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Chapter 12

Imaging of Brain Tumours

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59981

1. Introduction

The last 20 years have seen a dramatic and rapid improvement in imaging technology. Developments in magnetic resonance (MR) imaging and more recently in positron emission tomography (PET) have allowed unique insights into tumour biology. Although careful evaluation this technology's clinical value is still being undertaken, improved imaging techniques have potential to assist many of the difficult problems currently faced in neuro-oncology. [1, 2]

One of the most significant clinical issues following treatment for high grade glioma is injury to the blood-brain barrier; so called pseudoprogression. [3] This results in oedema and apparent deterioration in the CT and MRI images, often associated with increased steroid dose. Brandes et al have highlighted the need for better imaging biomarkers for the problem of pseudo-progression. [1]

There are two potential outcomes of improved medical imaging for conventional imaging techniques currently adopted in the clinic. Firstly, treating clinicians may abandon treatment if imaging shows it to have an apparent negative impact. Secondly, if imaging shows that treatment regimes are not working, clinicians can decide whether or not to continue the current regime given the opportunity cost and risk of the treatment to the patient. As the number of treatment options slowly increase; the impact of this opportunity cost grows. In addition, data from a study by Stupp et al suggests the survival with glioblastoma treated with temozolomide is 14.6 months; [4] allowing clinicians little time to change treatment course.

Further insights into tumour biology could be gained from a better understanding of treatment efficacy. There is a need for better ways to choose patients for treatment, assess when these treatments are working and move onto something else when they are not. As an example, the

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benefit of temozolomide has been obscured to some degree by overestimating progression when MRI alone is considered. [5]

Increasingly, radiotherapy (RT) technology, often combined with new drug treatments, is allowing clinicians to treat more aggressively than could have been the case in the past. Modern radiotherapy is a complex chain of procedures. [6] If the tumour is poorly delineated; the risks of geographic misses increase. If the volume of treatment is too large, the toxicity increases and limits the dose that can be achieved.

Clinical trials involving brain tumour imaging face a number of difficulties. Brain tumours are relatively rare (excluding skin tumours; glioblastoma accounts for about 1% of tumours diagnosed in Australia), often making patient recruitment difficult. There are also difficulties with patient consent, as patients have frequent cognitive problems; especially when it comes to salvage treatment regimes. Imaging trials are difficult to perform - requiring blinded comparison of current best practice methods with and without the new modality. Finally, patients may require multiple imaging sessions on separate machines, requiring a significant amount of organisation. With each significant advance in imaging the studies may have to be repeated. It is no surprise that progress has been slow.

The Cancer Genome Atlas has shown us a vast amount about the complex biology of brain tumours such as glioblastoma. We are gaining "a window into its mutational landscape". [7] However, the more we know, the more complex the situation appears. U87, a commonly studied glioma cell line, has at least 512 homozygously mutated genes. [7] Targeted therapies are a last bearing fruit; as evidenced by CML treatment with imatinib or non-small cell lung cancer with EGFR inhibitors. We are moving from a single drug to the era of the rationally designed therapeutic regimen. Traditional response measures used in the chemotherapy era are much less successful when the response is cytostatic – as it is with many targeted agents. [8] The challenge is how to assess and integrate new agents within existing protocols.

2. Current imaging techniques

Computed Tomography (CT) provides good delineation of bony anatomy, can show haemorrage or hydrocephalus and can be useful in planning resection of lesions. In combination with PET; CT provides both improved anatomical localisation and improved PET images by allowing attenuation correction. Although CT is often the initial imaging modality used, it has a relatively small role in the investigation of brain tumours and has not been shown to be useful in response assessment or to accurately delineate tumour outlines. [9]

In radiation oncology practice; a planning CT is routinely used to define the shape of the patient and to provide an electron density map to allow modelling of the dose deposited by the radiotherapy beam. The tumour itself, however, is usually delineated on a contrast enhanced MRI fused to a non-contrast planning CT. MRI provides much greater anatomic detail of the structures within the brain. Additionally, with increased magnet strength and better design of coils, images obtained have steadily improved. MRI is routinely used for delineation of the tumour both in neurosurgical and radiation oncology practice. [10]

A contrast agent containing gadolinium is usually added to assist with interpretation. While it is has been established that MRI can identify oedema and necrosis along with tumour microstructure in great anatomical detail, as well as regions displaying dysfunction of the blood-brain barrier (BBB). However, it is often the case that these regions do not correlate with areas of infiltration or other neoplastic molecular events. [11] This is particularly concerning in low-grade gliomas, where the blood brain barrier may not be disrupted.

Recently the growth in the use of MRI has stimulated a body of research aimed at estimating electron density from the MR data and using this alone for radiotherapy planning. This avoids the necessity for a CT, reducing both treatment costs and patient radiation burden. [12]

A variety of MR sequences are usually obtained – T1/ T2/ DCE and spin echo. The detailed evaluation of a glioma patient usually involves about 45 minutes on the scanner for the patient and would usually be repeated about every 3 months.

Diffusion weighted imaging (DWI), or the more elaborate Diffusion Tensor Imaging (DTI), are developments of MRI based on the diffusion of water molecules. This diffusion occurs preferentially down the axons rather than across cell membranes. DTI post-processing can identify white matter fibre tracts within the brain, allowing ablative therapies (such as radiosurgery) to eloquent areas to be avoided. [10]

Spectroscopy can be useful in certain clinical scenarios, particularly when radionecrosis is suspected post radiotherapy. It is most commonly undertaken using proton nuclei on commercial scanners. [13] Ratios of choline to N-acetyl aspartate (NAA) have been found to correlate with tumour tissue. [13] NAA, associated with mature neuronal cell density, [14] is decreased in tumours, while choline, involved in cell membrane turnover, [14] is increased, leading to an increase in the ratio of choline/NAA. [13] However, Horska makes the point that spectroscopy looks very different depending on the zone of the tumour being examined (necrotic core, actively growing tumour or peritumoural oedema) [13]. In clinical practice, spectroscopy is complicated by the need for large voxels; limiting the resolution and application in small lesions. There have been attempts to incorporate wider field MRS in radiotherapy planning; even using whole brain acquisition. [14] With the limitation of difficulty in the anterior cranial fossa and prolonged scan time; it looks potentially useful. Spectroscopy's clinical role currently is to provide confirmatory information to other modalities.

The issue of response assessment is critical to development in neuro-oncology, from early phase testing of drugs through to community oncology clinics delivering care to patients. The traditional approach to tumour response has been to base assessment on the change in size of the lesion. Volumetric criteria perform poorly in slowly growing lesions such as low grade glioma. [15] Initially, response assessment was based on two dimensional imaging (MacDonald criteria) of high grade lesions but it was appreciated that these criteria did not account for non-enhancing progression and so Response Assessment for Neuro-Oncology (RANO) criteria were developed. [9, 15]

CT and MRI are not sensitive for early malignant transformation – a significant problem with low grade glioma. The usual clinical situation is – has the patient progressed? The MRI is very difficult to interpret for the 3 months post chemo-radiotherapy. Limitations of both CT and

MRI have led to the increased interest and development of functional imaging. [16-18] Combined PET-MR scanners are finding their way into the clinical setting and may become more than the sum of their parts. It is clear to us that the skill set required for development runs across chemistry, medical physics, pharmacology, computational informatics, radiology, nuclear medicine and clinical oncology. [19] This chapter will concentrate on the clinical applications across a number of entities and review where advanced imaging may help us improve treatment.

3. Metabolic imaging of the brain

PET imaging involves injection of a radioactive tracer, which undergoes decay, with positron emission. Positrons collide with electrons, resulting in positron annihilation and the emission two photons at 180 degrees, detected by the scanner's detector ring. Following the acquisition, detected events are reconstructed into an image. PET scanning can be performed in static or dynamic mode. In static mode, a single PET image is acquired which is a sum of all events detected during the period of the scan. From this, a measure of tumour-to-background contrast can be used to provide both qualitative and quantitative results. In dynamic mode, the scan is divided up into temporal segments, allowing an insight into the pharmacokinetics and temporal path of the tracer, with kinetic modelling offering quantitative measures that can provide insights into tumour biology. Although dynamic imaging has been shown to provide more information, static acquisitions are still considered the norm in the clinical setting largely due to time and data storage constraints.

3.1. PET radiotracers

A large number of radiotracers have been developed for clinical imaging with many investigated for brain tumours. Selection of an appropriate radiotracer is critical for the investigation being performed, as many target a specific molecular process. A list of common radiotracers used for brain tumour imaging is presented in Table 1.

Radiotracer	Abbreviation	Molecular Target
[^{18}F]Fluorodeoxyglucose	^{18}F-FDG	Glycolysis
6-[^{18}F]fluoro-dihydroxy-l-phenylalanine	^{18}F-FDOPA	Dopamine / Amino acid transport
[^{18}F]fluoromisonidazole	^{18}F-FMISO	Hypoxia
[^{11}C]-L-methionine	^{11}C-MET	Amino Acid Transport
O-(2-[^{18}F]fluoroethyl)-l-tyrosine	^{18}F-FET	Amino Acid Transport
3-deoxy-3-[^{18}F]fluorothymidine	^{18}F-FLT	Thymidine Kinase Enzyme

Table 1. Common radiotracers used for imaging of brain tumours.

It should be remembered that the difficulty in synthesis and half-life of many of these tracers varies greatly. This can limit their availability, especially in areas with a widely dispersed population. The ultimate utility of an imaging molecule depends on a combination of cost, benefit over other modalities, availability and half-life of the tracer.

3.2. ^{18}F-Flurodeoxyglucose (FDG)

Tumours such as glioma have a predisposition for increased proliferation and metabolism and there is a wealth of literature investigating the clinical applications of FDG,. These include comparison to MRI [20], detection of glioma [21-28], tumour grading [29-36], choice of biopsy site and radiotherapy planning [37-39], detecting tumour progression [40], recurrence and necrosis [41-53], predicting prognosis and survival [54-58], and patient follow up [59]. FDG PET has the advantage that it is available in most centres due to its wide, relatively simple synthesis and low cost of production. However, the literature highlights numerous limitations in application to brain tumours. The brain is an obligate metaboliser of glucose,. This results in a higher tracer uptake in normal brain tissue. While high-grade gliomas such as glioblastoma are still detectable over background uptake, low-grade and slow progressing tumours often show uptake equal to that of surrounding normal tissue. Other pathologies such as inflammatory diseases can cause tracer up regulation, [60] leading to false positive diagnoses. More sensitive scanner technology has improved this to some degree but a number of studies have been performed exploring alternative radiotracers that may be more useful in brain tumour imaging, such as [^{11}C]-L-methionine (MET), 6- [^{18}F]fluoro-dihydroxy-l-phenylalanine (FDOPA), O-(2- [^{18}F]fluoroethyl)-l-tyrosine (FET) and 3-deoxy-3- [^{18}F]fluorothymidine (FLT).

3.3. [^{11}C]-L-Methionine (MET)

MET is an amino acid. MET has advantages over FDG due to both its low cortical uptake and high uptake in neoplastic tissues. (i.e better signal to noise ratio) Methionine is involved in protein synthesis, energy production. I t is clear that MET is a powerful diagnostic tool for the detection of primary [61-66] and recurrent [42, 52, 62, 66-70] glioma, as well as having some benefit in prediction of survival. [30, 55, 71-74] Numerous investigations have been performed comparing the diagnostic accuracy of FDG and MET, with reported findings clearly showing the superiority of MET in detection [21, 30, 75] and grading [30, 31] of primary glioma. Conflicting reports have been published, however, regarding the benefit of MET in detection of recurrent glioma. [20, 21, 41, 42, 47, 52]

The ability to provide complimentary information to that of MRI is a key strength of PET, assisting in diagnosis and treatment planning where differential diagnosis on MRI alone is difficult. However, while findings have been published showing the superiority of MET over standard MRI protocols for both primary [61] and recurrent [76] glioma, dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSCE MRI) [77] and perfusion MRI [45, 78] have been shown to be superior to MET PET for tumour detection.

Conflicting findings have been reported for the use of MET PET for grading gliomas. Ceyssens et al [74] and Moulin-Romsee et al [79] reported that MET could not differentiate between

glioma grades. However, Singhal et al [30] found that MET could discriminate between high and low-grade gliomas and Miyake et al [31] and Santoni et al [62] found the tracer could discriminate between grades II and IV and grades II, III and IV, respectively.

While the literature does support the integration of MET PET into the clinical setting, there remain two significant caveats for the tracer. The half-life of ^{11}C isotopes such as MET is considerably short at 20.3 minutes, limiting this isotope and its tracers to centres with onsite production capabilities. Finally, similar to FDG, MET accumulates in inflammatory lesions, complicating differential diagnosis.

3.4. 6- [^{18}F]fluoro-dihydroxy-l-phenylalanine (FDOPA)

An alternative to MET is 6- [^{18}F]fluoro-dihydroxy-l-phenylalanine (FDOPA), a tracer that is commonly used for the assessment of Parkinson's Disease and other neurodegenerative diseases. However, a case study was published in 1996 by Heiss et al [80] revealed the tracer's potential application to brain tumour imaging. While investigating a patient with suspected Parkinson's disease, F-DOPA uptake was visualized in a small region of the brain later pathologically confirmed to be a low-grade glioma. This discovery generated significant interest in FDOPA, with the subsequent literature showing that it provides complimentary information to that of MRI, assisting in diagnosis, prognosis and guiding treatment in primary and recurrent glioma patients.

Studies by Ledezma et al [81] and Karunanithi et al [82] have shown the potential for FDOPA to provide information complementary to that of MRI. Ledezma et al showed that using FDOPA PET along with MRI provided a good mechanism for detecting lesions in primary and recurrent glioma. Karunanithi et al compared the two modalities, finding that FDOPA PET was able to detect tumour recurrence in more cases that MRI. Hence, while MRI is currently implemented in the diagnosis and treatment of glioma, these studies support the potential of FDOPA as modality for complimentary assessment to MRI. Specifically, ^{18}F-FDOPA could have utility where the MRI findings are negative in primary/recurrent tumours or inconclusive in recurrent tumours.

A number of studies have been performed comparing the efficacy of FDOPA PET to that of other radiotracers such as FDG, FLT, FET, Ammonia (NH3) and MET. Investigations performed by Chen et al [50], Tripathi et al [28], Jora et al [27] and Jacob et al [83] all reported that FDOPA PET was more specific and sensitive to detecting primary and recurrent lesions than FDG. Tripathi et al and Jacob et al also showed that FDOPA PET was more sensitive than FLT and ammonia, respectively.

Given the aforementioned drawbacks of MET, Becherer et al [84] investigated FDOPA as a potential alternative, finding that both tracers had similar standard uptake values (SUVs) and almost identical patterns of spatial uptake.

Many factors are considered in determining prognosis of patients including Karnovsky performance status (KPS), age, tumour size, extent of surgery and tumour grade and histology. In addition, Karunanithi et al [85] have shown that numerous indices derived from FDOPA PET were independent predictors of survival, with Dowson et al further corroborating these

http://dx.doi.org/10.5772/59981

findings by showing that the uptake changes in the most treatment resistant region of tumour post-treatment are predictive of survival.

Another potential application of glioma PET imaging currently under investigation is tumour grading. Confirmation of a glioma diagnosis generally involves surgical biopsy or resection followed by a pathological assessment to determine tumour microvascularity. [86] There are some limitations to performing biopsies. Firstly, biopsy is an invasive procedure, sometimes not possible due to the anatomic location of the tumour, or the condition of the patient. Secondly, as biopsy tissue samples often represent only a small part of the entire tumour, there is a chance that the true tumour grade will be underestimated, as different tumour regions may be of a different grade. [74] Finally, surgery of certain regions may involve surrounding normal brain tissue, exacerbating the prognosis by causing additional neurological morbidity or dysfunction. [87] While FDG has been investigated for glioma grading, alternatives to biopsy methods are yet to be widely implemented in the clinical environment.

Numerous investigations have been performed in an attempt to discriminate high-grade gliomas from low-grade using FDOPA. However, reports are conflicting. Studies by Fueger et al [88], Pafundi et al [89] and Nioche et al [90] reported that FDOPA PET could discriminate between high and low-grade primary glioma. However, as part of their study, Chen et al found no significant difference in FDOPA uptake between the two classes. For recurrent glioma, only Nioche et al was able to discriminate between high and low-grade, while neither Fueger et al nor Kratochwil et al could differentiate the grades in their cohorts. While these studies do suggest that FDOPA has the potential to discriminate between tumour grades in newly diagnosed gliomas, further investigation is needed, especially for recurrent tumours.

While there are clear clinical benefits to using FDOPA for the assessment and management of patients with glioma, this tracer comes with its own set of caveats. The main drawback of FDOPA is synthesis. The most widely used method for FDOPA synthesis uses an electrophilic approach, based on a two-step process. [91, 92] A fully automated method for synthesis of FDOPA is now also available. [93, 94] However, there are limitations with this approach, such as the requirement of additional equipment, precautions for dealing with ^{18}F in gaseous form, and the low radiotracer production rate. [95, 96] Recent developments have seen the introduction of nucleophilic approaches. [97, 98] In contrast to electrophilic, nucleophilic pipelines produce ^{18}F in liquid form. In addition, nucleophilic methods for production of FDOPA are similar to that of FDG and thus require less additional equipment than electrophilic-based synthesis. Finally, the recent availability of single-use synthesis cassettes for FDOPA could make it more readily available..

3.5. O-(2- [^{18}F]fluoroethyl)-l-tyrosine (FET)

O-(2- [^{18}F]fluoroethyl)-l-tyrosine (FET) has also been widely investigated for imaging of brain tumours. FET is one of the first amino acid radiotracers that can be synthesised in large amounts for clinical purposes. Unlike MET and FDG, it has been shown in animal models that FET exhibits low uptake in inflammatory lesions.

A number of studies have been performed investigating FET in brain tumour imaging, with findings strongly supporting the use of the tracer for detecting both primary [99-10][4] and recurrent [52, 100, 105-108] glioma and showing superiority in detection, [25] treatment planning [24] and biopsy planning [24, 38] to that of FDG PET.

A key strength of FET PET is its apparent ability to differentiate between different grades of glioma. While some studies report that static imaging alone can provide the information necessary to grade tumours in vivo, [109-111] kinetic analysis from dynamic imaging appears to be superior for both primary [102, 110, 112, 113] and recurrent [114] cases. A combination of MRI, DWI and FET PET indices has also been investigated for grading tumours, providing promising results. [115]

In addition, like other radiotracers, FET PET has been investigated as a possible tool for predicting prognosis, [71, 100, 116-120] treatment planning, [121] and monitoring treatment response [122-124] with findings from all studies supporting its use.

Compared to FDG and MET, FET is a relatively new radiotracer, with the first human experiments performed in the late 1990s. It has been shown to be a cost effective tracer for adoption into the clinic, [123, 125] and future studies could see this tracer being brought closer towards clinical translation.

3.6. 3-deoxy-3- [^{18}F]fluorothymidine (FLT)

3-deoxy-3- [^{18}F]fluorothymidine (FLT) is another recently developed amino acid radiotracer that has been investigated for imaging of brain tumour proliferation. [126-131] FLT is an analogue of the thymidine nucleoside, altered to prevent it from following the full biochemical pathway of the nucleoside. Once the tracer is diffused into the cells by active transport, it is phosphorylated but not incorporated into the DNA, thus it becomes trapped within the cell.

FLT has been shown to effectively detect both primary [28, 132] and recurrent [22], [49, 127, 130, 133, 134] tumours, with a large body of work supporting it as a prognostic factor in both cases. [101, 135-141]

Further research has investigated FLT PET as a tool for assessing treatment response [142-145] as well as tumour grading. [129, 132, 134] A study by Jeong et al also found that FLT PET uptake in recurrent glioma correlated with the initial grade of the tumour.

However, despite the body of work supporting FLT as a surrogate biomarker for proliferation, [126-129] its use remains controversial [131, 146] and further studies are warranted to fully elucidate the role of FLT in future clinical practice.

3.7. Hypoxia and ^{18}F-Flouromisonidazole (FMISO)

Hypoxia has been shown to have a significant effect on treatment outcome for patients diagnosed with glioma. Low oxygen tension correlates with radioresistance, resulting in the development of local recurrence or metastasis. [147-149] It is well known that hypoxic tumour cells are significantly more resistant to radiation than normoxic cells, as the lack of oxygen inhibits permanent DNA damage. In fact, it has been shown that up to three times the radiation

dose is required to kill hypoxic cells. [150] While cell hypoxia is rare in normal tissue, it is a common occurrence in many solid tumours; [41, 42] classified as acute, chronic or anaemic.

Cells become acutely hypoxic when they are temporarily deprived of oxygen due to the closure or disruption of blood vessels, often caused by the hostile nature and abnormalities within the tumour environment. The abrupt changes in vasculature prevent the supply of oxygen and other nutrients to the cells. Upon return of oxygen to the cells, often due to angiogenesis or vasculogenesis, cells become normoxic again. Chronically hypoxic cells on the other hand, are cells that will remain hypoxic until they become necrotic, often due to the tumour outgrowing its blood supply or proliferation pressure forcing cells away from blood vessels. [151] In fact, necrosis is a requirement for the diagnosis of glioblastoma; as the highly proliferative nature of the tumour forces it to outgrow the blood supply in areas, resulting in a necrotic core usually visible from MRI. Anaemic hypoxia results from low oxygen concentrations within the blood supply and can be due to either pathology or the treatment itself.

There are numerous methods available for measuring hypoxia, both in vivo and in vitro, with the polarographic needle electrode regarded at the gold standard. While this method has been used extensively to assess hypoxia, [39, 44, 49-55] there are concerns with this approach. [74] Firstly, since the needle is invasive, not only is it uncomfortable for the patient, but there also exists a risk that it may cause trauma to the sample site, resulting in exacerbation of injury. Secondly, since only a small sample of the tumour is assessed, there is a risk of underestimating the level of hypoxia. Other, non-invasive methods exist for hypoxia assessment, including phosphorescent imaging, [152-154] which exploits the oxygen-depending quenching of phosphorescence, blood oxygen level dependent (BOLD) MRI, which is able to identify hypoxic vasculature using paramagnetic properties of deoxyheamaglobin, ^{19}F MRI, [155] which utilizes the linear relationship between ^{19}F and tissue oxygen concentration, and near infrared spectroscopy (NIRS), [156-159] which exploits the low absorption of near infrared wavelengths by tissue chromophores.

In addition to the above methods, there is now significant interest in the use of PET radiotracers for assessing tumour hypoxia. Many radiotracers exist for investigating tumour hypoxia [160-170], including ^{18}F-HX4, ^{18}F-FAZA, ^{18}F-EF5, [124]I-IAZA, [123]/ [125]I-IAZP, ^{64}Cu–ATSM, ^{18}F-FENI, ^{62}Cu-diacetyl-bis(N^4-methylthiosemicarbazone), ^{18}F-FETA, ^{18}F-EF1 and [^{18}F]fluoroerythronitroimidazole. However, ^{18}F-Fluoromisonidazole (FMISO) PET is clearly the most widely used, as it provides the best compromise between sensitivity, specificity and invasiveness.

FMISO is a derivative of nitroimidazole, which is metabolized by intracellular nitroreductases at low oxygen concentrations. They form covalent bonds with macromolecules and become biochemically trapped within these hypoxic cells. [171] This has been shown to occur in oxygen concentrations below 10mmHg [70], [71]. Nitroimidazole metabolism relies on active enzymes and thus does not get absorbed by necrotic tissue.

The first to investigate FMISO as a potential hypoxia imaging agent was Valk et al, [172] who elegantly showed that high-grade gliomas were clearly delineable 40 minutes post-injection

of the tracer. Since this pioneering work, many studies have been performed on both humans and animal models, bringing this tracer closer to clinical translation.

Further research has compared FMISO PET to other imaging modalities such as MRI and FDG PET. MR imaging sequences such as FLAIR, T_2 and contrast enhanced T_1 are regularly used in the diagnosis, treatment planning and treatment evaluation of glioma. However, there are limitations with MRI as described above, especially for low-grade glioma, due to the invasive nature of glioma beyond areas of BBB disruption. Hypoxia has been shown to promote neovascularization through the angiogenic cascade and other molecular signalling events, leading to leakage of the blood-brain barrier. [173, 174] Hence, an understanding of the relationship between hypoxia, as assessed by FMISO PET and MR imaging may lead to an improved understanding of tumour physiology.

Studies by Spence et al, [175] Swanson et al [176], Szeto et al [177] and Kawai et al [178] have confirmed that a relationship does in fact exist between the two imaging modalities. Spence et al showed that hypoxic regions delineated using FMISO PET correlated with contrast enhanced T_1 defined regions. This result was verified by Swanson et al, who reported on two important findings in their study on pre- and post- operative glioma patients: regions of hypoxia correlated with MRI defined volumes; and regions of hypoxia were not restricted to inside MRI defined volumes. Further corroboration came from Kawai et al, who found that individual hypoxic volumes significantly correlated with volumes defined on contrast enhanced T_1. Finally, Szeto et al used a mathematical model adopted from Swanson et al to show that regions of hypoxia correlated with quantitative measures of tumour aggressiveness and sphericity.

It is well established that hypoxic cells can increase their glycolysis to maintain energy levels, suggesting that a relationship between hypoxia and glycolysis does exist. However, proliferation is considerably inhibited in chronic hypoxia, significantly reducing glycolysis. [179-181] This suggests that a complex relationship may exist, the understanding of which may lead to a more comprehensive understanding of the tumour microenvironment.

Investigations by Rejendran et al, [182] Hatano et al [183] and Cher et al [184] have confirmed that any relationship that may exist between the two microbiological processes is complex. While Rejendran et al and Hatano et al found little to no correlation between FMISO and FDG Uptake, Cher et al found that a correlation did exist within individual tumour grades. These results suggest that complementary information can be obtained from FDG and FMISO imaging. However, further studies are warranted to fully elucidate any relationship between the two tracers.

Accurate grading of glioma cases is imperative for both patient prognosis and treatment planning, as patients diagnosed with higher-grade glioma fair significantly worse compared those with lower grade. While necrosis, usually visualized with MRI, is a key requirement for diagnosis of glioblastoma, the most widely accepted method for grading is pathological assessment from biopsy. However as described previously, there are concerns with this approach: Biopsy is not always possible due to tumour location; where biopsy is possible, further neurological dysfunction is a risk with such an invasive procedure; and the sample

only represents a small section of the tumour volume, possibly resulting in an underestimation of the tumour grade.

However, studies into FMISO PET have found that tracer uptake correlates very well with tumour grade, offering up a non-invasive method for tumour grading. Cher et al, [184] Hirata et al, [185] Yamamoto et al [186] and Kawai et al [187] all reported a higher uptake of ^{18}F-FMISO in glioblastoma patients than all other grades. While Cher et al and Hirata et al reported no tracer uptake in lower-grade tumours compared to normal tissue, Yamamoto et al and Kawai et al reported higher uptake in grade III than surrounding cortex. These results suggest that, at the very least, FMISO PET could be used to confirm a diagnosis of high-grade (grade III-IV) glioma. However, further studies are needed to conclude distinction between grade III and IV cases.

Probably the most fascinating property of hypoxia is its apparent strong negative correlation with patient prognosis, which has been investigated since the development of the polarographic electrode needle. Cher et al [184] and Hirata et al [185] both reported FMISO PET defined hypoxia as a significant negative prognostic factor, with Cher et al able to predict the site of recurrence in two patients from ^{18}F-FMISO images. Spence et al was also able to correlate FMISO PET images with time-to-tumour-progression (TTP), survival and KPS. Finally, Swanson et al was able to negatively correlate FMISO PET images with patient survival in pre-operative cases of glioblastoma. These studies add to the growing body of evidence that suggests hypoxia is a key factor in treatment success and patient survival.

Finally, Valable et al [188] performed an investigation into hypoxia and the anti-angiogenic treatment sunitinib. Anti-angiogenic treatments were proposed as a possible cancer therapy, as they target VEGF pathways, leading to a decrease in tumour vasculature. However, treatment results were disappointing, with treatment benefits being temporary, leading to a short increase in time to progression at best. However, the concept of vascular normalisation rekindled the idea of anti-angiogenic treatments, whereby therapy improves tumours vasculature, reducing tumour hypoxia and improving the efficacy of radiotherapy. Valable et al showed in a mouse model that tumours treated with sunitinib had a significant decrease in FMISO PET after 7 days, suggesting that the use of anti-angiogenic treatments may be viable to improve tumour oxygenation and therefore radiotherapy treatments.

The body of work surrounding hypoxia strongly suggests that important information can be obtained from F-MISO PET imaging of glioma and, while more needs to be done to fully elucidate tumour biology, it is clear that hypoxia is an important aspect of future treatment for patients diagnosed with glioma.

3.8. Dual-tracer imaging (multiplexing)

The current literature strongly supports the idea that, given the complex and heterogeneous nature of glioma, knowledge of multiple biological characteristics is needed for effective patient treatment. For example, amino acid activity from FDOPA PET, proliferation from FLT PET and hypoxia from FMISO PET. Currently, however, the physical limitations of PET imaging prevents ascertaining information from two radiotracers simultaneously. Thus, to

acquire the necessary biological information, PET acquisitions must be performed on separate days, allowing the first radiotracer to decay.

Unfortunately, however, there are many disadvantages to this approach. Firstly, performing multiple PET acquisitions requires that the patient be prepared multiple times, significantly increases the scanner time and increases the associated costs. Secondly, performing acquisitions on separate days introduces spatial uncertainty in two ways: Tumour evolution between scans can be significant, especially given the aggressive nature of glioma. In addition, registration of the images introduces uncertainty due to change in patient positions and image artefacts. This, however, can be mitigated provided there is enough mutual anatomical information available between the two scans.

With the need to image multiple biological characteristics becoming evident, and the obvious inherent logistical limitations in performing multiple scans, the field of dual-tracer imaging is gaining momentum.

Dual-tracer imaging, or multiplexing, allows for imaging of multiple PET radiotracers within a single scanning session by employing novel post-processing techniques to separate the two tracer signals. This approach trades-off tracer signal fidelity for logistics, circumventing some of these issues encountered when performing multiple acquisitions: The patient need only be prepared for scanning once; the required scanning time is shorter than that of two individual acquisitions; tumour evolution between the two images is negligible; and, provided the patient does not move during the scan, registration is no longer required.

However, this technique has one major logistical limitation, requiring that multiple radiotracers be synthesized and available at the same time. This is a difficult task in most centres, as simultaneous synthesis of two ^{18}F radiotracers, for example, would be impossible without two cyclotrons. This limitation may be mitigated, however, by either using radiotracers with differing isotopes and/or synthesis methods, or using radiotracers with sufficiently long half-lives that allow the two tracers to be synthesized consecutively before application.

Since dual-tracer imaging was first proposed by Huang et al, [189] a number of methods have been proposed and can be loosely grouped by their method for signal separation. Methods that allow both tracers to be injected simultaneously reduce the scanning time but require that both tracers have different half-lives, with signal separation performed by exploiting the difference in tracer decay rates. Such methods include those by Huang et al, [189] who investigated ^{13}N, ^{18}F, ^{68}Ga and ^{64}Cu isotopes in phantoms, Figueiras et al, [190] who investigated FDG and ammonia in both phantoms and an ischemic rat model, and Kadrmas et al, [191] who exploited differing decay rates in conjunction with differing kinetics and distribution for FDG, ATSM and PTSM. Other methods, such as those by Koeppe et al [192] and Kadrmas et al, [193] employ a staggered injection that allows for the discrimination of tracer signals with the same half-life, increasing the selection of available radiotracers that can be used. Both methods rely on kinetic modeling to separate the two signals. In addition, Verhaeghe et al [194] and Ikoma et al [195] proposed methods that exploit differing tracer half-lives in addition to a staggered injection interval and kinetic analysis to separate tracer signals.

The above studies propose methods that require scanning to be initiated at the injection of the first tracer. To reduce the required scanning time further, a study by Bell et al [196] investigated separation of two ^{18}F radiotracers by staggering the injection interval and initiating the PET acquisition once the first tracer had reached steady state. Using this method, scanning time was only increased by 10 to 20 minutes over a standard PET acquisition.

Finally, two studies have been performed investigating performing signal separation at the reconstruction level. Gao et al [197] and Cheng et al [198] incorperate kinetic modelling into the reconstruction process to separate tracer information.

Dual-tracer imaging offers a viable alternative to performing multiple PET acquisitions, with the above methods illustrating its potential in future research practices. However, further studies are required to fully develop the concept of simultaneous multiplexing, with particular attention to circumventing the logistical issue of simultaneous radiotracer synthesis.

4. Clinical applications

Medical imaging is important at many junctures during the course of the treatment path for glioma patients, from the initial diagnosis and grading of the disease to planning and assessing response to therapy. MRI is the gold standard for obtaining morphological information on tumours, but has some limitations as mentioned previously. One role of imaging is in establishing a continually updated prognosis at all stages during treatment. So in addition to detecting and localising tumours, the differentiation of treatment induced pseudo-progression from recurrence is important. The latter is a particular challenge, as is establishing the grade of diffuse tumours and the late identification of recurrence. [199]

Non-structural MR modalities can assist in overcoming the difficulties of differentiating recurrence from post treatment radiation effect. A previous study [200] examined the use of relative cerebral blood volume, and measured a sensitivity of 92% with a specificity of 100%. Relative cerebral blood volume (rCBV) has shown superior abilities in distinguishing recurrence from radiation necrosis than either FDG or MET-PET. [45]

The sensitivity of molecular imaging techniques such as PET can be used to surmount some limitations of MRI, [16] for instance FDG, the most widely used PET tracer, can predict anaplastic transformation in low-grade gliomas. However PET should be used in conjunction with anatomical imaging as greater sensitivity and specificity is demonstrated when PET is combined with MRI. [16] In clinical practice, PET is considered useful for resolving ambiguities between recurrence and treatment induced changes. [201] It is broadly acknowledged that the augmentation of MRI and CT with other modalities such as PET, SPECT and diffusion imaging may assist in differentiating treatment effects from progression, but more research is needed, [202, 203] and efforts have been made to standardize assessments when considering metabolic imaging modalities, at least when using FDG. [204] As mentioned however, although FDG has demonstrated efficacy for many oncologic applications, it is of less utility in cortical regions where healthy tissue has high FDG-avidity preventing the unambiguous differentiation of

normal and neoplastic tissue. FDG retains some utility for glioma applications, for instance in a study of 19 patients changes in glucose metabolism measured using FDG-PET predicted response to temozolomide, but not when combined with radiotherapy. [205]

Amino acid tracers, such as MET and F-DOPA. are more sensitive for imaging recurrent tumours, especially LGG, [16] as amino acid transport is up-regulated in malignant lesions. [206] Some debate exists around the relative efficacy of different amino-acid tracers, with a number of tracers examined in the literature. [52] MET is popular choice due it its relative ease of synthesis [207] MET-PET is a better prognostic predictor and improves inter-observer consistency compared to FDG, [42] although it is noted combining FDG with MET further improves prognostic predictions. However, the aforementioned limitations with the half life of MET have seen FDOPA to be a viable alternative to MET, which more accessible in the clinic due to its longer half-life. [84]

FDOPA precisely localizes tumours as verified on MRI [81] and can also identify tumour not visible on MRI. FDOPA has also been shown to better identify regions of higher density disease than MRI on a study examining 23 biopsy specimens from 10 patients. [89] When evaluating 28 of 30 patients on anti-angiogenic therapy, the absolute volume based on FDOPA two weeks after initiation of therapy, was the most significant predictor of overall survival. [208] This slightly out-performed MRI, possibly implying that the overall tumour burden is a factor in survival, and that metabolic images potentially provide better estimates of disease burden. Such early yet accurate predictions of treatment response offer the potential to select more appropriate therapeutic strategies.

FLT has also been examined as an alternative to FDG for the purposes of estimating tumour margins, and in a study of 25 patients, FLT demonstrated greater with Ki-67 proliferation index. [127] FLT demonstrated superior performance to MET in the grading and assessment of proliferation in 41 newly diagnosed glioma of different grade, [132] with no complimentary information being observed. In comparison to FDOPA, the kinetic parameters of FLT were more predictive of overall survival in 126 glioma patients treated with Bevacizumab-Irinotecan, [145] although combining the modalities further improved predictive performance. However, for low grade glioma FDOPA offers better visualisation than either FLT or FDG for primary and recurrent low grade glioma. [28]

Considering low grade glioma in particular, FET has demonstrated efficacy. [209] In a retrospective study of 59 patients [210] found that the presence of FET uptake was not predictive of outcome, but in the subset of 30 patients with abnormal uptake and dynamic data, a decrease in FET was significantly predictive of outcome. FET PET has also accurately predicted antiangiogenic treatment failure in 11 patients, predicting treatment failure earlier than MRI alone. [211] However changes in FET was found to only be prognostic in astrocytic tumours and not for oligodendral tumours in a cohort of 83 patients. [212]

However, in addition to assessing glioma at the various stages of treatment, functional imaging has a role to play in the treatment of the disease by supplying metabolic information during the planning of surgery and of radiotherapy. The augmentation of MRI with PET to assist surgical planning, has demonstrated the potential to improve cost effectiveness for two

scenarios of varying disease severity. [213] Recently, a fluorescent biological markers that is tumour specific, 5-Aminolevulinic Acid (5-ALA), is becoming available following its proposal and the improvement in progression free survival in stage III trials. [214] 5-ALA is efficacious not only because tumour remains easily identifiable despite tissue movement, but because anaplastic foci are not always detectable on MRI. However 5-ALA is less sensitive than FET for low grade glioma, [215] although for high grade glioma regions of high FET uptake also fluoresce. Even so there is some motivation for the use of PET during surgical planning even when in-vivo biomarkers are available, especially since the greater tumour extent made visible by FDOPA imaging compared to MRI has been revealed by biopsies to be pathological in almost all cases. [89] The latter result also has implications for radiotherapy planning.

The availability of PET imaging influences the definition of GTV when it is used to augment MR images, which has the benefit of reducing inter-observer variability and better sparing normal tissues, at least for some oncology applications. [216] A further study [121] examined patterns of failure in a cohort of 10 patients, and found that treatment failures are generally in the central region, but that neither FET-PET nor MRI optimally predicted recurrence, and that the two modalities were complementary. However inadequate coverage of GTVs as defined by increased MET-PET activity in 5 of 34 patients were associated with an increased risk of treatment failure. [217] Such contradictions mean that although the potential of PET to assist radiotherapy planning is acknowledged, more research is required before consensus is reached on what strategy should be used to define treatment volumes. [218]

Although increased metabolic activity is useful to establishing target volumes, the margins added for infiltration and patient movement to respectively obtain clinical and planned target volumes are probably sufficient to prevent geographic misses, and focal radio-resistance plays a larger role in recurrence. A recent study [219] showed that the uptake in focal regions was a better predictor of recurrence, than uptake over the tumour as a whole, highlighting the importance of intra-tumour heterogeneity. The importance of heterogeneity was confirmed for FDOPA in a study examining high-grade gliomas, [220]where focal uptake was significantly correlated with survival time while tumour-global uptake was not. At the intra-tumour scale, patterns of FET kinetic parameters have been correlated with histopathology in suspected grade II gliomas, and focal regions of anaplastic change were identified. [103]

Given the large treatment volumes, the fact that treatment failure is typically focal, and that the radio-resistance associated with local hypoxia is a contender for the cause of treatment failures, the imaging of hypoxia in conjuction with MRI could have greater efficacy than imaging using amino-acid tracers. FMISO is a PET tracer that can be used to identify hypoxic regions.

Typically only static PET images are analysed, but PET is intrinsically a dynamic modality and kinetic analysis of the dynamic data contained by PET images can reveal supplementary biological factors that are of clinical relevance. Hence, the kinetic analysis of PET data is of increasing interest, for instance Pyka et al [219] demonstrated that recurrence can be best predicted using parameters derived from dynamic data in cohort of 34 patients, and static uptake had a lower significance for low grade gliomas. The kinetics of PET uptake have been investigated for some time. Kinetic parameters derived from FDOPA demonstrated the

potential to distinguishing between low and high grade gliomas for 37 patients. [221] Ellingson et al [222] have also proposed using parametric response maps to evaluate treatment response, especially for slow growing tumours. FET-PET has been shown to predict recurrence on a cohort of 14 patients with a sensitivity of 83% and a specificity 88% [219], when using the relative slope of FET uptake. Parameters derived from dynamic PET appear to offer advantages over the analysis static PET images for FET, when applied to grading gliomas. [114]

The role of medical imaging varies depending on type and grade of tumour in addition to the clinical application. When planning the surgery of low grade glioma, the intrinsic plasticity of the brain can be established using fMRI and diffusion imaging to better trade-off the resection of tumour tissue with the prevention of damage to eloquent areas. [223] PET has applicability in a wide range of clinical settings including biopsy guidance, estimating the true extent of tumours, establishing a prognosis, planning resections, detecting recurrence and monitoring therapy, [224] but benefits fewer patients for radiotherapy planning. [225] For low grade glioma the most promising PET tracers appear to be the amino acid markers FET and MET. [224] Examples of the complementary nature of PET to MRI have been noted by Berntsson et al, [226] where no correlation between tumour metabolism (MET uptake) and vascularity was found, and Rahm et al [227] where no agreement between FET uptake and anisotropic diffusion occurred. The pattern of MET uptake has also been found to differ from the pattern of neuronal cell loss and membrane proliferation shown by Cho/NAA ratios obtained from MRS and should potentially be taken into account when planning biopsies. [228]

FDOPA was found to be prognostic of low grade gliomas with non-enhancing T2 changes on MRI in a cohort of 93 patients by Rangan et al. [229] FET was also found to be prognostic in 59 patients by Jansen et al, [210] who found a rapid roll-off uptake dynamics to be predictive of shortened progression free survival although lack of uptake was not indicate of indolent disease. The pattern of uptake MRI uptake (circumscribed versus diffuse) augmented with FET PET has been found to significantly predict malignant transformation in 33 patients. [230] FET has also been used to establish whether brain lesions are neo-plastic. [111]

Static FET uptake when normalized to background is useful for predicting the malignant transformations, as is the dynamic parameter time-to-peak, [112] although the repeated PET scans suggested to detect malignant transformation early might not be possible in general clinical practice.

PET has potential utility in radiotherapy planning for recurrent and high-grade glioma. In a study of 39 patients with high-grade glioma MET defined gross tumour volumes exceeded those of MRI defined volumes in 74% of cases. [68] For the re-irradiation of recurrent high-grade glioma, in a cohort of 44 patients, patients planned using metabolic imaging (MET-PET and IMT-SPECT) had a significantly longer survival time than those planned using anatomical images alone. [231] However, Hutterer et al [232] note that the specificity of PET may be limited by passive tracer influx through the disrupted blood brain barrier and non-neoplastic lesions. The utility of PET for surgical planning for high-grade glioma has also been demonstrated, where 66 patients whose tumours were completely resected according to PET images used in planning had a prolonged survival. [233] In terms of response measurement, FET PET uptake has been demonstrated to be better than MRI at predicting the failure of Bevacizumab-

Irotocenin treatment. [234]Galldiks et al [122] also found tumour to background ratio (both mean and max) to be significant and independent predictors of progression free survival and overall survival.

For meningioma, the use of MET-PET was shown to improve inter-observer consistency for delineating margins of neoplasticity compared to MRI/CT alone in a study of 10 patients. [235] Another tracer, DOTATOC has also been used to delineate the extent of infracranial invasion [236] and has more recently been incorporated into radiotherapy planning. [237] Notably there were some masses that only DOTA could adequately identify. Cornelius et al [238] has highlighted the efficacy of PET for planning the surgery of meningioma as compliment to MRI and 5-ALA. [239]

Such observations motivate for the use of PET/MR during the planning of radiotherapy and surgery; initial experiences in the clinic have found few drawbacks for such systems in comparison to standard PET/CT and separate MRI systems. [240-242] While MRI will remain the standard baseline modality, PET has demonstrated applicability for several types of brain tumour. Applications include grading of tumours, detecting conversion to an aggressive phenotype, establishing a prognosis, planning surgery and planning radiotherapy. The enhanced sensitivity and specificity of metabolic imaging could assist in further delaying progression and improving survival time by reducing the risk of geographic misses and by identifying regions of infiltration that are occult to MRI, but only when used in concert with structural MRI. The increased availability and use of PET/MR scanners will be key to realising such ambitions.

5. Future developments in PET

5.1. Macromolecular imaging

Molecular imaging, in particular nuclear imaging, has been integral to the development and growth of the field of nanomedicine [243, 244]. The development of nanomedicines occurs over several stages, from materials development, characterisation and understanding at a molecular level to in vitro testing and eventually into in vivo models in the preclinical environment. Molecular imaging techniques have become the cornerstone of in vivo investigations in nanomedicine development and this, in turn, has led to the development of macromolecular imaging agents. The birth of the field of theranostics [245], therapeutic delivery and diagnostic reporter combined in the same molecule, has highlighted the potential of macromolecular imaging agents, which has translated into the field of neuro-oncology. The shift from a highly specific targeting molecule such as an antibody, fragment antibody, peptide or synthetic polymer to an imaging agent has become achievable with the development of facile and commercially available chemistries for the attachment of chelating ligands specific to radiometals [246]. Essentially, the library of nuclear imaging agents has expanded to the almost infinite library of specific biomolecules that have been developed over the past 40 years in the biotechnology field. The power of this approach in the imaging of brain tumours is yet to be fully realised in the clinical environment. However, an increasing number of preclinical studies

are beginning to show the potential of the approach [243, 244, 247-257]. The attraction of a macromolecular imaging agent is very similar to the attractions of antibody-based therapeutics. Whereas with a targeted therapeutic the desired effect is increased anti-tumour efficacy with decreased toxicity, the advantage of an imaging agent is greater contrast between diseased and healthy tissue leading to a lower risk of misinterpretation. Additional benefits lie in the half-life of the radionuclides used to label macromolecules. Radiometals commonly used in labelling macromolecules are ^{68}Ga (68 minute half-life), ^{64}Cu (762.06 minute half-life) and ^{89}Zr (4704.6 minute half-life) each offering distinct advantages over the commonly used ^{11}C (half life = 20.3 minutes) and ^{18}F (half-life = 109.8 minutes). Due to the short half-life, a prerequisite for using ^{11}C and ^{18}F tracers is access to a cyclotron and radiochemistry facilities. The enormous expense of installation of these facilities often limits the use of PET based brain tumour imaging. The long half-life of ^{64}Cu and ^{89}Zr allows production of the isotope at one location, shipment overnight and conjugation to the macromolecular imaging agent at the imaging facility without significant loss of tracer activity. Although the short half-life of ^{68}Ga excludes this approach, ^{68}Ga is produced from a generator and not by cyclotron methods, which are comparatively inexpensive and have small footprints, leading to relative ease of installation in the majority of facilities [258].

5.2. Macromolecular theranostics

As the chelators used to conjugate imaging nuclides can also be used to conjugate therapeutics, beta emitting nuclides such as ^{90}Y and ^{177}Lu the use of highly specific labelled macromolecules leads to a unique solution for personalised medicine. Essentially, what you see is what you treat. Imaging with a radiolabelled macromolecule will give the clinician a quantitative map of macromolecule tracer within the body. This can be used to either recommend the patient for treatment with the diagnostic analogue of the tracer, or rule out the patient as a successful candidate and recommend another course of treatment. The potential of this approach can be evidenced with translation of materials and regimes to the clinic. The family of octreotate peptides specific to the somatostatin family of receptors are used with increasing success in the management of neuroendocrine tumours [259-261]. A ^{68}Ga labelled version of the peptide can be used for diagnosis and treatment planning and, if the patient is likely to display a response, a ^{177}Lu labelled version of the peptide is administered as the treatment.

5.3. Molecular imaging switches

Further potential for macromolecular imaging lies in switchable imaging agents. Hardware developments in MRI have led to the possibility of multinuclear MRI. ^{19}F (not to be confused with ^{18}F) MRI shows great promise as a molecular imaging modality and is being investigated for a number of applications [262-269]. The gyromagnetic ratio of ^{19}F is very close to that of ^{1}H (^{19}F = 40.052, ^{1}H = 42.576), the natural abundance of ^{19}F is 100 % and the only endogenous ^{19}F in the body is in the bones and the teeth. Essentially this means that ^{19}F can be imaged on most clinical MRI scanners with the addition of a ^{19}F radiofrequency coil, providing a higher resolution molecular imaging modality. The use of ^{19}F MRI is most predominant in cell tracking and many cell types have been labelled with highly fluorinated polyether emulsions. Both

preclinical [269] and clinical [269, 270] trials have shown that imaging labelled cells in vivo is feasible at sub millimetre resolution, enough to visualise 10^3 – 10^5 cells. [269] ^{19}F MRI however comes with an additional bonus: the signal can be switched on and off in response to a biological signal. There have been several reports of ^{19}F containing molecules that can be imaged in vivo and are sensitive to pH changes [271-275], temperature [276] and enzyme activity [277]. This is largely achieved through changes to the T_2 relaxation rate induced by a physical change to the environment of the polymer. The potential of this approach is high as, in theory, the same mechanism could be used to monitor the release of a drug from a nano-medicine. In this way, and with multimodal imaging platforms such as PET/MRI, key questions surrounding the efficacy of targeted therapeutics, 'how much reaches the target?', 'how fast is it cleared from the target?', 'is the drug delivered to the target?' and 'what is the response to the therapy?' can be answered by molecular imaging.

6. Conclusions

CT and MR imaging are currently considered the gold standard when treating patients diagnosed with a brain tumour but these techniques are much harder to interpret after treatment has commenced. Developing new therapies and improving care in the clinic will depend on overcoming these shortcomings. The introduction of PET offers the ability to gain complimentary information to that of MR and CT imaging, with many radiotracers developed for investigating tumour microbiology. While each radiotracer has its own set of caveats, there are continuing advances in tracer development and synthesis.

Hypoxia has been shown to significantly affect treatment outcomes, and although many radiotracers have been developed for imaging hypoxia, FMISO continues to be the most applicable. In addition, hypoxia has been shown to provide information on patient prognosis, tumour grading and response to therapy. Multiplexing PET imaging may provide further advances in treatment regimes, offering the ability to image with multiple radiotracers within a single acquisition, although further investigations will need to be performed to bring the technique towards clinical translation.

PET imaging has shown application far beyond the detection of tumours, including tumour grading, detecting transformation to a more aggressive phenotype, predicting outcome, planning surgery and radiotherapy. It's application to surgery and radiotherapy planning offers the potential to improve treatment by reducing the risk of geographic misses and by identifying regions of infiltration that are not seen on MRI.

Future developments in PET technology as well as radiopharmaceutical developments should see the wide adoption of theranostics, providing qualitative and quantitative measures of therapeutic efficacy. With the incorporation of molecular imaging switches in conjunction with newly developed PET/MR technology, the ability to answer vital questions about therapeutic delivery to the tumour can be answered, significantly advancing treatment development for the treatment of glioma.

Acronyms

PET - Positron emission tomography

MRI - Magnetic resonance imaging

FET - [18F]-fluoroethyl-L-tyrosine

FDG - [18F]-Flurodeoxyglucose

FLT - [18F]fluorothymidine

LGG - Low grade glioma

FDOPA - [18F]fluoro-L-dihydroxyphenylalanine

MET - Methyl- [11C]-l-methionine

GTV - Gross tumour volume

IMT - 123I-α-methyl-tyrosine

5-ALA - 5-Aminolevulinic acid

DOTA - 68-Ga-DOTATOC-PET

SUV - Standard uptake value

KPS - Karnofsky performance status

NAA – N-acetyl asparte

MRS - Magnetic resonance spectroscopy

BOLD MRI - Blood oxygen level dependant magnetic resonance imaging

NIRS - near infrared spectroscopy

FLAIR - Fluid attenuated inversion recovery

MVD – Microvessel density

VEGF - Vascular endothelial growth factor

HIF-1α - Hypoxia inducible factor-1α

TTP - Time to tumour progression

DSCE MRI - Dynamic susceptibility contrast-enhanced magnetic resonance imaging

BBB - Blood brain barrier

RANO – Response Assessment for Neuro-Oncology

CT - computed tomography

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