain diseases [69] because an increase in cellular metabolism is associated with changes in Na^+/K^+-ATPase activity. For example, when ATP utilization is increased in a proliferating tumor, the activity of the sodium pump may be reduced, resulting in changes in the gradient of sodium ions across the membrane [9].

In 2003, Ouwerkerk *et al.*[70] demonstrated that sodium concentration is increased both in malignant tumors and in the surrounding non-enhancing FLAIR hyperintense parenchyma (Fig. 1). The signal increase was attributed to a combination of changes in the extracellular volume fraction and intracellular sodium concentration. In an attempt to disentangle the extracellular and intracellular sodium component, Nagel *et al.* explored the use of relaxation-weighted ^{23}Na sequences (^{23}NaR) to quantify the intracellular compartment [71]. An increased ^{23}NaR signal intensity was observed in GBMs and in a cerebral metastasis which may relate to higher cellular proliferation as demonstrated by a strong correlation between the intracellular sodium concentration and the expression of mindbomb homolog-1 (MIB-1), a marker of proliferation rate [72,73]. Further studies have shown an increased apparent total sodium concentration and extracellular sodium concentration within tumors compared to the normal appearing white matter demonstrating the ability of ^{23}Na MRI to distinguish different tissue compartments [9,71,74–76]. Moreover, ^{23}Na MRI has been shown to correlate with the IDH mutation and could therefore act as a prognostic factor [77]: for example, the ratio of ^{23}NaR to the total sodium signal has been shown to correlate with mutant IDH expression, accurately classify glioma grade, and to predict survival [77].

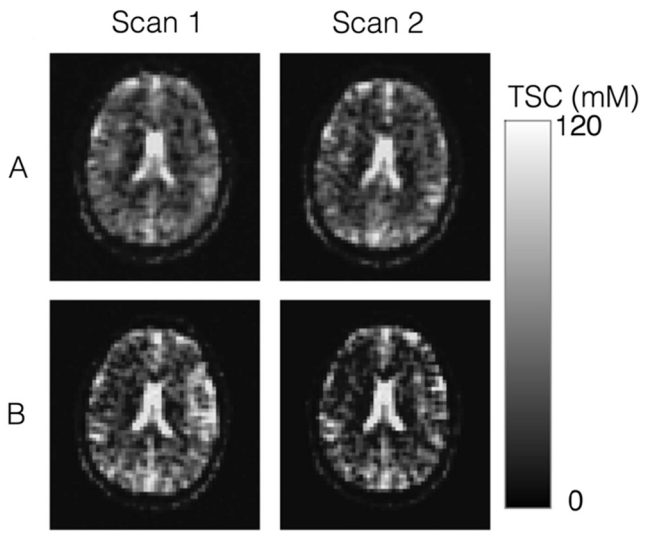

Fig. 1. 3D ^{23}Na-MRI of a healthy volunteer showing total sodium concentrations across brain regions from two different sites (A and B) and at two different time points (scan 1 and scan 2). Images demonstrate repeatability and reproducibility of the technique. Adapted with permission from Riemer *et al.* [68].

^{23}Na MRI has also been evaluated as an imaging biomarker for therapy evaluation in GBM combined with 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT)-PET. Laymon *et al.* have demonstrated that ^{23}Na MRI and [^{18}F]FLT-PET are complementary in assessing therapy response [78]. More recently, Thulborn *et al.*[79] assessed the potential utility of ^{23}Na MRI as an early biomarker of therapy response in patients undergoing fractionated chemoradiation. Using a two-compartment model, they converted the total sodium concentration maps into cell volume fraction bioscale maps from which they subsequently derived the residual tumor volume and tumor cell death component. Changes in cell volume fraction, residual tumor volume, and tumor cell death were identified during the course of the 6-week regimen but over the same period, there was little biological variation in the normal appearing tissue. However, these changes did not correlate with prognosis which may reflect the heterogeneity of GBM response treatment.

3.3. Hyperpolarized carbon-13 magnetic resonance imaging (HP ^{13}C MRI)

Hyperpolarized ^{13}C MRI is an emerging clinical technique with the potential to increase the understanding of neurological, psychiatric, and

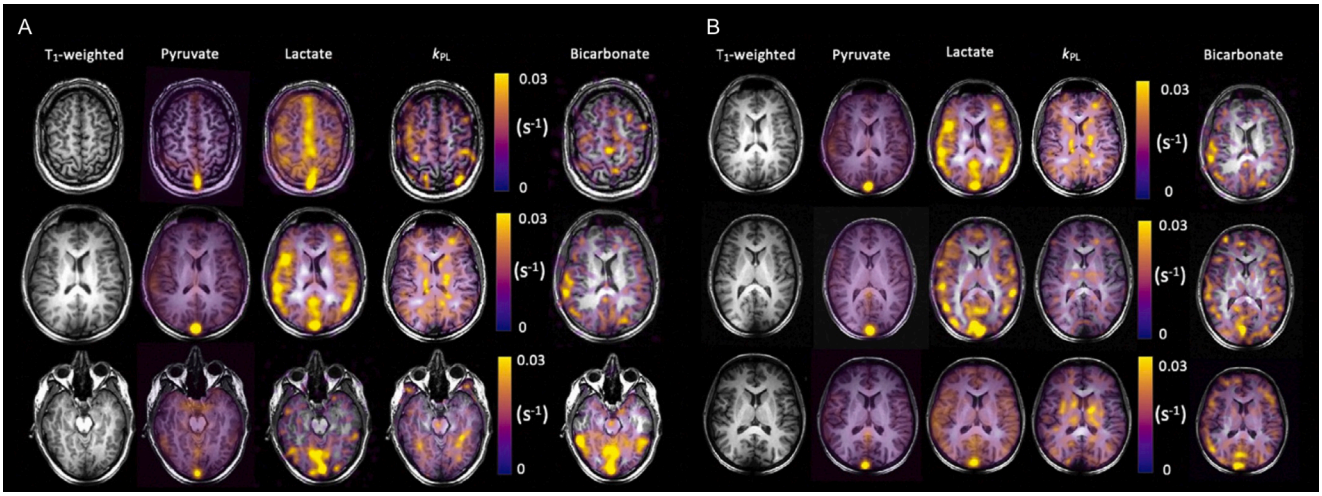

Fig. 2. Hyperpolarized ^{13}C-MRI in two healthy volunteers (A and B) demonstrating metabolite distribution within the healthy human brain following injection of hyperpolarized ^{13}C-pyruvate. Adapted with permission from Grist *et al.* [86].

neuro-oncological conditions by probing cerebral metabolism [80]. The most commonly used compound in clinical studies to date has been [1-^{13}C]pyruvate, which informs upon both oxidative and glycolytic metabolism. The hallmark of oxidative metabolism is the formation of CO_2 by pyruvate dehydrogenase, which exchanges with bicarbonate. Tricarboxylic acid (TCA) cycle metabolism in mitochondria is an efficient process for ATP generation, whilst glycolytic metabolism is less energetically efficient and results in the formation of lactate through the action of lactate dehydrogenase (LDH).

The process of hyperpolarization involves the mixing of a ^{13}C-labelled metabolic substrate of interest with a source of free electrons known as a radical. The sample is then stored inside a sterile unit known as a 'fluid path' and placed inside a magnetic field (commonly 5 T for clinical applications) in a bath of liquid helium at approximately 0.8 K while undergoing irradiation with a microwave source. These conditions increase the available signal from the molecule in the order of $>$ 10,000 fold [81]. To make use of this transient increase in signal, a bolus of super-heated water is used to dissolve the molecule-radical mix, which is then filtered to remove the radical before neutralization and cooling. The final product is then checked against quality control parameters, notably the pH of the mixture and the concentration of the molecule of interest in solution, and subsequently rapidly released into the participant within the clinical MRI scanner [82]. Owing to the difference in chemical shift between the injected substrate and its subsequent downstream metabolites, either slice localized spectroscopy or imaging are commonly performed. Post-processing of data commonly relies either upon ratiometric (for example the lactate-to-pyruvate ratio) or model-based approaches to derive the apparent forward rate constant for the enzyme LDH (k_{PL})[83–85].

Hyperpolarized ^{13}C MRI has been undertaken in the healthy brain and in small studies of patients with brain tumors. Initial results have demonstrated the feasibility of imaging both glycolytic and oxidative metabolism within the healthy brain [86,87], detecting lactate and bicarbonate formation within the parenchyma (Fig. 2). The spatial variation of lactate formation across the healthy brain is well preserved across individuals and could be used to detect dysregulated metabolism in cerebral pathology [88]. Results from initial neuro-oncological studies have demonstrated lactate formation within both metastases and HGGs [89,90]. There have been a number of preclinical studies showing the potential for hyperpolarized MRI to demonstrate early response of brain diseases to therapeutic intervention [91–95] with preliminary evidence of an increase in the rate constants in patients treated with bevacizumab [96].

3.4. Chemical-exchange-dependent saturation transfer MRI (CEST MRI)

Chemical-exchange-dependent saturation transfer (CEST) is based on the proton exchange between bulk water and a target molecule,

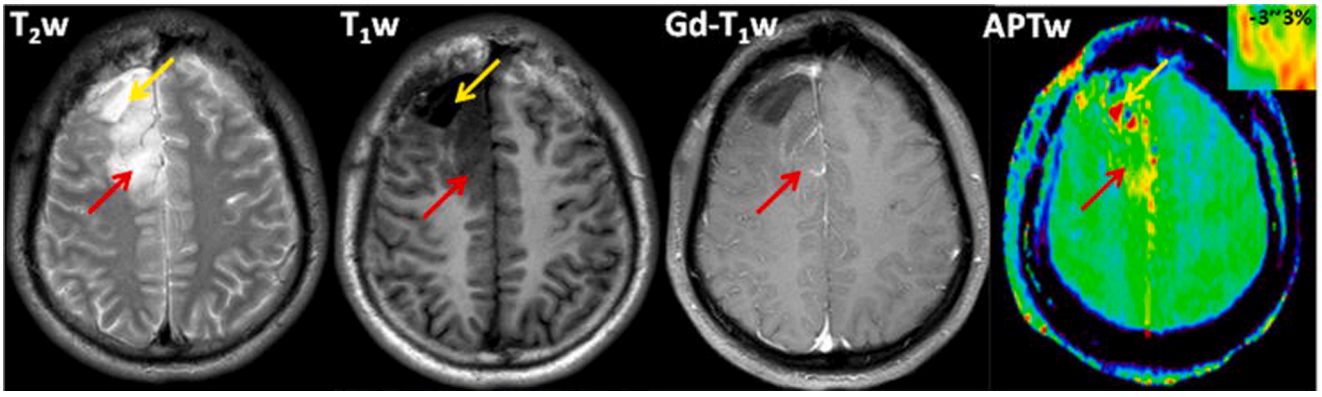

Fig. 3. Proton and Amide Proton Transfer (APT)-weighted MR images of a patient with an IDH-wildtype, WHO grade-II diffuse astrocytoma. The tumor (red arrows) was heterogeneously hyperintense on the T_2-weigthed image, hypointense on the T_1-weigthed image, with no definite enhancement after contrast injection. On the APT-weighted image, the lesion showed scattered areas of hyperintensity. The yellow arrow indicates a cystic-appearing component. Adapted with permission from Jiang *et al.* [104].

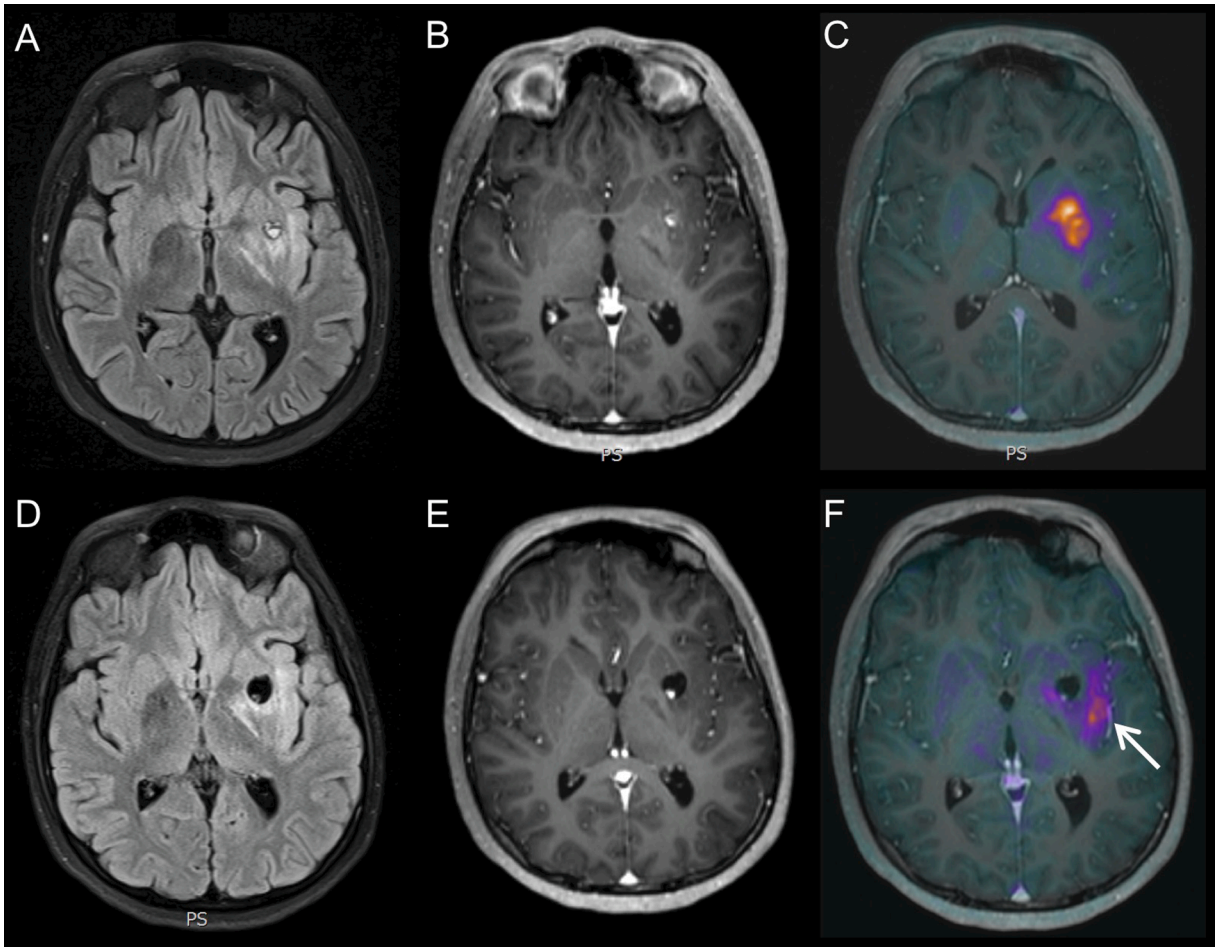

Fig. 4. 13-year-old female with a diffuse anaplastic astrocytoma of the left basal ganglia. MRI performed 1 month after initiation of radiotherapy. (A) Axial FLAIR, (B) axial T_1-weighted (T_1W) after injection of a gadolinium-based contrast agent (GBCA) and (C) axial fused [^{18}F]DOPA /T_1W post GBCA. FLAIR signal changes centered in the left thalamic region. The nodular bright spot represents post biopsy hemorrhage with no enhancement. [^{18}F]DOPA-PET shows intense uptake centered at the level of the thalamic region. Follow up MRI at 8 months: (D) axial FLAIR, (E) axial T_1W post GBCA and (F) axial fused [^{18}F]DOPA/T_1W post GBCA. A similar FLAIR signal abnormality is seen with the expected evolution of the previous hemorrhagic changes without contrast enhancement. The [^{18}F]DOPA-PET demonstrated response at the original tumor site with new spread of disease along the lateral border (white arrow).

either of endogenous or exogenous origin [97]. Depending on which mobile protons are used to generate the signal, several techniques are possible with the most common being amide CEST (also known as amide proton transfer - APT), amine CEST and hydroxyl CEST [98]. In neuro-oncological imaging, APT and GlucoCEST, a type of hydroxyl CEST, have been the most widely investigated [99–108].

APT derives its signal from cytosolic proteins abundant in cancer cells, therefore components of gliomas show higher values than peritumoral edema or necrosis [99,100]. Similarly, APT can be used to differentiate radiation necrosis and tumor progression [101] and as an early biomarker for tumor proliferation [102,103]. Recent evidence suggests that APT could potentially differentiate IDH-wildtype gliomas (Fig. 3)[104] and detect tumor methylation status [105].

GlucoCEST is based on exogenously injected D-glucose to generate the CEST effect [106]. Preclinical models studied at ultra-high field strength have demonstrated the potential of the technique to assess tumor blood volume and blood–brain barrier (BBB) permeability [106,107]. Recently, Xu *et al.* proposed a novel method to acquire GlucoCEST at clinical field strength [108] which showed a discrepancy between the glucose enhancement and the enhancement after GBCA, suggesting that it measures tissue metabolism in addition to BBB permeability. Further optimization of the procedure is required, including the ideal mode of D-glucose injection [108], but potentially the technique offers a novel method to study tumor metabolism.

4. Developments in positron emission tomography (PET) for brain tumor imaging

PET imaging may play a role in addressing several unmet clinical needs. Owing to the heterogeneous nature of brain tumors, image-guided biopsies based on morphological features may not accurately target the tumor, or precisely sample the most biologically aggressive tumor regions [109–111]. PET can provide an *in vivo* metabolic tumor map to guide tissue collection from the most metabolically active tumor area, allowing improved grading compared to sampling based on morphological or functional information [111,112]. Guiding biopsy or treatment using metabolic changes may identify patients with a more aggressive histological or molecular tumor profile, or a higher risk of recurrence and worse outcome, who may benefit from tailored treatments and stricter imaging follow-up. Pirotte *et al.* demonstrated the superiority of L-[methyl-^{11}C]-methionine ([^{11}C]MET) over [^{18}F]FDG in guiding tissue sampling [113]. However, the half-life of ^{11}C is approximately 20 min, thus limiting its application to facilities with a cyclotron on site [114].

[^{18}F]FLT is a marker of DNA synthesis and consequently, cellular proliferation. Interestingly, the volume of tumor assessed using [^{18}F]FLT is similar to that measured using [^{11}C]MET suggesting the possibility of using this tracer for lesion delineation [115]. Suchorska *et al.* demonstrated that a smaller biological tumor volume (BTV) delineated by

Table 1
Some of the main PET radiotracers currently in use in neuro-oncological routine imaging (indicated with *) or with potential utility in the future. FDA approved tracers are currently in use with specific indication for brain tumor imaging. Non-FDA approved tracers are still being investigated with mounting evidence for their future use.

Radiotracer	Biological target	FDA status	EMA status
[^{18}F]FDG*	Glucose metabolism	Approved	Approved
[^{11}C]acetate	Oxidative metabolism	Not approved	Not approved
[^{18}F]F-DOPA*	Amino acid transport	Orphan Drug Designation	Approved
[^{11}C]MET*	Protein metabolism and amino acid transport	Not approved	Not approved
[^{18}F]FET	Amino acid transport	Orphan Drug Designation	Not approved
[^{18}F]FMISO	Tumor hypoxia	Not approved	Not approved
[^{18}Ga]FAPI	Marker of cancer-associated fibroblasts	Not approved	Not approved

means of O-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]FET) PET, correlates with improved progression-free survival (PFS) and overall survival (OS), suggesting that maximal PET guided-tumor resection may be beneficial [116].

6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]DOPA, Fig. 4) is another promising radiotracer in neuro-oncology [117]. [^{18}F]DOPA-PET and MRS were compared by Morana *et al.* in 27 patients with infiltrative gliomas showing similar accuracy in differentiating gliomas from non-neoplastic lesions (accuracy of 78% for PET *vs.* 93% for MRS) [118]. More recently, Fraioli *et al.* compared [^{18}F]DOPA-PET images against cross-sectional MRI in 40 patients with brain tumors investigated using hybrid PET/MRI imaging, and concluded that the combined PET/MRI approach, including use of conventional ^{1}H sequences and contrast-enhanced perfusion-weighted imaging, improved overall tumor detection post-treatment [119].

PET imaging may also be advantageous for the early evaluation of treatment response and for the discrimination of tumor recurrence, pseudoprogression and radionecrosis [12,120,121]. Although an overall good performance has been described for the assessment of recurrence using [^{18}F]FDG-PET/CT in patients with gliomas [122], a relatively high rate of false negative results has been reported in LGGs [123]. Amino acid tracers in this setting appear more effective, reaching a sensitivity of 88% (95% CI: 85–91%) and a specificity of 85% (95% CI: 80–89%), according to a recent *meta*-analysis of 23 studies that included a total of 889 patients [124].

Radiotherapy planning may also benefit from the routine use of metabolic PET imaging to delineate PET-adapted treatment volumes reflecting metabolic activity, and to perform dose escalation [15,111]. In a series of 26 patients followed-up for 15 months after radiotherapy, [^{11}C]MET-PET identified areas of high risk of recurrence, suggesting the utility of incorporating this tracer into standard radiotherapy planning [125]. The evaluation of hypoxia in HGGs is important to minimize resistance to radiotherapy and chemotherapy within hypoxic tumor regions. The main hypoxic radiotracer used to study brain tumors is [^{18}F]fluoromisonidazole ([^{18}F]FMISO). Toyonaga *et al.* showed hypoxic glucose metabolism to be a clinically significant prognostic factor in 32 patients with GBM using [^{18}F]FMISO, and [^{18}F]FDG [126]. Second-generation hypoxic radiotracers with improved pharmacodynamics have been developed with the aim to improve tumor-to-background tissue localization and faster clearance from normal tissue.

Recently, the fibroblast activation protein (FAP) expressed on cancer-associated fibroblasts has emerged as a novel target for PET imaging [127]. ^{68}Ga-labeled inhibitors of FAP, ^{68}Ga-FAPI, have been evaluated in patients with GBM demonstrating tumor volumes that differed from those obtained using T_1W MRI, suggesting potential additional information for targeting biopsy or radiotherapy planning [128]. Interestingly, ^{68}Ga-FAPI was found to be positive in IDH-wildtype GBMs and grade III/IV IDH-mutant gliomas, but not in IDH-mutant grade II gliomas [129]. A list of the main PET radiotracers currently used or under development for imaging brain tumors is found in Table 1.

5. Theranostics

Brain tumors constitute a major therapeutic challenge [3] as surgery, radiotherapy and chemotherapy have well recognized limitations and new therapeutic approaches are required. Theranostics is a broad concept referring to the use of a diagnostic agent or method to guide a therapeutic intervention, mostly relevant to the field of cancer. Radionuclide based methods are well suited for this approach because radiolabeled targeting agents can both visualize and characterize biochemical properties of tumors, while informing on the possibility of specifically delivering therapeutic radiation to the target volume sparing non-target tissues. This general concept has been applied since the 1950s when sodium iodide (^{131}I) was first used to image and treat advanced differentiated thyroid cancers [130]. Over the years a number of cancer-specific, highly expressed targets have emerged with clinical approval for use in neuroendocrine tumors [131] and hematological malignancies [132].

Several biological and molecular targets are currently under investigation for potential theranostic applications in brain tumors as combination treatments intended to provide a local radiation boost for supplementary therapeutic benefit. These targets cover the spectrum of tumor biology: metabolism, proteins or receptors overexpressed on the surface of glioma cells, markers expressed on neovasculature, proteins within the extracellular matrix, and cells within the tumor microenvironment. Consequently, a wide range of targeting agents are being investigated such as peptides and small molecules, antibodies and antibody fragments, and metabolic substrates. Imaging with these agents has largely been undertaken using PET. The therapeutic counterparts for these drugs are generally the same or very similar compounds labelled with beta-emitting, and recently alpha-emitting, radionuclides that provide a high linear energy transfer (LET) and localized absorbed dose necessary for therapeutic efficacy.

Traditionally theranostic agents are delivered through intravenous injection, and tumor targeting is based on the biological properties of the radiolabeled agent and its ability to concentrate in the tumor due to the expression of the molecular target. Targeting gliomas offers additional challenges due to the poor diffusion of molecules from the systemic circulation into the tumor. Concurrent administration of drugs to increase BBB permeability has been attempted with limited success [133]. For targeted radionuclide therapy, there are several examples where the theranostic agent has been administered directly into the tumor or into an existing surgical cavity [134]. In convection enhanced delivery, hydraulic pressure provided by a pumping device attached to a catheter introduced into the tumor or surgical cavity is used to improve diffusion within the tumor [135]. The aim of these strategies is to obtain higher concentrations of the agent within the tumor which should ultimately result in improved binding to the molecular target, longer retention in or around tumor cells, increased local absorbed dose, and lower systemic toxicity. Imaging of the distribution of the agent can be used to monitor distribution of radioactivity within the tumor and to estimate the tumor absorbed dose, which could potentially be modulated on a patient-by-patient basis.

5.1. Antibody based approaches

Monoclonal antibodies have traditionally been used as vehicles to deliver targeted radionuclide therapy. Tenascin, an extracellular matrix

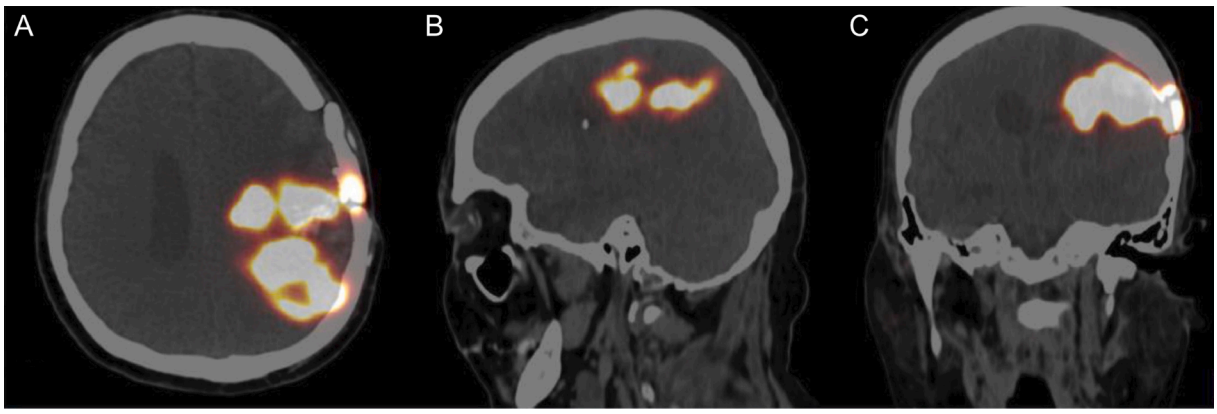

Fig. 5. Axial (A), sagittal (B) and coronal (C) PET/CT images obtained after local co-injection of 10 MBq ^{68}Ga-DOTA labelled Substance P (SP) with a therapeutic dose of ^{225}Ac-DOTAGA-SP into the resection cavity of a GBM, demonstrating that the activity is concentrated within the lesion. Adapted with permission from: L. Królicki *et al.*[156]

protein expressed on multiple cancer types, is the most investigated radioimmunotherapy target for gliomas. In the early 1990s locally administered ^{131}I-labelled murine monoclonal antibodies against tenascin were used in a small series of patients with newly diagnosed and recurrent glioma showing 40% overall response rates [136]. The same target was also investigated in several early phase clinical studies in the 2000s using a chimeric antibody (81C6) against tenascin labelled with ^{131}I [137,138] or the alpha emitter ^{211}At [139]. This approach showed promising results and orphan drug designation for [^{131}I]-81C6 was obtained in the United states in 2006, no additional steps toward approval have occurred since then. An ^{125}I-labelled murine antibody against the epidermal growth factor receptor (EGFR) known as mAb 425 has been used for adjuvant treatment of gliomas through multiple intravenous injections, either alone or in combination with temozolomide [140]. This phase II study involved nearly 200 patients over 20 years and showed a survival benefit of several months in the combination arm with very limited side effects. This is one of the rare examples of successful use of a poorly penetrating Auger electron emitter such as ^{125}I for targeted therapy and is attributed to internalization of the labeled antibody/receptor complex after binding. An additional target addressed by radioimmunotherapy with convection enhanced delivery in an early phase clinical trial is DNA histone H1 complex [141].

Alternative immune based targeting strategies have been investigated mostly aimed at developing lower molecular weight agents that would display more favorable pharmacokinetics and diffusion. A derivative of a monoclonal antibody against the extra domain B of fibronectin (L19), a marker of tumor neoangiogenesis, has been engineered to an 80 kDa small immunoprotein (L19-SIP). Early phase clinical studies in patients with brain metastases using a systemically administered ^{124}I-labeled derivative for PET imaging and dosimetry have been carried out to guide radioimmunotherapy with an ^{131}I-labeled counterpart [142]. Along these general lines, a class of very low molecular weight antibody derivatives known as affibodies (~6 kDa) show rapid circulation times, high stability and high target affinity. Preliminary proof of concept of this approach in targeting vascular endothelial growth factor receptor (VEGFR) has been obtained in an animal model of glioma [143].

5.2. Peptides and small molecules

Lower molecular weight radiopharmaceuticals such as peptide-based agents (1–2 kDa) or small molecules binding to specific cell surface receptors or other proteins are proving to be very successful in theranostic applications in solid tumors outside the CNS. Most notable is the theranostic application of somatostatin analogs in neuroendocrine tumors, which has now been applied for well over two decades and is clinically approved [144]. These classes of ligands show better diffusion and may achieve higher concentrations in the target tissue when administered systemically compared to higher molecular weight compounds. There is histological evidence of expression of somatostatin receptors in gliomas [145] and very high levels of expression have been demonstrated in grade 2 gliomas [146]. The potential for this approach has not been fully explored in clinical studies. There is poor correlation between histologically determined somatostatin receptor expression in gliomas and uptake of [^{68}Ga] somatostatin on PET imaging [145]. This again indicates that diffusion and BBB permeability issues may be impairing access to the target. However, findings from a small case series suggest that local injection of the therapeutic [^{90}Y]DOTA-TOC can provide lasting responses in progressive recurrent gliomas [147].

The prostate specific membrane antigen (PSMA) is highly expressed on neovasculature of various tumors including gliomas [148]. Preliminary evidence has shown a high target-to-background uptake ratio in PET imaging of gliomas [149] and higher uptake in HGGs compared to LGGs [150]. There is anecdotal evidence that this approach may be relevant to treating gliomas [151] but dedicated clinical therapeutic trials have not been conducted.

Intracavitary injection of radiolabeled substance P, a small peptide that binds the neurokinin-1 receptor which is highly expressed in gliomas and other cancers [152], has been evaluated in small case series. This peptide coupled to the chelator DOTAGA (DOTAGA-SP) was initially labeled with ^{111}In for imaging and ^{90}Y for therapy and applied in 12 patients in a dosimetry study [153]. Expansion of this series reported on results of therapy in 17 patients [154]. More recently the same approach has been utilized for therapy with the alpha emitters ^{213}Bi [155] and ^{225}Ac [156](Fig. 5), which have been monitored using PET imaging by co-injecting ^{68}Ga labeled peptide. These approaches, while safe and well tolerated, require validation in terms of efficacy.

5.3. Metabolism

Very low molecular weight metabolic substrates are rapidly diffusible and theranostic applications have been considered. While imaging applications have been relatively straightforward through standard PET labeling procedures, application of these drugs for therapy is quite challenging as there are limited possibilities for labeling these compounds with therapeutic radioisotopes without altering their biological properties. One of the few theranostic approaches attempted in the clinic is the use of iodinated phenyl alanine (IPA). [^{123}I]IPA has been used to image gliomas [157] and [^{131}I]IPA has been used in combination with external beam radiotherapy in glioma patients in a small case series [158]. A phase 1–2 study addressing this approach is currently recruiting (clinicaltrials.gov, NCT03849105).

6. Conclusion

Molecular imaging has been evolving rapidly over the past two decades and will have a significant role in improving our understanding of brain tumor biology and metabolism, aid tumor stratification, and may foster the discovery of new treatments [3]. The growing availability of hybrid PET/MRI systems and the possibility of obtaining multinuclear imaging opens up the possibility of using multimodal imaging to provide a wealth of information in individual patients [159]. Advances in imaging will pave the way for better outcomes from personalized care and identification of new targets. In parallel, there are extensive research efforts in expanding theranostic applications through development of new ligands, novel approaches for drug delivery and the application of more effective radionuclides such as alpha emitters. Future neuroradiological practice will be based on the integration of a multitude of diagnostic tools but will also have an increasing role on brain tumor treatments moving towards less invasive and more targeted approaches.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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