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PET Imaging of Gliomas

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1. Introduction

Noninvasive imaging methods, including positron emission tomography (PET), have become essential for diagnosis and staging of gliomas, and monitoring of treatment response. The utility of these techniques have been found to be highly dependent on tumor grade. According to the World Health Organization (WHO) classification of tumors (Kleihues and Sobin 2000), gliomas are classified into 3 main histological types: astrocytoma, oligodendroglioma and glioblastoma. These histological types are further classified on the basis of anaplasia and degree of malignancy as: grade I, noninvasive glioma (pilocytic astrocytoma); grade II, less-invasive glioma (astrocytomas and oligodendrogliomas); grade III, invasive glioma (analplastic astrocytoma/oligodendrogliomas); and grade IV, highly invasive glioma (glioblastoma, or GBM).

Low-grade gliomas (grade I and II) typically affect younger patients. Grade I glioma is the most common form of glioma in children and is less frequent in adults (Burkhard et al. 2003) while grade II gliomas are common in adults (mean age of onset is 40 years) (Hagerstrand et al. 2008). Median survival for low-grade glioma is varied but prognosis and treatment require regular follow ups. Low-grade gliomas grow slowly or stabilize spontaneously and with surgical resection, median survival can be 20 years or more (Burkhard et al. 2003). For high-grade gliomas, the mean age of onset is 40 years for grade III glioma and 61 years for GBM (Ohgaki and Kleihues 2005). GBM is the most malignant and most common glioma, accounting for 45% - 50% of all adult gliomas. Median survival for grade III glioma is 2-3 years and for GBM is 1 year (Chen 2007). For optimal disease prognosis, treatment and follow up, one should be able to delineate the tumor lesion and most importantly, differentiate benign lesions from neoplastic lesions, low-grade from high grade tumors, and tumor progression from therapy induced necrosis. As will be discussed later, efforts are also being directed toward defining early imaging predictors of response to therapy.

Conventional imaging with magnetic resonance imaging (MRI) provides excellent anatomical definition of brain tumors. MRI is highly sensitive in identifying lesions, mass effect, edema, hemorrhage, necrosis and signs of increased intracranial pressure (Chen 2007). Pathologic changes are characterized on MRI by increased water content (edema) and blood-brain barrier (BBB) disruption, visualized as contrast enhancement (Grosu et al. 2002). Most tumors (low-grade or high-grade) have prolonged T1 and T2 relaxation times and thus

appear hypointense on T1-weighted images but hyperintense on T2-weighted images relative to normal brain (Grosu et al. 2002; Sartor 1999). In low-grade gliomas, peritumoral edema is minimal or absent and no contrast enhancement is seen due to intact BBB. Whereas, in high-grade gliomas, peritumoral edema is frequently seen and the tumor lesions usually show contrast enhancement, correlated with the extent of neovascularization and loss of integrity of the BBB owing to tumor infiltration and production of vascular endothelial growth factor. The anatomical features obtained by MRI are not sufficient to differentiate low-grade from high-grade gliomas with intact BBB, tumor lesions from inflammatory or vascular processes, and post-operative residual/relapse from necrosis (Chen 2007).

In contrast to MRI, positron emission tomography (PET) provides unique functional information of tumors on a range of biological processes such as glucose metabolism, protein/DNA synthesis, cell proliferation, membrane synthesis, angiogenesis and oxygen tension that can reflect the changes in neoplasm (Basu and Alavi 2009). Assessment of the status of these processes in areas of interest in brain has been shown to be helpful in detection and grading of gliomas, delineation of tumor margins, disease prognosis and treatment. PET has also been useful in differentiating post-operative residual tumor from therapy induced necrosis and edema. This review discusses radiopharmaceuticals and progress in the development of PET techniques for imaging of gliomas in the following areas: glucose uptake, amino acid transport, cellular proliferation rate, choline uptake, somatostatin receptor density, angiogenesis and hypoxia.

2. Glucose-based probes

Increased glucose uptake and glycolysis are hallmark characteristics of a variety of neoplasms (Pedersen 2007; Warburg 1956). This makes radiolabeled glucose analogs logical tracers of choice for imaging of tumors. The radiofluorinated analog of glucose, [18F]fluorodeoxyglucose, or [18F]FDG, is the most common PET tracer for clinical PET oncology studies. A practical synthesis, suitable half-life ($T_{1/2}$=109.7 min), negligible circulating metabolites, and well-established kinetics of uptake and retention of [18F]FDG makes it a preferred imaging probe in cancer imaging (Spence et al. 1998). [18F]FDG is transported into cancer cells by glucose transporters (GLUT1 and GLUT3) and, like glucose, it is phosphorylated via hexokinase to form [18F]fluorodeoxyglucose-6-phosphate. However, in contrast to glucose-6-phosphate, [18F]fluorodeoxyglucose-6-phosphate is very slowly metabolized further and hence is effectively trapped in the cancer cell (Spence et al. 1998). The trapped [18F]FDG-6-phosphate can be detected by [18F]FDG-PET thereby allowing non-invasive evaluation of glucose uptake and glycolysis. In general, [18F]FDG-PET performs well in identifying highly malignant, high-grade gliomas because they typically exhibit higher glycolysis rates than the normal cerebral cortex (Di Chiro et al. 1982, 1987a). Di Chiro et al. (1985, 1987a, 1987b) were first to correlate [18F]FDG uptake with WHO grading of gliomas on the basis of a semiquantitative index of the ratio of [18F]FDG uptake in tumor to the average [18F]FDG uptake in normal cerebral cortex. [18F]FDG uptake ratio in high-grade glioblastoma was almost twice that of low-grade gliomas. In a different study, Delbeke et al. (1995) reported that high-grade gliomas can be detected with high sensitivity of 94% and specificity of 77% when tumor-to-white matter ratios exceed 1.5, and tumor-to-grey matter ratios exceed 0.6. In addition,[18F]FDG-PET was able to indicate anaplastic transformation of grade II gliomas into grade III gliomas by an increase in 18F-FDG uptake (Chen 2007).

[18F]FDG-PET has also been useful to differentiate hypoglycolytic non-malignant toxoplasmosis common in AIDS patients from hyperglycolytic CNS lymphoma (Hoffman et al. 1993).

Assessment of [18F]FDG uptake in gliomas has high prognostic value (Di Chiro 1987). De Witte et al. (1996) studied 28 patients with histologically proven low-grade gliomas with [18F]FDG–PET and followed progression of disease for a mean of 27 months. All 19 patients with tumors that were hypoglycolytic on PET were alive at the end of the follow-up period, whereas 6 of 9 patients with hyperglycolytic patterns on PET died. The prognostic utility of [18F]FDG–PET has been confirmed in several other studies (Alavi et al. 1988; Barker et al. 1997; Padma et al. 2003; Patronas et al. 1985).

Although [18F]FDG-PET is accurate to detect high-grade gliomas, it has limited usefulness in detection of low-grade gliomas and some high-grade gliomas such as post-operative residual and recurrent glioma (Olivero et al. 1995; Ricci et al. 1998). Since glucose is the preferred fuel in normal brain, high [18F]FDG uptake in surrounding normal tissues in brain is unavoidable (Di Chiro et al. 1982). Low grade gliomas tend to have the same or lower [18F]FDG uptake as compared to average [18F]FDG uptake in white matter, thus resulting in false negative readings (Kawai et al. 2005). This is also true for certain high-grade gliomas, especially hypoglycolytic residual (Padma et al. 2003) and recurrent tumors (Chao et al. 2001) that may exhibit less or similar [18F]FDG uptake to average [18F]FDG uptake in grey matter. In addition, in the case of patients with Alzheimer disease and epilepsy, affected regions in brain can show decreased [18F]FDG uptake compared to background (Fazekas et al. 1989; McGeer et al. 1986). On the other hand, brain regions with abscess or acute necrosis occurring hours of weeks after radiotherapy, chemotherapy can show increased [18F]FDG uptake compared to background leading to false positive readings (Floeth et al. 2006). Thus, low tumor-to-normal background radioactivity concentration (T/N) ratios and difficult to interpret contrasts between normal and pathological regions limit the specificity of [18F]FDG-PET to detect low-grade and residual or relapsed high-grade brain tumors.

Given these concerns, attempts have been made to improve the accuracy of [18F]FDG for imaging of gliomas. In cases where T/N (white or grey matter) ratios for [18F]FDG uptake are not useful for delineating low-grade, residual or relapsed high-grade glioma, two strategies have been reported to help: (1) co-registration of [18F]FDG–PET images with MR images (Chao et al. 2001; Wang et al. 2006) and (2) delayed [18F]FDG–PET imaging (Spence et al. 2004). Co-registration and interpretation of [18F]FDG–PET images with MR images can improve the performance of [18F]FDG–PET **(Figure 1)** for detecting low-grade (Borgwardt et al. 2005; Wong et al. 2004), residual or relapsed high-grade gliomas (Chao et al. 2001; Wang et al. 2006). Low grade gliomas can be identified by similar [18F]FDG uptake to white matter in regions with increased signal on T2-weighted MRI (Borgwardt et al. 2005; Wong et al. 2004), while recurrent high grade gliomas are often indicated as [18F]FDG uptake in regions with contrast enhancement on T1-weighted MRI (Chao et al. 2001; Wang et al. 2006). Delayed PET imaging, as proposed by Spence et al. (2004), is another strategy to improve the contrast between tumor lesion and background. In this study, nineteen patients with gliomas were imaged from 0 to 90 min and once or twice at 3–8 h after injection. In 12 of 19 patients, visual analysis of delayed images up to 8 h after injection showed these images to better distinguish relapsed tumors in grey matter (**Figure 2**). Standardized uptake values (SUVs) were also greater in tumors than in normal grey or white matter on delayed imaging. Using kinetic modeling, they demonstrated that the rate constant of

[18F]fluorodeoxyglucose-6-phosphate degradation (k4) was not significantly different between tumor and normal brain tissue for shorter datasets but was lower in tumor than in normal brain tissue for the longer dataset (8 h), suggesting that higher [18F]Fluorodeoxyglucose-6-phosphate degradation rates are present in normal brain tissue than tumor. Since this report, other studies have shown the utility of delayed PET imaging for delineating brain tumors (Farid et al. 2009; Kim et al. 2010).
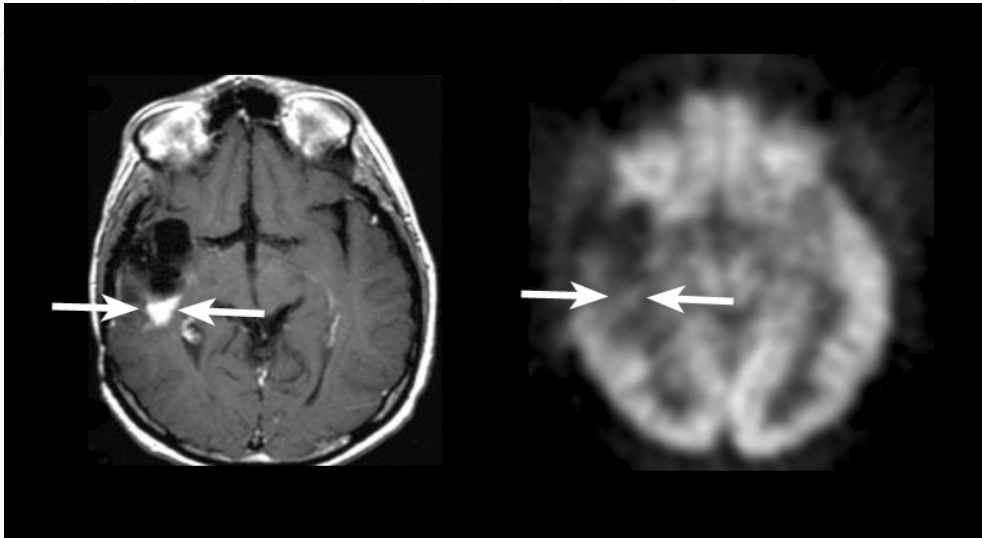

Fig. 1. A patient who had received surgery, radiation, and chemotherapy for anaplastic astrocytoma. Axial gadolinium-enhanced T1-weighted image (left) demonstrates nodular enhancement posterior to the surgical resection cavity. Co-registered [18F]FDG-PET image demonstrates increased [18F]FDG activity corresponding to this region, similar to gray matter, compatible with recurrent tumor. Correlation of the MRI and PET imaging findings is necessary to make this determination, and accurate image co-registration is essential.
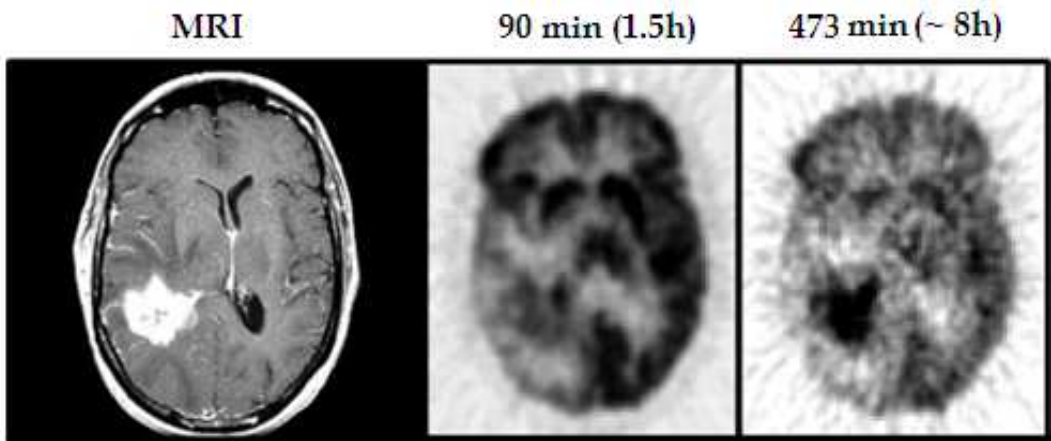

Fig. 2. A 45-year-old woman with recurrent right temporal GBM. T1-weighted gadolinium-enhanced (T1Gd) MRI showing contrast enhancement in right temporal region of the brain. [18F]FDG–PET scan with much more prominent T/N delineation in this right temporal region at the later time point, 473 min (~8 h), compared to 90 min (1.5 h). *Image reproduced from work by Spence et al. (2004) and used with permission.*

3. Amino acid-based probes

Amino acids play a central role in protein synthesis and intermediary metabolism (Cellarier et al. 2003; Morowitz et al. 2000). The enhanced uptake of essential amino acids into neoplasms through specific amino acid transporters has motivated the design and evaluation of a large number of positron-labeled essential amino acid analogs. In addition, the low uptake of essential amino acids in normal brain tissue relative to tumor tissue renders amino acid tracers advantageous for imaging gliomas (Lilja et al. 1985). The most studied essential amino acid tracers are [11C]methionine ([11C]MET), [18F]fluoroethyl-L-tyrosine ([18F]FET) and 3,4-dihydroxy-6-18F-fluoro-L-phenylalanine ([18F]FDOPA).

3.1 [11C]MET

Increased uptake of methionine by cancer cells results from increased transport flux, primarily by L-amino acid transporters, enhanced protein synthesis, increased need for polyamines, and a high rate of trans-methylation and trans-sulfuration reactions (Leskinen-Kallio et al. 1991). [11C]MET uptake in tumor lesions is not dependent on disruption of the BBB (Roelcke et al. 1995; Sasajima et al. 2004). This is a major advantage compared to MRI where contrast enhancement for detection of tumor lesions is dependent on BBB disruption. Studies with [11C]MET-PET have shown that amino acid tracer, [11C]MET, accumulates in all gliomas, including low-grade glioma that are difficult to detect on contrast-enhanced MRI and [18F]FDG-PET (Ogawa et al. 1993).

[11C]MET-PET can be used to predict histological grades of gliomas. Lilja et al. (1985) evaluated 14 patients with gliomas and found that [11C]MET-PET could differentiate high-grade glioma from low-grade glioma on the basis of T/N ratio. The ratio of the uptake of [11C]MET in high-grade tumors was 1.9-4.8 and low-grade tumor was 0.8-1.0. Derlon et al. (1989) too confirmed positive correlation of T/N ratio with the histological grade of gliomas. Later study with large set of 196 patients, Herholz et al. (1998) showed that [11C]MET could differentiate among high-grade gliomas, low-grade gliomas, and chronic or subacute nontumoral lesions. In this study, [11C]MET-PET was also useful in detecting recurrent or residual tumors as they showed higher [11C]MET uptake than primary gliomas.

[11C]MET-PET has been shown to have high prognostic potential. Kaschten et al. (1998) performed [18F]FDG-PET and [11C]MET-PET in 54 patients with gliomas. [11C]MET was superior to [18F]FDG in predicting the histologic grade and prognosis of gliomas. With a larger set of 85 patients, De Witte et al. (2001) applied qualitative and quantitative scoring systems for [11C]MET uptake. Both scoring systems confirmed the prognostic importance of [11C]MET-PET. In this study, gliomas were histologically graded following [11C]MET-PET guided resection (42 cases) or stereotactic biopsy (43 cases). Uptake of [11C]MET was present in 98% of the gliomas studied. The T/N ratio was significantly correlated with the histological grade of glioma. A statistically poor patient outcome was demonstrated during follow-up when this ratio was higher than a threshold of 2.2 for grade II gliomas and 2.8 for grade III gliomas. A high [11C]MET uptake was statistically associated with short survival times. Better prognostic utility of [11C]MET-PET relative to [18F]FDG-PET was also shown in other studies (Kim et al. 2005; Van Laere et al. 2005).

[11C]MET-PET is also useful to differentiate recurrent tumor from post-operative radiation injury (Gehrke et al. 1991; Ogawa et al. 1991; Sonoda et al. 1998). Tsuyuguchi et al. (2003) examined 21 adult patients with [11C]MET-PET to differentiate radiation necrosis from recurrent metastatic brain tumor following stereotactic radiosurgery. They observed mean

T/N ratio and mean SUV for [^{11}C]MET to be 1.15 and 1.78, respectively, in the radiation necrosis group (12 cases); and 1.62 and 2.5, respectively, in the tumor recurrence group (9 cases). The sensitivity and specificity of [^{11}C]MET-PET for detection of tumor recurrence were determined to be 77.8% and 100%, respectively. In a separate study, [^{11}C]MET-PET was shown to be superior to [^{18}F]FDG-PET in detecting recurrent brain lesions (Chung et al. 2002). A recent study by Okamoto et al. (2010) further confirmed the utility of [^{11}C]MET-PET to detect recurring lesions. Mean T/N ratio of all recurrent tumors and necrosis were 1.98 ± 0.62 and 1.27 ± 0.28, respectively (p < 0.01) (Okamoto et al. 2010). In smaller lesions (20 – 30 mm), T/N ratio for recurrent tumor (1.72 ± 0.44) was also significantly higher than that for necrosis (1.20 ± 0.11) (p < 0.01) (Okamoto et al. 2010). Thus, [^{11}C]MET-PET provides high diagnostic value for recurring tumor lesions, with particular value in early diagnosis of recurrence.

3.2 [^{18}F]FET

Wester et al. (1999) were the first to introduce the fluorinated tyrosine analog [^{18}F]FET for imaging gliomas. The longer half-life of ^{18}F (109.7 min) relative to ^{11}C (20 min) is more practical for production and distribution to multiple PET scanning facilities. The high *in vivo* stability of [^{18}F]FET, fast brain and tumor uptake kinetics, low accumulation in non-tumor tissue, and ease of synthesis strongly supported evaluation of [^{18}F]FET as an amino acid tracer for imaging gliomas.

Weber et al. (2000) compared uptakes of [^{18}F]FET and [^{11}C]MET by gliomas in 13 patients. On the basis of the [^{11}C]MET-PET, viable tumor tissue were delineated in all 13 patients. The same tumors showed rapid uptake of [^{18}F]FET with high image contrast. The mean uptake (SUV) of [^{11}C]MET was slightly higher than [^{18}F]FET in normal grey matter (1.4 ± 0.2 for [^{11}C]MET and 1.1 ± 0.2 for [^{18}F]FET); normal white matter (0.9 ± 0.1 for [^{11}C]MET and 0.8 ± 0.2 for [^{18}F]FET); and tumor lesions (3.3 ± 1.0 for [^{11}C]MET, 2.7 ± 0.8 for [^{18}F]FET). However, contrast between tumor and normal tissue background was not significantly different between [^{11}C]MET and [^{18}F]FET (**Figure 3**). In comparison to [^{18}F]FDG-PET, a recent study found [^{18}F]FET-PET was more accurate to detect malignant brain lesions, especially low-grade gliomas (Lau et al. 2010).

Although there is doubt on the potential of [^{18}F]FET-PET for grading gliomas (Popperl et al. 2004), a clinical study by Pauleit et al. (2005) showed that co-registration of [^{18}F]FET-PET and MRI could significantly improve the sensitivity and specificity of tumor detection and correlation to histological grade of tumor. In addition, a separate study showed have shown that the kinetic profile of [^{18}F]FET uptake for high- and low-grade lesions may be useful in grading tumors (Spence et al. 2004). In their study, tumors were classified into low (grade I and II) and high grade (grade III and IV) prior to [^{18}F]FET-PET scans. A significant difference (p<0.05) in T/N ratio was observed between high-grade (ratio = 3.2) and low-grade tumors (ratio = 2.0) in early time points (0-10 min post-injection). No significant differences were found at later time points (30-40 min post-injection). The importance of the kinetics of [^{18}F]FET is not limited to grading primary tumor lesions. Low-grade recurrent tumors associated with good prognosis were differentiated from high-grade recurrent tumor associated with poor prognosis on the basis of kinetics of [^{18}F]FET uptake (Popperl et al. 2006).

A major strength of [^{18}F]FET-PET is that it reliably distinguishes post-operative benign lesions from recurrent tumors (Popperl et al. 2004; Popperl et al. 2006). Popperal et al. (2004)

studied 53 patients with low grade (1 grade I, 9 grade II) or high grade gliomas (16 grade III, 27 grade IV) and clinically suspected recurrent tumors. The patients underwent [18F]FET-PET scans 4-180 months after various treatments. In the 42 patients with confirmed recurrence, there was additional distinct focal [18F]FET uptake with significantly higher values compared with those in the 11 patients without clinical signs of recurrence.
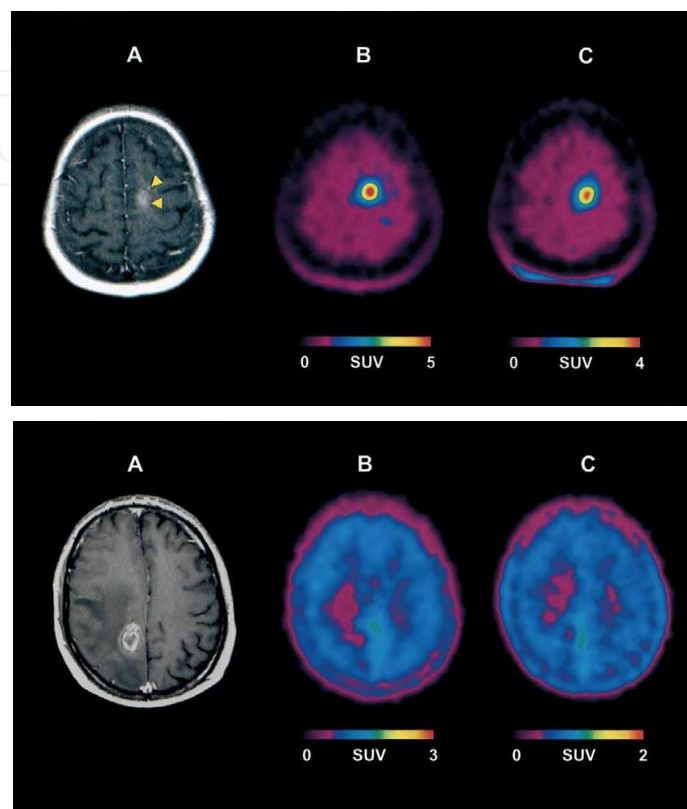

Fig. 3. Patient with residual tumor after subtotal resection of GBM (top) and a patient with radiation induced changes after radiotherapy for metastatic melanoma (bottom). T1-weighted contrast-enhanced MRI showing contrast enhancement in both residual tumor (A, top) and radiation induced injury (A, bottom). In the patient with residual GBM, [11C]MET-PET (B, top) and [18F]FET-PET (C, top) shows markedly increased tracer uptake. However, there is no increased uptake of [11C]MET (B, bottom) and [18F]FET (C, bottom) in radiation induced injury. *Image reproduced from work by Wolfgang A. Weber et al. (2000) and used with permission.*

3.3 [^{18}F]FDOPA

In mammalian cells, L-DOPA is synthesized from the amino acid, L-tyrosine, by the enzyme tyrosine hydroxylase (Kaufman 1995). L-DOPA is a precursor of the neurotransmitters: dopamine, norepinephrine, and epinephrine (Nagatsu 1995). L-DOPA is taken up by the brain through the blood-brain barrier (BBB) mediated by large neutral amino acid transporters (Lemmens et al. 2005). The [18F]fluorinated L-DOPA analog, [18F]FDOPA was initially developed as a radiotracer for use in patients with movement disorders (Heiss et al. 1996). In an early study, [18F]FDOPA-PET of a 57 y old patient revealed pathologically increased [18F]FDOPA accumulation in the right frontal lobe (Heiss et al. 1996). Unexpectedly, further PET examinations demonstrated increased [11C]MET uptake and low [18F]FDG uptake in this

right frontal region, suggesting a low-grade glioma lesion. MRI, ^{1}H-MRSI and histological examination later confirmed presence of a grade II oligo-astrocytoma in the lesion.

Following this incidental discovery, various studies were performed to evaluate the potential of [18F]FDOPA-PET for imaging of gliomas. Chen et al. (2006) compared [18F]FDOPA-PET with [18F]FDG-PET to evaluate the potential of [18F]FDOPA-PET to detect tumor lesions in patients with newly diagnosed or previously treated brain tumors. The [18F]FDOPA-PET images were acquired for 10–30 min post-injection. In this study, [18F]FDOPA-PET demonstrated excellent visualization of both low-grade and high-grade tumors, although the absolute uptake was not significantly different between the different tumor grades. [18F]FDOPA-PET was more sensitive and specific than [18F]FDG-PET for evaluating and distinguishing recurrent tumors from radiation necrosis. Specific transport of [18F]FDOPA (Lemmens et al. 2005) independent of disruption of BBB and low background activity rendered it superior to MRI and [18F]FDG for detecting recurrent gliomas.

A number of subsequent studies have suggested that tumor grade does not significantly affect [18F]FDOPA uptake (**Figure 4**) (Chen et al. 2006; Duan et al. 2004; Jager et al. 2001; Li and Zhang 2004; Ono et al. 2004). However, Schiepers et al. (2007) used kinetic modeling of [18F]FDOPA time courses out to 75 min to show that high-grade tumors had significantly higher transport rate constant, k1, equilibrium distribution volumes, and influx rate constant K than did low-grade tumors (P< 0.01). A 3-compartment model with corrections for tissue blood volume, metabolites, and partial volume, suggested that [18F]FDOPA was transported but not trapped in tumors. The shape of the uptake curve appeared to be related to tumor grade. After an early maximum, high-grade tumors had a steep descending branch, whereas low-grade tumors had a slowly declining curve, like that for the cerebellum but on a higher scale. A high correlation was found between SUV in tumors and influx rate constant K, indicated that simple uptake measurements at 60-70 min should be sufficient in clinical practice for grading tumors.
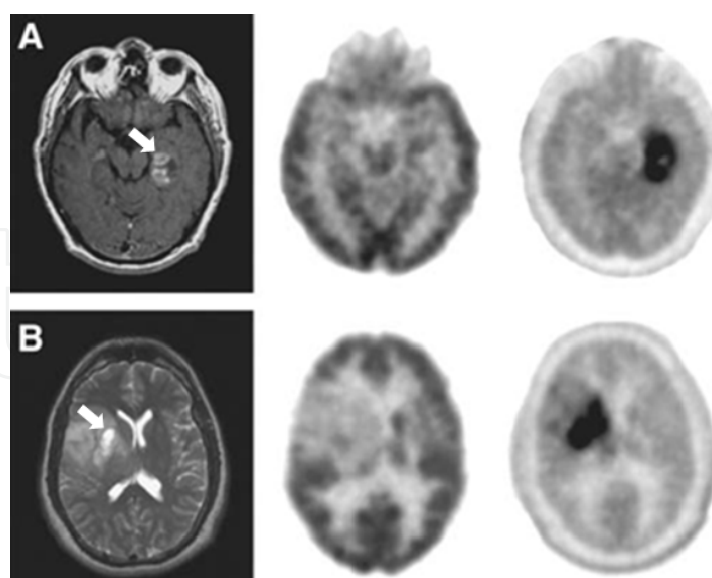

Fig. 4. Patient with newly diagnosed (A) GBM (B) Grade II oligodendroglioma. Tumor lesion shown as region with contrast enhancement in T1-weighted MRI (left). This region is not visible in [18F]FDG-PET scan (middle) but a prominent [18F]FDOPA uptake is seen in this region in [18F]FDOPA-PET scan (right). *Image adapted from work by Wei Chen et al. (2006) and used with permission.*

Potential use of [18F]FDOPA in tumor grading was also supported by a recent study by Chen et al. (2006) that showed significantly higher uptake in high-grade than in low-grade tumors in newly diagnosed tumors. This correlation was not seen in recurrent tumors that had been treated previously. In summary, [18F]FDOPA-PET has been found useful in detecting and differentiating recurrent tumors from radiation necrosis and may also have potential in grading newly diagnosed tumors, although more studies are needed to fully define the potential of [18F]FDOPA-PET.

A number of other positron-labeled amino acid analogs have been developed for imaging of brain tumors, although having fewer clinical trials to determine their characteristics for imaging of gliomas. These include [124I]iodophenylalanine (Farmakis et al. 2008), [18F]fluoromethylphenylalanine (FMP), [18F]fluoroboronophenylalanine (FBP) (Hsieh et al. 2005; Imahori et al. 1998), [18F]fluoroethylphenylalanine (FEP) (Wang et al. 2011) and [18F]fluoropropylphenylalanine (FPP) (Wang et al. 2011), and 1-Aminocyclobutane-1-[11C]carboxylic acid (1-[11C]-ACBC) (Hubner et al. 1998).

4. Choline-based probes

In recent years, choline metabolism has received a growing interest in cancer research. Choline is incorporated into membrane phospholipid in the form of phosphatidylcholine through the multistep Kennedy pathway. Phosphatidylcholine is one of the major lipid components of plasma membranes in mammalian cells and is essential for membrane structural stability and cell proliferation. Following its transport into the cell, choline undergoes ATP-dependent phosphorylation to form phosphocholine, a reaction catalyzed by choline kinase. High levels of choline uptake and increased choline kinase activity relative to normal tissues have been reported in various cancers including brain tumors (Fulham et al. 1992). This has motivated the development of choline based PET imaging for noninvasive evaluation of gliomas.

Shinoura et al. (1997) were the first to use choline as a PET tracer of brain tumor imaging. They evaluated 20 patients with brain tumors using [11C]choline PET. Progressive uptake of [11C]choline was observed in brain tumors, while uptake by surrounding normal cerebral cortex was 10-fold lower. Later, Ohtani et al. (2001) compared [11C]choline-PET with [18F]FDG-PET in 22 patients with histopathologically confirmed benign lesions and brain tumors from grade I-IV. Higher uptake of [11C]choline relative to [18F]FDG was observed in high-grade grade III and grade IV gliomas. Furthermore, [11C]choline was able to detect the extent of tumor better than MRI and could differentiate high-grade from low-grade lesions, but could not differentiate low-grade lesions from benign lesions.

The short half-life of [11C]choline limits the use of this tracer to facilities having an on-site cyclotron. In view of this, a choline radiotracer with a longer half-life is highly desirable. [18F]Fluorinated analogs of choline [18F]FCH are promising options for choline based PET tumor imaging.

DeGrado et al. (2001) first reported brain tumor imaging with [18F]FCH in a patient with previously resected anaplastic astrocytoma. The maximal T/N ratio of ~10:1 was attained within 5 min after injection. [18F]FDG -PET revealed a corresponding area of increased [18F]FDG uptake; however, the tumor boundaries were difficult to assess with FDG because of high uptake by normal cortex. Hara et al. (2003) performed studies with [18F]fluoroethylcholine (FECH) in 12 glioma patients. The T/N ratio of [18F]FECH was 10.5-12 in anaplastic astrocytoma and 13.2-21 in glioblastoma. These ratios were slightly higher

than those obtained with [11C]choline in the same patients. A preliminary study by Kwee et al. (2004) in 2 patients suggested that [18F]FCH uptake was significantly higher in glioblastoma multiforme (GBM) than benign demyelinating disease. Subsequently, Kwee et al. (2007) performed a more extensive [18F]FCH PET study on 30 consecutive patients (14 women, 16 men; age range, 26-79 years) with solitary brain lesions defined by MRI. In this study, the order of SUV and T/N ratios were benign lesions < high-grade gliomas < metastases from distant tumors with appreciable separation of these classes. [18F]FCH is also useful in detecting recurrent GBMs (**Figure 5**).

Pre-clinical studies on the *in vivo* kinetics and metabolism of [18F]FCH and choline in a 9L glioma allograft tumor model showed marked washout from the tumor possibly resulting from the hypoxic nature of these tumors. However, a strong association of [18F]FCH uptake and angiogenesis was found in the C6 glioma xenograft model (Wyss et al. 2007) and increased [18F]FCH uptake was observed in a multidrug resistant U87MG glioma tumor model (Vanpouille et al. 2009).
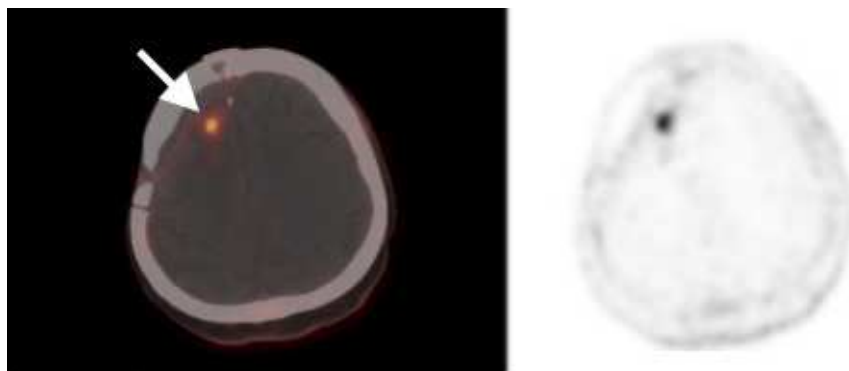

Fig. 5. [18F]FCH uptake in recurrent GBM. PET/CT (left) and [18F] FCH-PET (right) image shows a 6 mm focus of increased [18F]FCH uptake along a right frontal lobe resection cavity. This lesion was noted to increase in size on serial brain MRI consistent with the diagnosis of recurrent tumor. A post-craniotomy defect is evident on the PET/CT image. [18F] FCH-PET is potentially advantageous for imaging brain tumors such as GBM given the low amounts of physiologic cerebral [18F]FCH uptake. *Image Courtesy of Dr. Sandi A. Kwee, MD, Nuclear Medicine Department, Queen's Medical Center, Honolulu, HI, USA.*

5. Integrin-based probes

Angiogenesis is a crucial process for tumor growth and metastasis (Kountouras et al. 2005). This process requires intracellular and extracellular interactions in which integrins play an important role (Brooks et al. 1994). Antagonists against alpha$_v\beta_3$ integrin have been shown to block angiogenesis and reduce tumor growth in preclinical animal models (MacDonald et al. 2001) and clinical trials (Carter 2010). This integrin is a membrane bound receptor that mediates intracellular signal transduction by recognizing and binding to Arg-Gly-Asp (RGD) containing proteins in the extracellular matrix (Main et al. 1992). On binding to different types of RGD containing protein, it senses the external microenvironment and accordingly regulate cellular shape, mobility and cell cycle progression along with angiogenesis and metastatsis (Brooks et al. 1994). Alpha$_v\beta_3$ integrin is expressed at low levels on epithelial cells and mature endothelial cells but highly expressed on activated endothelial cells of the neovasculature of gliomas (Liu 2009). Its expression correlates well

with tumor progression and invasiveness of gliomas (Bello et al. 2001). Therefore, this integrin has received attention as a target for imaging probe development.

The most common integrin-targeting radiopharmaceuticals are radiolabeled RGD containing peptides. Cyclic RGD peptides (cRGD peptides) are preferred over linear RGD peptides due to their higher metabolic stability (Bogdanowich-Knipp et al. 1999). However, radiolabeled cRGD peptides ([18F]-FB-cRGDs (Chen et al. 2004) and [64Cu]-DOTA-cRGDs (Chen et al. 2004)) commonly suffer the drawback of poor tumor retention and high renal and/or hepatic uptake. To improve the tumor imaging properties of these tracers, dimeric (Chen et al. 2004) and tetrameric (Wu et al. 2005) cyclic RGD congeners have been developed. The multimeric cyclic RGD probes showed higher tumor uptake but nevertheless exhibited rapid uptake by liver and kidneys. To decrease uptake in liver and kidneys, modifications such as glycosylation (Schnell et al. 2009) or PEGylation (Chen et al. 2004) have helped to achieve higher uptake in tumors along with decreased uptake in liver and kidney in U87MG glioblastoma models (Chen et al. 2004; Chen et al. 2004; Wu et al. 2005) and in patients with *de novo* or recurrent GBM (Schnell et al. 2009).

New developments to integrin imaging are in progress. Recently, a new generation of RGD containing probes have been designed that show better potential for imaging gliomas. The new approach is based on cystine knot proteins or knottins that are relatively stable in physical, chemical and biological environments due to presence of scaffold of disulfide-bonded framework and a triple-stranded ß-sheet fold (Kimura et al. 2009). The Knottin family members also possess one or more surface-exposed loops that can tolerate sequence diversity. RGD peptides have been grafted into these surface-exposed loops, while radiolabeling accomplished with conjugation of PET radionuclide, [18F]-FB or [64Cu]-DOTA. In a U87MG glioblastoma model, a knottin based probe demonstrated rapid and high tumor accumulation, fast clearance from blood and normal organs, and low uptake in the kidney and liver (Miao et al. 2009).

6. Cellular proliferation probes

Increased cellular proliferation is an integral part of the cancer phenotype (Bading and Shields 2008). The primary requirement for cell proliferation is replication of nuclear DNA. Of the 4 nucleotides (adenine, guanine, cytosine and thymidine) required for DNA synthesis, thymidine is the only one that is specific for DNA. In cells, thymidine is derived either *de novo* or through the salvage pathway (Bading and Shields 2008). The *de novo* pathway is not a viable alternative for monitoring DNA synthesis in proliferating cells because the relevant precursors (deoxyuridine, uridine, and uracil) are routed into both DNA and RNA (Bading and Shields 2008). Thus, thymidine salvage pathway is a better choice for indication of proliferation. PET radiotracers of thymidine have been developed, including [11C]thymidine ([11C]TdR) (De Reuck et al. 1999) and 3'-deoxy-3'-fluorothymidine ([18F]FLT). These probes are currently being evaluated for their potential for imaging cellular proliferation in gliomas. The thymidine-based tracers are transported into cells and subsequently phosphorylated by thymidine kinase-1 (TK-1), thereby rendering them trapped within the cell. Since TK-1 activity correlates to a significant extent with the cellular proliferation rate, the PET-measurement of tissue retention of radioactivity is a non-invasive indicator of proliferation. The advantage of using the fluorinated thymidine tracer [18F]FLT over [11C]TdR is twofold. First, replacement of the hydroxy group of

deoxyribose with radiofluorine makes it resistant to degradation (Shields et al. 1998) and second, the longer half-life of ^{18}F is more practical for clinical imaging.

Increased glucose metabolism in inflammatory tissues and other non-specific lesions is the main source of false-positive [18F]FDG-PET findings in oncology. Van Waarde et al. (2004) used a rodent model with C6 glioma tumor and inflammatory lesion to show that [18F]FLT was more specific than [18F]FDG for uptake by glioma lesions relative to inflammation. However, the ability of [18F]FLT to detect tumors was dependent on disruption of the BBB (Muzi et al. 2006), rendering it more suitable for detecting high-grade gliomas than low-grade ones. In a separate clinical study (Chen et al. 2005), [18F]FLT–PET was more sensitive than [18F]FDG-PET for imaging recurrent high-grade tumors, correlated better with the Ki-67 proliferation index and was a more powerful predictor of tumor progression and survival. The reason for superiority of [18F]FLT–PET over [18F]FDG–PET was low [18F]FLT uptake in the normal brain tissue leading to higher T/N contrast (**Figure 6**). When compared with [11C]MET, Jacobs et al. (2005) showed that [18F]FLT was less sensitive in detecting tumors than [11C]MET, especially for low-grade astrocytomas. Nevertheless, Kawai et al. (2009) found a high correlation between histological tumor grade and [18F]FLT uptake in gliomas. A significant difference in SUV_{max} of [18F]FLT was observed between grade II (0.27 ± 0.06, n=6) and grade IV (2.18 ± 0.93, n=10) gliomas (P < 0.0001), and grade III (0.70 ± 0.45, n=7) and grade IV gliomas (P < 0.001). Importantly, [18F]FLT uptake correlated significantly better with the Ki-67 index (r = 0.86, P < 0.0001) than did methionine uptake in gliomas. Studies have also reported the use of [18F]FLT-PET in investigating the effectiveness of therapy and prognosis of gliomas (Chen et al. 2007; Kawai et al. 2009). Increased [18F]FLT accumulation is also observed in other brain tumors including malignant lymphoma (Kawai et al. 2009).
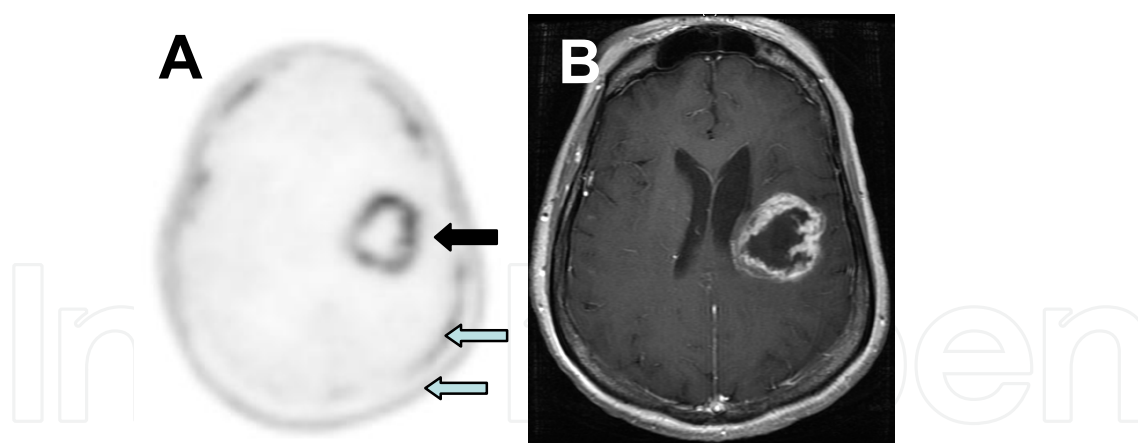

Fig. 6. Patient with glioblastoma. FLT-PET scan (A) and contrast-enhanced MRI (B) of biopsy-proven glioblastoma multiforme (GBM) in a 58 year-old female, just prior to the initiation of chemoradiation. Thick black arrow points to the highly proliferative rim of tumor surrounding a photopenic region of central necrosis. FLT uptake in the normal brain parenchyma is minimal, allowing a favorable lesion-to-background ratio. Physiologic uptake is also seen within the bone marrow (short thin arrow) and scalp (long thin arrow) *Image Courtesy of Dr. Laura Horky, Brigham and Women's Hospital, Boston.*

Another strategy for imaging of cell proliferation in tumor lesions involves non-invasive assessment of the concentration of sigma receptors in cells using sigma-receptor ligands

(Wheeler et al. 2000). Sigma-receptors are expressed more in proliferating tumor cells than in quiescent tumor cells (Wheeler et al. 2000). Using a preclinical tumor model, Van Waarde et al. (2004) were the first to report feasibility of using sigma-receptor binding ligands, [11C]SA4503 and [18F]FE-SA5845 for detecting gliomas. It is known that tumors are heterogenous in nature, including areas of low and high proliferation rates. The proportion of cells with low proliferation rate increases with increase in tumor size, especially in the necrotic center. In the C6 glioma rat model, tumor uptake of [18F]FE-SA5845 showed a negative correlation with tumor size (P < 0.0001), in contrast to that of [11C]SA4503, suggesting that tissue binding of [18F]FE-SA5845 is solely related to cellular proliferation. Later Van Waarde et al. (2006) compared the bio-distribution of 4 PET tracers ([11C]SA4503, [18F]FE-SA5845, [11C]choline and [11C]MET) with previously published bio-distribution data of [18F]FLT and [18F]FDG in C6 glioma rat tumor model. In their study, sigma-receptor ligands and [18F]FLT were more tumor selective than [18F]FDG, [11C]choline, or [11C]MET in the C6 glioma model. However, [11C]SA4503 and [18F]FE-SA5845 were less sensitive than were [11C]choline, [11C]MET, and [18F]FDG. Clinical PET studies for evaluation of sigma receptor expression in gliomas are ongoing.

7. Somatostatin-based probes

Meningiomas are the most common non-glial primary tumors of the central nervous system accounting for approximately 15% of all intracranial tumors (Buetow et al. 1991). More than 90% of intracranial meningiomas are slow growing and histopathologically benign but malignant meningiomas are not rare (Buetow et al. 1991; Goldsmith et al. 1994). [18F]FDG uptake in tumor lesions is dependent on glycolytic rate and disruption of blood brain barrier (Roelcke et al. 1995). High expression of the somatostatin receptor (SSTR) subtype 2 (Dutour et al. 1998) in meningiomas offer the possibility of receptor-targeted imaging (Henze et al. 2005; Henze et al. 2001) of meningiomas. In the case of meningiomas with low glycolytic rate and intact BBB (Roelcke et al. 1995), somatostatin receptor based tracers might be more useful for tumor detection and disease management than [18F]FDG. In a clinical study, a somatostatin receptor analog, 68Ga-DOTA-D-Phe1-Tyr3-octreotide (DOTA-TOC) labeled with the positron emitter 68Ga (half-life, 68 min) was evaluated for imaging meningioma (Henze et al. 2001). In contrast to [18F]FDG, this ligand showed higher T/N uptake ratios. The initial results are encouraging but more clinical studies are needed to fully assess the potential of somatostatin receptor based tracers for imaging meningiomas.

8. Hypoxia-based probes

Hypoxia, a hallmark of aggressive tumor behavior often noted in high grade glioblastomas, is associated with resistance to therapy, poorer survival, invasion and aggressiveness (Szeto et al. 2009). Estimation of hypoxia could be an important determinant of overall survival in several tumors including gliomas. PET imaging with the hypoxia radiotracer [18F]fluoromisonidazole ([18F]FMISO) presents a possible means of noninvasively detecting tumor hypoxia in gliomas (Rasey et al. 2000; Valk et al. 1992). In a preclinical C6 glioma tumor model study (Tochon-Danguy et al. 2002), [18F]FMISO uptake was significantly higher in tumor tissue compared to normal brain and the uptake was independent of tumor size. [18F]FMISO uptake was observed homogeneously throughout viable glioma tissue in tumor sizes ranging from 2 mm to almost 1 cm. Quantitation of uptake of [18F]FMISO

showed a tumor-to-brain ratio of 1.9 and a tumor-to-blood ratio of 2.6 at 2 hours post-injection. In a recent clinical study by Shibahara et al. (2010), 8 patients with gliomas of different grades underwent PET studies with a new imidazole based hypoxia imaging agent, 1-(2-[18F]fluoro-1-[hydroxymethyl]ethoxy)methyl-2-nitroimidazole ([18F]FRP-170). The new agent showed higher image contrast and faster clearance than [18F]FMISO. [18F]FRP-170 images showed positive correlation with HIF-1α expression, a weak correlation with [18F]FDG-PET and MR, but no correlation with [11C]MET-PET. The [18F]FRP-170-PET images showed marked uptake in the 3 GBM, and moderate uptake in recurrent anaplastic astrocytoma and oligodendroglioma, but no uptake in the other tumors (oligodendroglioma and diffuse astrocytoma). It is suggested that the use of hypoxia markers in patients with primary or recurrent gliomas could potentially assist in defining hypoxic tumor regions and predicting response to radiotherapy, but is not effective for grading tumors.

9. Acetate-based probes

Acetate is transported into the cell via the monocarboxylic acid transporter where it is converted in mitochondria to acetyl-coenzyme A (acetyl-CoA) (Lopresti and Mason 2009). Acetyl-CoA is a substrate for several biochemical pathways, most notably the tricarboxylic acid (TCA) cycle, and for glutamine and lipid synthesis. Additional studies have demonstrated that the preferential use of acetate by astrocytes is mediated by transport, although the exact mechanism is not fully understood (Lopresti and Mason 2009). In a clinical study, Yamamoto et al. (2008) evaluated [11C]acetate for detecting brain gliomas and differentiating high-grade gliomas. Sensitivities of [11C]acetate, [11C]MET, and [18F]FDG were 90%, 100%, and 40%, respectively. The T/N ratios of [11C]acetate and [11C]MET were significantly higher than that of [18F]FDG. With respect to tumor grades, uptakes (SUVs) of [11C]acetate and [18F]FDG in high-grade gliomas were significantly higher than those in low-grade gliomas while no significant differences were observed with [11C]MET. In another clinical study (Tsuchida et al. 2008), [11C]acetate was superior to [18F]FDG in differentiating high-grade tumors from low-grade tumors. In a recent preclinical animal study (Marik et al. 2009), the fluorinated form of acetate, [18F]fluoroacetate, was evaluated for the assessment of several neuropathologies including glioblastoma represented by the orthotopic U87 xenografts, ischemia associated with stroke or hypoxia. In this study, [18F]fluoroacetate showed the highest T/N ratio in glioblastoma followed by stroke-ischemia and hypoxia-ischemia.

10. Conclusions

PET imaging offers a growing "toolbox" of molecular imaging probes for noninvasive evaluation of gliomas. In general, [18F]FDG-PET has high prognostic value, performs well in identifying anaplastic transformations and detecting malignant high grade gliomas. But due to high normal cerebral uptake, it has limited use in detection of low-grade gliomas and residual/recurrent gliomas. Amino acid based probes (e.g, [11C]MET, [18F]FET and [18F]FDOPA) have low normal cerebral uptake, resulting in improved detection of low-grade lesions. They have shown utility for grading of gliomas and they can differentiate residual/recurrent tumor from post-operative radiation injury. Preclinical studies with sigma receptor ligands suggest them to be more selective but less sensitive for tumor lesions than [18F]FDG, [11C]MET and [11C]choline. Use of somatostatin receptor ligands may be

limited to detecting meningiomas, while hypoxia markers are best suited for disease prognosis and predicting response to radiotherapy. Recent studies with choline-, acetate- and integrin-based PET probes seem encouraging but more work is needed to fully appreciate their potential. In conclusion, positron-labeled amino acids are showing highest general utility for staging and therapy management of gliomas, while other metabolic probes are undergoing validation to answer selected clinical questions such as assessment of hypoxia and angiogenesis.

11. Acknowledgement

12. References

Alavi, J. B.; Alavi, A.; Chawluk, J.; Kushner, M.; Powe, J.; Hickey & W., Reivich, M. (1988). Positron emission tomography in patients with glioma. A predictor of prognosis, *Cancer*, Vol. 62, No. 6, pp. 1074-1078, ISSN 0008-543X

Bading, J. R. & Shields, A. F. (2008). Imaging of cell proliferation: status and prospects, *J Nucl Med*, Vol. 49 Suppl. 2, pp. 64S-80S, ISSN 0161-5505

Barker, F. G. ; Chang, S. M.; Valk, P. E.; Pounds, T. R. & Prados, M. D. (1997). 18-Fluorodeoxyglucose uptake and survival of patients with suspected recurrent malignant glioma, *Cancer*, Vol. 79, No. 1, pp. 115-126, ISSN 0008-543X

Basu, S. & Alavi, A. (2009). Molecular imaging (PET) of brain tumors, *Neuroimaging Clin N Am*, Vol. 19, No. 4, pp. 625-646, ISSN 1557-9867

Bello, L.; Francolini, M.; Marthyn, P.; Zhang, J.; Carroll, R. S.; Nikas, D. C. & Black, P. M. (2001). Alpha(v)beta3 and alpha(v)beta5 integrin expression in glioma periphery, *Neurosurgery*, Vol. 49, No. 2, pp. 380-389; discussion 390, ISSN 0148-396X

Bogdanowich-Knipp, S. J.; Jois, D. S. & Siahaan, T. J. (1999). The effect of conformation on the solution stability of linear vs. cyclic RGD peptides, *J Pept Res*, Vol. 53, No. 5, pp. 523-529, ISSN 1397-002X

Borgwardt, L.; Hojgaard, L.; Carstensen, H.; Laursen, H.; Nowak, M.; Thomsen, C. & Schmiegelow, K. (2005). Increased fluorine-18 2-fluoro-2-deoxy-D-glucose (FDG) uptake in childhood CNS tumors is correlated with malignancy grade: a study with FDG positron emission tomography/magnetic resonance imaging coregistration and image fusion, *J Clin Oncol*, Vol. 23, No. 13, pp. 3030-3037, ISSN 0732-183X

Brooks, P. C.; Montgomery, A. M.; Rosenfeld, M.; Reisfeld, R. A.; Hu, T.; Klier, G. & Cheresh, D. A. (1994). Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels, *Cell*, Vol. 79, No. 7, pp. 1157-1164, ISSN 0092-8674

Buetow, M. P.; Buetow, P. C. & Smirniotopoulos, J. G. (1991). Typical, atypical, and misleading features in meningioma, *Radiographics*, Vol. 11, No. 6, pp. 1087-1106, ISSN 0271-5333

Burkhard, C.; Di Patre, P. L.; Schuler, D.; Schuler, G.; Yasargil, M. G.; Yonekawa, Y.; Lütolf, U. M.; Kleihues, P. & Ohgaki, H. (2003). A population-based study of the incidence and survival rates in patients with pilocytic astrocytoma, *J Neurosurg*, Vol. 98, No. 6, pp. 1170-1174, ISSN 0022-3085

Carter, A. (2010). Integrins as target: first phase III trial launches, but questions remain, *J Natl Cancer Inst*, Vol. 102, No. 10, pp. 675-677, ISSN 1460-2105

Cellarier, E.; Durando, X.; Vasson, M. P.; Farges, M. C.; Demiden, A.; Maurizis, J. C.; Madelmont, J. C. & Chollet, P. (2003). Methionine dependency and cancer treatment, *Cancer Treat Rev*, Vol.29, No.6, pp. 489-499, ISSN 0305-7372

Chao, S. T.; Suh, J. H.; Raja, S.; Lee, S. Y. & Barnett, G. (2001). The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery, *Int J Cancer*, Vol. 96, No. 3, pp. 191-197, ISSN 0020-7136

Chen, W. (2007). Clinical applications of PET in brain tumors, *J Nucl Med*, Vol. 48, No. 9, pp. 1468-1481, ISSN 0161-5505

Chen, W.; Cloughesy, T.; Kamdar, N.; Satyamurthy, N.; Bergsneider, M.; Liau, L.; Mischel, P.; Czernin, J.; Phelps, M. E. & Silverman, D. H. (2005). Imaging proliferation in brain tumors with 18F-FLT PET: comparison with 18F-FDG, *J Nucl Med*, Vol.46, No.6, pp. 945-952, ISSN 0161-5505

Chen, W.; Delaloye, S.; Silverman, D. H.; Geist, C.; Czernin, J.; Sayre, J.; Satyamurthy, N.; Pope, W.; Lai, A.; Phelps. M. E. & Cloughesy T. (2007). Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [^{18}F] fluorothymidine positron emission tomography: a pilot study, *J Clin Oncol*, Vol. 25, No. 30, pp. 4714-4721, ISSN 1527-7755

Chen, W.; Silverman, D. H.; Delaloye, S.; Czernin, J.; Kamdar, N.; Pope, W.; Satyamurthy, N.; Schiepers, C. & Cloughesy, T. (2006). 18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy, *J Nucl Med*, Vol.47, No.6, pp. 904-911, ISSN 0161-5505

Chen, X.; Hou, Y.; Tohme, M.; Park, R.; Khankaldyyan, V.; Gonzales-Gomez, I.; Bading, J. R.; Laug, W. E. & Conti, P. S. (2004). Pegylated Arg-Gly-Asp peptide: 64Cu labeling and PET imaging of brain tumor alphavbeta3-integrin expression, *J Nucl Med*, Vol.45, No.10, pp. 1776-1783, ISSN 0161-5505

Chen, X.; Park, R.; Shahinian, A. H.; Tohme, M.; Khankaldyyan, V.; Bozorgzadeh, M. H.; Bading, J. R.; Moats, R.; Laug, W. E. & Conti, P. S. (2004). 18F-labeled RGD peptide: initial evaluation for imaging brain tumor angiogenesis, *Nucl Med Biol*, Vol.31, No.2, pp. 179-189, ISSN 0969-8051

Chen, X.; Park, R.; Tohme, M.; Shahinian, A. H.; Bading, J. R. & Conti, P. S. (2004). MicroPET and autoradiographic imaging of breast cancer alpha v-integrin expression using 18F- and 64Cu-labeled RGD peptide, *Bioconjug Chem*, Vol.15, No.1, pp. 41-49, ISSN 1043-1802

Chen, X.; Tohme, M.; Park, R.; Hou, Y.; Bading, J. R. & Conti, P. S. (2004). Micro-PET imaging of alphavbeta3-integrin expression with 18F-labeled dimeric RGD peptide, *Mol Imaging*, Vol.3, No.2, pp. 96-104, ISSN 1535-3508

Chung, J. K.; Kim, Y. K.; Kim, S. K.; Lee, Y. J.; Paek, S.; Yeo, J. S.; Jeong, J. M.; Lee, D. S.; Jung, H. W. & Lee, M. C. (2002). Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo- or isometabolic on 18F-FDG PET, *Eur J Nucl Med Mol Imaging*, Vol.29, No.2, pp. 176-182, ISSN 1619-7070

De Reuck, J.; Santens, P.; Goethals, P.; Strijckmans, K.; Lemahieu, I.; Boon, P.; Achten, E.; Lemmerling, M.; Vandekerckhove, T. & Caemaert, J. (1999). [Methyl-11C]thymidine positron emission tomography in tumoral and non-tumoral cerebral lesions, *Acta Neurol Belg*, Vol.99, No.2, pp. 118-125, ISSN 0300-9009

De Witte, O.; Goldberg, I.; Wikler, D.; Rorive, S.; Damhaut, P.; Monclus, M.; Salmon, I.; Brotchi, J. & Goldman, S. (2001). Positron emission tomography with injection of methionine as a prognostic factor in glioma, *J Neurosurg*, Vol. 95, No. 5, pp. 746-750, ISSN 0022-3085

De Witte, O.; Levivier, M.; Violon, P.; Salmon, I.; Damhaut, P.; Wikler, D.; Hildebrand, J.; Brotchi, J. & Goldman, S. (1996). Prognostic value positron emission tomography with [18F]fluoro-2-deoxy-D-glucose in the low-grade glioma, *Neurosurgery*, Vol. 39, No. 3, pp. 470-476; discussion 476-477, ISSN 0148-396X

DeGrado, T. R.; Baldwin, S. W.; Wang, S.; Orr, M. D.; Liao, R. P.; Friedman, H. S.; Reiman, R.; Price, D. T. & Coleman, R. E. (2001). Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers, *J Nucl Med*, Vol. 42, No. 12, pp. 1805-1814, ISSN 0161-5505

Delbeke, D.; Meyerowitz, C.; Lapidus, R. L.; Maciunas, R. J.; Jennings, M. T.; Moots, P. L. & Kessler, R. M. (1995). Optimal cutoff levels of F-18 fluorodeoxyglucose uptake in the differentiation of low-grade from high-grade brain tumors with PET, *Radiology*, Vol.195, No.1, pp. 47-52, ISSN 0033-8419

Derlon, J. M.; Bourdet, C.; Bustany, P.; Chatel, M.; Theron, J.; Darcel, F. & Syrota, A. (1989). [11C]L-methionine uptake in gliomas, *Neurosurgery*, Vol. 25, No. 5, pp. 720-728, ISSN 0148-396X

Di Chiro, G.; DeLaPaz, R. L.; Brooks, R. A.; Sokoloff, L.; Kornblith, P. L.; Smith, B. H.; Patronas, N. J.; Kufta, C. V.; Kessler, R. M.; Johnston, G. S.; Manning, R. G. & Wolf, A. P. (1982). Glucose utilization of cerebral gliomas measured by [18F] fluorodeoxyglucose and positron emission tomography, *Neurology*, Vol.32, No.12, pp. 1323-1329, ISSN 0028-3878

Di Chiro, G. (1985). Brain imaging of glucose utilization in cerebral tumors, *Res Publ Assoc Res Nerv Ment Dis*, Vol. 63, pp. 185-197, ISSN 0091-7443

Di Chiro, G. (1987a). Positron emission tomography using [18F]fluorodeoxyglucose in brain tumors. A powerful diagnostic and prognostic tool, *Invest Radiol*, Vol. 22, No. 5, pp. 360-371, ISSN 0020-9996

Di Chiro, G.; Hatazawa, J.; Katz, D. A.; Rizzoli, H. V. & De Michele, D. J., (1987b). Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study, *Radiology*, Vol. 164, No. 2, pp. 521-526, ISSN 0033-8419

Duan, L.; Aoyagi, M.; Tamaki, M.; Yoshino, Y.; Morimoto, T.; Wakimoto, H.; Nagasaka, Y.; Hirakawa, K.; Ohno, K. & Yamamoto, K. (2004). Impairment of both apoptotic and cytoprotective signalings in glioma cells resistant to the combined use of cisplatin and tumor necrosis factor alpha, *Clin Cancer Res*, Vol.10, No.1 Pt 1, pp. 234-243, ISSN 1078-0432

Dutour, A.; Kumar, U.; Panetta, R.; Ouafik, L.; Fina, F.; Sasi, R. & Patel, Y. C. (1998). Expression of somatostatin receptor subtypes in human brain tumors, *Int J Cancer*, Vol. 76, No. 5, pp. 620-627, ISSN 0020-7136

Farid, K.; Sibon, I.; Fernandez, P.; Guyot, M.; Jeandot, R. & Allard, M. (2009). Delayed acquisition and hyperglycemia improve brain metastasis detection on F-18 FDG PET, *Clin Nucl Med*, Vol.34, No.8, pp. 533-534, ISSN 1536-0229

Farmakis, G.; Brandau, W.; Hellwig, D.; Wollenweber, F.; Schaefer, A.; Kirsch, C. M. & Samnick, S. (2008). PET imaging with p-[I-124]iodo-l-phenylalanine as a new tool

for diagnosis and postoperative control in patients with glioma, *Clin Nucl Med*, Vol.33, No.6, pp. 441-442, ISSN 1536-0229

Fazekas, F.; Alavi, A.; Chawluk, J. B.; Zimmerman, R. A.; Hackney, D.; Bilaniuk, L.; Rosen, M.; Alves, W. M.; Hurtig, H. I.; Jamieson, D. G. & et al. (1989). Comparison of CT, MR, and PET in Alzheimer's dementia and normal aging, *J Nucl Med*, Vol.30, No.10, pp. 1607-1615, ISSN 0161-5505

Floeth, F. W.; Pauleit, D.; Sabel, M.; Reifenberger, G.; Stoffels, G.; Stummer, W.; Rommel, F.; Hamacher, K. & Langen, K. J. (2006). 18F-FET PET differentiation of ring-enhancing brain lesions, *J Nucl Med*, Vol.47, No.5, pp. 776-782, ISSN 0161-5505

Fulham, M. J.; Bizzi, A.; Dietz, M. J.; Shih, H. H.; Raman, R.; Sobering, G. S.; Frank, J. A.; Dwyer, A. J.; Alger, J. R. & Di Chiro, G. (1992). Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance, *Radiology*, Vol.185, No.3, pp. 675-686, ISSN 0033-8419

Gehrke, J.; Haring, C.; Konig, H.; Marin, H.; Schmidt, H. & Stolze, G. (1991). [Use of a computer in a clinical-toxicological laboratory with a fuzzy search], *Z Med Lab Diagn*, Vol.32, No.3-4, pp. 197-203, ISSN 0323-5637

Goldsmith, B. J.; Wara, W. M.; Wilson, C. B. & Larson, D. A., (1994). Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990, *J Neurosurg*, Vol. 80, No. 2, pp. 195-201, ISSN 0022-3085

Grosu, A. L.; Feldmann, H.; Dick, S.; Dzewas, B.; Nieder, C.; Gumprecht, H.; Frank, A.; Schwaiger, M.; Molls, M. & Weber, W. A. (2002). Implications of IMT-SPECT for postoperative radiotherapy planning in patients with gliomas, *Int J Radiat Oncol Biol Phys*, Vol.54, No.3, pp. 842-854, ISSN 0360-3016

Hagerstrand, D.; Smits, A.; Eriksson, A.; Sigurdardottir, S.; Olofsson, T.; Hartman, M.; Nister, M.; Kalimo, H. & Ostman, A. (2008). Gene expression analyses of grade II gliomas and identification of rPTPbeta/zeta as a candidate oligodendroglioma marker, *Neuro Oncol*, Vol.10, No.1, pp. 2-9, ISSN 1522-8517

Hara, T.; Kondo, T. & Kosaka, N., (2003). Use of 18F-choline and 11C-choline as contrast agents in positron emission tomography imaging-guided stereotactic biopsy sampling of gliomas, *J Neurosurg*, Vol. 99, No. 3, pp. 474-479, ISSN 0022-3085

Heiss, W. D.; Wienhard, K.; Wagner, R.; Lanfermann, H.; Thiel, A.; Herholz, K. & Pietrzyk, U. (1996). F-Dopa as an amino acid tracer to detect brain tumors, *J Nucl Med*, Vol.37, No.7, pp. 1180-1182, ISSN 0161-5505

Henze, M.; Dimitrakopoulou-Strauss, A.; Milker-Zabel, S.; Schuhmacher, J.; Strauss, L. G.; Doll, J.; Mäcke, H. R.; Eisenhut, M.; Debus, J. & Haberkorn, U. (2005). Characterization of 68Ga-DOTA-D-Phe1-Tyr3-octreotide kinetics in patients with meningiomas, *J Nucl Med*, Vol. 46, No. 5, pp. 763-769, ISSN 0161-5505

Henze, M.; Schuhmacher, J.; Hipp, P.; Kowalski, J.; Becker, D. W.; Doll, J.; Mäcke, H. R., Hofmann, M., Debus, J., Haberkorn, U. (2001). PET imaging of somatostatin receptors using [68GA]DOTA-D-Phe1-Tyr3-octreotide: first results in patients with meningiomas, *J Nucl Med*, Vol. 42, No. 7, pp. 1053-1056, ISSN 0161-5505

Herholz, K.; Holzer, T.; Bauer, B.; Schroder, R.; Voges, J.; Ernestus, R. I.; Mendoza, G.; Weber-Luxenburger, G.; Löttgen, J.; Thiel, A.; Wienhard, K. & Heiss WD. (1998). 11C-methionine PET for differential diagnosis of low-grade gliomas, *Neurology*, Vol. 50, No. 5, pp. 1316-1322, ISSN 0028-3878

Hoffman, J. M.; Waskin, H. A.; Schifter, T.; Hanson, M. W.; Gray, L.; Rosenfeld, S. & Coleman, R. E. (1993). FDG-PET in differentiating lymphoma from nonmalignant central nervous system lesions in patients with AIDS, *J Nucl Med*, Vol.34, No.4, pp. 567-575, ISSN 0161-5505

Hsieh, C. H.; Chen, Y. F.; Chen, F. D.; Hwang, J. J.; Chen, J. C.; Liu, R. S.; Kai, J. J.; Chang, C. W. & Wang, H. E. (2005). Evaluation of pharmacokinetics of 4-borono-2-(18)F-fluoro-L-phenylalanine for boron neutron capture therapy in a glioma-bearing rat model with hyperosmolar blood-brain barrier disruption, *J Nucl Med*, Vol.46, No.11, pp. 1858-1865, ISSN 0161-5505

Hubner, K. F., Thie, J. A., Smith, G. T., Kabalka, G. W., Keller, I. B., Kliefoth, A. B., Campbell, S. K., Buonocore, E. (1998). Positron Emission Tomography (PET) with 1-Aminocyclobutane-1-[(11)C]carboxylic Acid (1-[(11)C]-ACBC) for Detecting Recurrent Brain Tumors, *Clin Positron Imaging*, Vol. 1, No. 3, pp. 165-173, ISSN 1095-0397

Imahori, Y.; Ueda, S.; Ohmori, Y.; Kusuki, T.; Ono, K.; Fujii, R. & Ido, T. (1998). Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma, *J Nucl Med*, Vol.39, No.2, pp. 325-333, ISSN 0161-5505

Jacobs, A. H.; Thomas, A.; Kracht, L. W.; Li, H.; Dittmar, C.; Garlip, G.; Galldiks, N.; Klein, J. C.; Sobesky, J.; Hilker, R.; Vollmar, S.; Herholz, K.; Wienhard, K. & Heiss, W. D. (2005). 18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumors, *J Nucl Med*, Vol.46, No.12, pp. 1948-1958, ISSN 0161-5505

Jager, P. L.; Vaalburg, W.; Pruim, J.; de Vries, E. G.; Langen, K. J. & Piers, D. A. (2001). Radiolabeled amino acids: basic aspects and clinical applications in oncology, *J Nucl Med*, Vol.42, No.3, pp. 432-445, ISSN 0161-5505

Kaschten, B.; Stevenaert, A.; Sadzot, B.; Deprez, M.; Degueldre, C.; Del Fiore, G.; Luxen, A. & Reznik, M. (1998). Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine, *J Nucl Med*, Vol. 39, No. 5, pp. 778-785, ISSN 0161-5505

Kaufman, S. (1995). Tyrosine hydroxylase, *Adv Enzymol Relat Areas Mol Biol*, Vol.70, pp. 103-220, ISSN 0065-258X

Kawai, N.; Kagawa, M.; Miyake, K.; Nishiyama, Y.; Yamamoto, Y. & Shiraishi, H. (2009). Use of 18F-fluorothymidine positron emission tomography in brain tumor, *No Shinkei Geka*, Vol. 37, No. 7, pp. 657-664, ISSN 0301-2603

Kawai, N.; Kawanishi, M.; Tamiya, T. & Nagao, S. (2005). Crossed cerebellar glucose hypermetabolism demonstrated using PET in symptomatic epilepsy--case report, *Ann Nucl Med*, Vol.19, No.3, pp. 231-234, ISSN 0914-7187

Kim, D. W.; Jung, S. A.; Kim, C. G. & Park, S. A. (2010). The efficacy of dual time point F-18 FDG PET imaging for grading of brain tumors, *Clin Nucl Med*, Vol.35, No.6, pp. 400-403, ISSN 1536-0229

Kim, S.; Chung, J. K.; Im, S. H.; Jeong, J. M.; Lee, D. S.; Kim, D. G.; Jung, H. W. & Lee, M. C. (2005). 11C-methionine PET as a prognostic marker in patients with glioma: comparison with 18F-FDG PET, *Eur J Nucl Med Mol Imaging*, Vol.32, No.1, pp. 52-59, ISSN 1619-7070

Kimura, R. H.; Cheng, Z.; Gambhir, S. S. & Cochran, J. R. (2009). Engineered knottin peptides: a new class of agents for imaging integrin expression in living subjects, *Cancer Res*, Vol.69, No.6, pp. 2435-2442, ISSN 1538-7445

Kleihues, P. & Sobin, L. H. (2000). World Health Organization classification of tumors, *Cancer*, Vol.88, No.12, pp. 2887, ISSN 0008-543X

Kountouras, J.; Zavos, C. & Chatzopoulos, D. (2005). Apoptotic and anti-angiogenic strategies in liver and gastrointestinal malignancies, *J Surg Oncol*, Vol.90, No.4, pp. 249-259, ISSN 0022-4790

Kwee, S. A.; Coel, M. N.; Lim, J. & Ko, J. P., (2004). Combined use of F-18 fluorocholine positron emission tomography and magnetic resonance spectroscopy for brain tumor evaluation, *J Neuroimaging*, Vol. 14, No. 3, pp. 285-289, ISSN 1051-2284

Kwee, S. A.; Ko, J. P.; Jiang, C. S.; Watters, M. R. & Coel, M. N., (2007). Solitary brain lesions enhancing at MR imaging: evaluation with fluorine 18 fluorocholine PET, *Radiology*, Vol. 244, No. 2, pp. 557-565, ISSN 0033-8419

Lau, E. W.; Drummond, K. J.; Ware, R. E.; Drummond, E.; Hogg, A.; Ryan, G.; Grigg, A.; Callahan, J. & Hicks, R. J. (2010). Comparative PET study using F-18 FET and F-18 FDG for the evaluation of patients with suspected brain tumour, *J Clin Neurosci*, Vol.17, No.1, pp. 43-49, ISSN 1532-2653

Lemmens, K. P.; Abraham, C.; Hoekstra, T.; Ruiter, R. A.; De Kort, W. L.; Brug, J. & Schaalma, H. P. (2005). Why don't young people volunteer to give blood? An investigation of the correlates of donation intentions among young nondonors, *Transfusion*, Vol.45, No.6, pp. 945-955, ISSN 0041-1132

Leskinen-Kallio, S.; Nagren, K.; Lehikoinen, P.; Ruotsalainen, U. & Joensuu, H. (1991). Uptake of 11C-methionine in breast cancer studied by PET. An association with the size of S-phase fraction, *Br J Cancer*, Vol.64, No.6, pp. 1121-1124, ISSN 0007-0920

Li, G. Q. & Zhang, H. F. (2004). Mad2 and p27 expression profiles in colorectal cancer and its clinical significance, *World J Gastroenterol*, Vol.10, No.21, pp. 3218-3220, ISSN 1007-9327

Lilja, A.; Bergstrom, K.; Hartvig, P.; Spannare, B.; Halldin, C.; Lundqvist, H. & Langstrom, B. (1985). Dynamic study of supratentorial gliomas with L-methyl-11C-methionine and positron emission tomography, *AJNR Am J Neuroradiol*, Vol.6, No.4, pp. 505-514, ISSN 0195-6108

Liu, S. (2009). Radiolabeled cyclic RGD peptides as integrin alpha(v)beta(3)-targeted radiotracers: maximizing binding affinity via bivalency, *Bioconjug Chem*, Vol.20, No.12, pp. 2199-2213, ISSN 1520-4812

Lopresti, B. J. & Mason, N. S., (2009). 2-^{18}F-fluoroacetate: a useful tool for assessing gliosis in the central nervous system?, *J Nucl Med*, Vol. 50, No. 6, pp. 841-843, ISSN 0161-5505

MacDonald, T. J.; Taga, T.; Shimada, H.; Tabrizi, P.; Zlokovic, B. V.; Cheresh, D. A. & Laug, W. E. (2001). Preferential susceptibility of brain tumors to the antiangiogenic effects of an alpha(v) integrin antagonist, *Neurosurgery*, Vol.48, No.1, pp. 151-157, ISSN 0148-396X

Main, A. L.; Harvey, T. S.; Baron, M.; Boyd, J. & Campbell, I. D. (1992). The three-dimensional structure of the tenth type III module of fibronectin: an insight into RGD-mediated interactions, *Cell*, Vol.71, No.4, pp. 671-678, ISSN 0092-8674

Marik, J.; Ogasawara, A.; Martin-McNulty, B.; Ross, J.; Flores, J. E.; Gill, H. S.; Tinianow, J. N.; Vanderbilt, A. N.; Nishimura, M.; Peale, F.; Pastuskovas, C.; Greve, J. M.; van Bruggen, N. & Williams, S.P. (2009). PET of glial metabolism using 2-^{18}F-fluoroacetate, *J Nucl Med*, Vol. 50, No. 6, pp. 982-990, ISSN 0161-5505

McGeer, P. L.; Kamo, H.; Harrop, R.; McGeer, E. G.; Martin, W. R.; Pate, B. D. & Li, D. K. (1986). Comparison of PET, MRI, and CT with pathology in a proven case of Alzheimer's disease, *Neurology*, Vol.36, No.12, pp. 1569-1574, ISSN 0028-3878

Miao, Z.; Ren, G.; Liu, H.; Kimura, R. H.; Jiang, L.; Cochran, J. R.; Gambhir, S. S. & Cheng, Z. (2009). An engineered knottin peptide labeled with 18F for PET imaging of integrin expression, *Bioconjug Chem*, Vol.20, No.12, pp. 2342-2347, ISSN 1520-4812

Morowitz, H. J.; Kostelnik, J. D.; Yang, J. & Cody, G. D. (2000). The origin of intermediary metabolism, *Proc Natl Acad Sci U S A*, Vol.97, No.14, pp. 7704-7708, ISSN 0027-8424

Muzi, M.; Spence, A. M.; O'Sullivan, F.; Mankoff, D. A.; Wells, J. M.; Grierson, J. R.; Link, J. M. & Krohn, K.A. (2006). Kinetic analysis of 3'-deoxy-3'-18F-fluorothymidine in patients with gliomas, *J Nucl Med*, Vol. 47, No. 10, pp. 1612-1621, ISSN 0161-5505

Nagatsu, T. (1995). Tyrosine hydroxylase: human isoforms, structure and regulation in physiology and pathology, *Essays Biochem*, Vol.30, pp. 15-35, ISSN 0071-1365

Ogawa, T.; Kanno, I.; Shishido, F.; Inugami, A.; Higano, S.; Fujita, H.; Murakami, M.; Uemura, K.; Yasui, N. & Mineura, K. (1991). Clinical value of PET with 18F-fluorodeoxyglucose and L-methyl-11C-methionine for diagnosis of recurrent brain tumor and radiation injury, *Acta Radiol*, Vol.32, No.3, pp. 197-202, ISSN 0284-1851

Ogawa, T.; Shishido, F.; Kanno, I.; Inugami, A.; Fujita, H.; Murakami, M.; Shimosegawa, E.; Ito, H.; Hatazawa, J. & Okudera, T. (1993). Cerebral glioma: evaluation with methionine PET, *Radiology*, Vol.186, No.1, pp. 45-53, ISSN 0033-8419

Ohgaki, H. & Kleihues, P. (2005). Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas, *J Neuropathol Exp Neurol*, Vol.64, No.6, pp. 479-489, ISSN 0022-3069

Ohtani, T.; Kurihara, H.; Ishiuchi, S.; Saito, N.; Oriuchi, N.; Inoue, T. & Sasaki T. (2001). Brain tumour imaging with carbon-11 choline: comparison with FDG PET and gadolinium-enhanced MR imaging, *Eur J Nucl Med*, Vol. 28, No. 11, pp. 1664-1670, ISSN 0340-6997

Okamoto, S.; Shiga, T.; Hattori, N.; Kubo, N.; Takei, T.; Katoh, N.; Sawamura, Y.; Nishijima, K.; Kuge, Y. & Tamaki, N. (2010). Semiquantitative analysis of C-11 methionine PET may distinguish brain tumor recurrence from radiation necrosis even in small lesions, *Ann Nucl Med*, ISSN 1864-6433

Olivero, W. C.; Dulebohn, S. C. & Lister, J. R. (1995). The use of PET in evaluating patients with primary brain tumours: is it useful?, *J Neurol Neurosurg Psychiatry*, Vol.58, No.2, pp. 250-252, ISSN 0022-3050

Ono, Y.; Ito, T.; Watanabe, T.; Koshio, O.; Tansho, S.; Ikeda, T.; Kawakami, S. & Miyazawa, Y. (2004). Opsonic activity assessment of human intravenous immunoglobulin preparations against drug-resistant bacteria, *J Infect Chemother*, Vol.10, No.4, pp. 234-238, ISSN 1341-321X

Padma, M. V.; Said, S.; Jacobs, M.; Hwang, D. R.; Dunigan, K.; Satter, M.; Christian, B.; Ruppert, J.; Bernstein, T.; Kraus, G. & Mantil, J. C. (2003). Prediction of pathology and survival by FDG PET in gliomas, *J Neurooncol*, Vol.64, No.3, pp. 227-237, ISSN 0167-594X

Patronas, N. J.; Di Chiro, G.; Kufta, C.; Bairamian, D.; Kornblith, P. L.; Simon, R. & Larson, S. M. (1985). Prediction of survival in glioma patients by means of positron emission tomography, *J Neurosurg*, Vol.62, No.6, pp. 816-822, ISSN 0022-3085

Pauleit, D.; Floeth, F.; Hamacher, K.; Riemenschneider, M. J.; Reifenberger, G.; Muller, H. W.; Zilles, K.; Coenen, H. H. & Langen, K. J. (2005). O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas, *Brain*, Vol. 128, No. Pt 3, pp. 678-687, ISSN 1460-2156

Pedersen, P. L. (2007). Warburg, me and Hexokinase 2: Multiple discoveries of key molecular events underlying one of cancers' most common phenotypes, the "Warburg Effect", i.e., elevated glycolysis in the presence of oxygen, *J Bioenerg Biomembr*, Vol.39, No.3, pp. 211-222, ISSN 0145-479X

Popperl, G.; Gotz, C.; Rachinger, W.; Gildehaus, F. J.; Tonn, J. C. & Tatsch, K. (2004). Value of O-(2-[18F]fluoroethyl)- L-tyrosine PET for the diagnosis of recurrent glioma, *Eur J Nucl Med Mol Imaging*, Vol.31, No.11, pp. 1464-1470, ISSN 1619-7070

Popperl, G.; Kreth, F. W.; Herms, J.; Koch, W.; Mehrkens, J. H.; Gildehaus, F. J.; Kretzschmar, H. A.; Tonn, J. C. & Tatsch, K. (2006). Analysis of 18F-FET PET for grading of recurrent gliomas: is evaluation of uptake kinetics superior to standard methods?, *J Nucl Med*, Vol.47, No.3, pp. 393-403, ISSN 0161-5505

Rasey, J. S.; Casciari, J. J.; Hofstrand, P. D.; Muzi, M.; Graham, M. M. & Chin, L. K. (2000). Determining hypoxic fraction in a rat glioma by uptake of radiolabeled fluoromisonidazole, *Radiat Res*, Vol.153, No.1, pp. 84-92, ISSN 0033-7587

Ricci, P. E.; Karis, J. P.; Heiserman, J. E.; Fram, E. K.; Bice, A. N. & Drayer, B. P. (1998). Differentiating recurrent tumor from radiation necrosis: time for re-evaluation of positron emission tomography?, *AJNR Am J Neuroradiol*, Vol.19, No.3, pp. 407-413, ISSN 0195-6108

Roelcke, U.; Radu, E. W.; von Ammon, K.; Hausmann, O.; Maguire, R. P. & Leenders, K. L. (1995). Alteration of blood-brain barrier in human brain tumors: comparison of [18F]fluorodeoxyglucose, [11C]methionine and rubidium-82 using PET, *J Neurol Sci*, Vol.132, No.1, pp. 20-27, ISSN 0022-510X

Sartor, K. (1999). MR imaging of the brain: tumors, *Eur Radiol*, Vol.9, No.6, pp. 1047-1054, ISSN 0938-7994

Sasajima, T.; Miyagawa, T.; Oku, T.; Gelovani, J. G.; Finn, R. & Blasberg, R. (2004). Proliferation-dependent changes in amino acid transport and glucose metabolism in glioma cell lines, *Eur J Nucl Med Mol Imaging*, Vol.31, No.9, pp. 1244-1256, ISSN 1619-7070

Schnell, O.; Krebs, B.; Carlsen, J.; Miederer, I.; Goetz, C.; Goldbrunner, R. H.; Wester, H. J.; Haubner, R.; Popperl, G.; Holtmannspotter, M.; Kretzschmar, H. A.; Kessler, H.; Tonn, J. C.; Schwaiger, M. & Beer, A. J. (2009). Imaging of integrin alpha(v)beta(3) expression in patients with malignant glioma by [18F] Galacto-RGD positron emission tomography, *Neuro Oncol*, Vol.11, No.6, pp. 861-870, ISSN 1523-5866

Shibahara, I.; Kumabe, T.; Kanamori, M.; Saito, R.; Sonoda, Y.; Watanabe, M.; Iwata, R.; Higano, S.; Takanami, K.; Takai, Y. & Tominaga, T. (2010). Imaging of hypoxic lesions in patients with gliomas by using positron emission tomography with 1-(2-[18F]fluoro-1-[hydroxymethyl]ethoxy)methyl-2-nitroimidazole, a new 18F-labeled 2-nitroimidazole analog, *J Neurosurg*, Vol. 113, No. 2, pp. 358-368, ISSN 1933-0693

Shields, A. F.; Grierson, J. R.; Dohmen, B. M.; Machulla, H. J.; Stayanoff, J. C.; Lawhorn-Crews, J. M.; Obradovich, J. E.; Muzik, O. & Mangner, T. J. (1998). Imaging proliferation in vivo with [F-18]FLT and positron emission tomography, *Nat Med*, Vol. 4, No. 11, pp. 1334-1336, ISSN 1078-8956

Schiepers, C.; Chen, W.; Cloughesy, T.; Dahlbom, M. & Huang, S. (2007). 18F-FDOPA Kinetics in Brain Tumors, *J Nucl Med*, Vol. 48, pp. 1651–1661, ISSN 0161-5505

Shinoura, N.; Nishijima, M.; Hara, T.; Haisa, T.; Yamamoto, H.; Fujii, K.; Mitsui, I.; Kosaka, N. & Kondo, T. (1997). Brain tumors: detection with C-11 choline PET, *Radiology*, Vol.202, No.2, pp. 497-503, ISSN 0033-8419

Sonoda, Y.; Kumabe, T.; Takahashi, T.; Shirane, R. & Yoshimoto, T. (1998). Clinical usefulness of ^{11}C-MET PET and 201T1 SPECT for differentiation of recurrent glioma from radiation necrosis, *Neurol Med Chir (Tokyo)*, Vol. 38, No. 6, pp. 342-347; discussion 347-348, ISSN 0470-8105

Spence, A. M.; Muzi, M.; Graham, M. M.; O'Sullivan, F.; Krohn, K. A.; Link, J. M.; Lewellen, T. K.; Lewellen, B.; Freeman, S. D.; Berger, M. S. & Ojemann, G. A. (1998). Glucose metabolism in human malignant gliomas measured quantitatively with PET, 1-[C-11]glucose and FDG: analysis of the FDG lumped constant, *J Nucl Med*, Vol.39, No.3, pp. 440-448, ISSN 0161-5505

Spence, A. M.; Muzi, M.; Mankoff, D. A.; O'Sullivan, S. F.; Link, J. M.; Lewellen, T. K.; Lewellen, B.; Pham, P.; Minoshima, S.; Swanson, K. & Krohn, K. A. (2004). 18F-FDG PET of gliomas at delayed intervals: improved distinction between tumor and normal gray matter, *J Nucl Med*, Vol.45, No.10, pp. 1653-1659, ISSN 0161-5505

Szeto, M. D.; Chakraborty, G.; Hadley, J.; Rockne, R.; Muzi, M.; Alvord, E. C., Jr.; Krohn, K. A.; Spence, A. M. & Swanson, K. R. (2009). Quantitative metrics of net proliferation and invasion link biological aggressiveness assessed by MRI with hypoxia assessed by FMISO-PET in newly diagnosed glioblastomas, *Cancer Res*, Vol.69, No.10, pp. 4502-4509, ISSN 1538-7445

Tochon-Danguy, H. J.; Sachinidis, J. I.; Chan, F.; Chan, J. G.; Hall, C.; Cher, L.; Stylli, S.; Hill, J.; Kaye, A. & Scott, A. M. (2002). Imaging and quantitation of the hypoxic cell fraction of viable tumor in an animal model of intracerebral high grade glioma using [18F]fluoromisonidazole (FMISO), *Nucl Med Biol*, Vol.29, No.2, pp. 191-197, ISSN 0969-8051

Tsuchida, T.; Takeuchi, H.; Okazawa, H.; Tsujikawa, T. & Fujibayashi, Y. (2008). Grading of brain glioma with 1-^{11}C-acetate PET: comparison with ^{18}F-FDG PET, *Nucl Med Biol*, Vol. 35, No. 2, pp. 171-176, ISSN 0969-8051

Tsuyuguchi, N.; Sunada, I.; Iwai, Y.; Yamanaka, K.; Tanaka, K.; Takami, T.; Otsuka, Y.; Sakamoto, S.; Ohata, K.; Goto, T. & Hara M. (2003). Methionine positron emission tomography of recurrent metastatic brain tumor and radiation necrosis after stereotactic radiosurgery: is a differential diagnosis possible?, *J Neurosurg*, Vol. 98, No. 5, pp. 1056-1064, ISSN 0022-3085

Valk, P. E.; Mathis, C. A.; Prados, M. D.; Gilbert, J. C. & Budinger, T. F. (1992). Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole, *J Nucl Med*, Vol. 33, No. 12, pp. 2133-2137, ISSN 0161-5505

Van Laere, K.; Ceyssens, S.; Van Calenbergh, F.; de Groot, T.; Menten, J.; Flamen, P.; Bormans, G. & Mortelmans, L. (2005). Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: sensitivity, inter-observer variability and prognostic value, *Eur J Nucl Med Mol Imaging*, Vol.32, No.1, pp. 39-51, ISSN 1619-7070

van Waarde, A.; Cobben, D. C.; Suurmeijer, A. J.; Maas, B.; Vaalburg, W.; de Vries, E. F.; Jager, P. L.; Hoekstra, H. J. & Elsinga, P. H. (2004). Selectivity of 18F-FLT and 18F-

FDG for differentiating tumor from inflammation in a rodent model, *J Nucl Med*, Vol.45, No.4, pp. 695-700, ISSN 0161-5505

van Waarde, A.; Cobben, D. C.; Suurmeijer, A. J.; Maas, B.; Vaalburg, W.; de Vries, E. F.; Jager, P. L.; Hoekstra, H. J. & Elsinga, P. H. (2004). Selectivity of ^{18}F-FLT and ^{18}F-FDG for differentiating tumor from inflammation in a rodent model, *J Nucl Med*, Vol. 45, No. 4, pp. 695-700, ISSN 0161-5505

van Waarde, A.; Jager, P. L.; Ishiwata, K.; Dierckx, R. A. & Elsinga, P. H., (2006). Comparison of sigma-ligands and metabolic PET tracers for differentiating tumor from inflammation, *J Nucl Med*, Vol. 47, No. 1, pp. 150-154, ISSN 0161-5505

Vanpouille, C.; Le Jeune, N.; Kryza, D.; Clotagatide, A.; Janier, M.; Dubois, F. and Perek, N. (2009). Influence of multidrug resistance on (18)F-FCH cellular uptake in a glioblastoma model, *Eur J Nucl Med Mol Imaging*, Vol. 36, No. 8, pp. 1256-1264, ISSN 1619-7089

Wang, L.; Qu, W.; Lieberman, B. P.; Plossl, K. & Kung, H. F., (2011). Synthesis, uptake mechanism characterization and biological evaluation of (18)F labeled fluoroalkyl phenylalanine analogs as potential PET imaging agents, *Nucl Med Biol*, Vol. 38, No. 1, pp. 53-62, ISSN 1872-9614

Wang, S. X.; Boethius, J. & Ericson, K. (2006). FDG-PET on irradiated brain tumor: ten years' summary, *Acta Radiol*, Vol. 47, No. 1, pp. 85-90, ISSN 0284-1851

Warburg, O. (1956). On the origin of cancer cells, *Science*, Vol. 123, No. 3191, pp. 309-314, ISSN 0036-8075

Weber, W. A.; Wester, H. J.; Grosu, A. L.; Herz, M., Dzewas, B.; Feldmann, H. J.; Molls, M.; Stöcklin, G. & Schwaiger, M. (2000). O-(2-[^{18}F]fluoroethyl)-L-tyrosine and L-[methyl-^{11}C]methionine uptake in brain tumours: initial results of a comparative study, *Eur J Nucl Med*, Vol. 27, No. 5, pp. 542-549, ISSN 0340-6997

Wester, H. J.; Herz, M.; Weber, W.; Heiss, P.; Senekowitsch-Schmidtke, R.; Schwaiger, M., et al. & Stöcklin G. (1999). Synthesis and radiopharmacology of O-(2-[^{18}F]fluoroethyl)-L-tyrosine for tumor imaging, *J Nucl Med*, Vol. 40, No. 1, pp. 205-212, ISSN 0161-5505

Wheeler, K. T.; Wang, L. M.; Wallen, C. A.; Childers, S. R.; Cline, J. M.; Keng, P. C. & Mach, R. H. (2000). Sigma-2 receptors as a biomarker of proliferation in solid tumours, *Br J Cancer*, Vol. 82, No. 6, pp. 1223-1232, ISSN 0007-0920

Wong, T. Z.; Turkington, T. G.; Hawk, T. C. & Coleman, R. E. (2004). PET and brain tumor image fusion, *Cancer J*, Vol. 10, No. 4, pp. 234-242, ISSN 1528-9117

Wu, Y., Zhang, X.; Xiong, Z.; Cheng, Z.; Fisher, D. R.; Liu, S.; Gambhir, S. S. & Chen, X. (2005). microPET imaging of glioma integrin {alpha}v{beta}3 expression using (64)Cu-labeled tetrameric RGD peptide, *J Nucl Med*, Vol. 46, No. 10, pp. 1707-1718, ISSN 0161-5505

Wyss, M. T.; Spaeth, N., Biollaz, G.; Pahnke, J.; Alessi, P.; Trachsel, E.; Treyer, V.; Weber, B.; Neri, D. & Buck A. (2007). Uptake of ^{18}F-Fluorocholine, ^{18}F-FET, and ^{18}F-FDG in C6 gliomas and correlation with ^{131}I-SIP(L19), a marker of angiogenesis, *J Nucl Med*, Vol. 48, No. 4, pp. 608-614, ISSN 0161-5505

Yamamoto, Y.; Nishiyama, Y.; Kimura, N.; Kameyama, R.; Kawai, N.; Hatakeyama, T.; Kaji, M. & Ohkawa, M. (2008). ^{11}C-acetate PET in the evaluation of brain glioma: comparison with ^{11}C-methionine and ^{18}F-FDG-PET, *Mol Imaging Biol*, Vol. 10, No. 5, pp. 281-287, ISSN 1536-1632
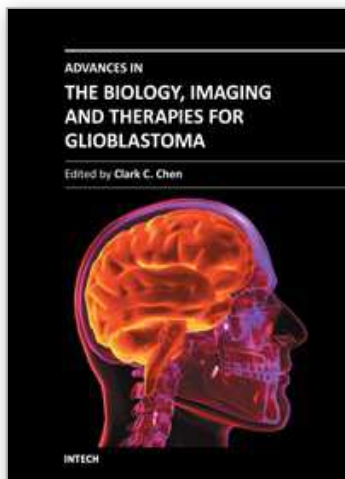
Advances in the Biology, Imaging and Therapies for Glioblastoma

Edited by Prof. Clark Chen

This book is intended for physicians and scientists with interest in glioblastoma biology, imaging and therapy. Select topics in DNA repair are presented here to demonstrate novel paradigms as they relate to therapeutic strategies. The book should serve as a supplementary text in courses and seminars as well as a general reference.

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