

Imaging Gliomas with Positron Emission Tomography and Single-Photon Emission Computed Tomography

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Over the last two decades the large volume of research involving various brain tracers has shed invaluable light on the pathophysiology of cerebral neoplasms. Yet the question remains as to how best to incorporate this newly acquired insight into the clinical context. Thallium is the most studied radiotracer with the longest track record. Many, but not all studies, show a relationship between ^{201}Tl uptake and tumor grade. Due to the overlap between tumor uptake and histologic grades, ^{201}Tl cannot be used as the sole noninvasive diagnostic or prognostic tool in brain tumor patients. However, it may help differentiating a high-grade tumor recurrence from radiation necrosis. MIBI is theoretically a better imaging agent than ^{201}Tl but it has not convincingly been shown to differentiate tumors according to grade. MDR-1 gene expression as demonstrated by MIBI does not correlate with chemoresistance in high grade gliomas. Currently, MIBI's clinical role in brain tumor imaging has yet to be defined. IMT, a radio-labeled amino acid analog, may be useful for identifying postoperative tumor recurrence and, in this application, appears to be a cheaper, more widely available tool than positron

emission tomography (PET). However, its ability to accurately identify tumor grade is limited. 18 F-2-Fluoro-2-deoxy-D-glucose (FDG) PET predicts tumor grade, and the metabolic activity of brain tumors has a prognostic significance. Whether FDG uptake has an independent prognostic value above that of histology remains debated. FDG-PET is effective in differentiating recurrent tumor from radiation necrosis for high-grade tumors, but has limited value in defining the extent of tumor involvement and recurrence of low-grade lesions. Amino-acid tracers, such as MET, perform better for this purpose and thus play a complementary role to FDG. Given the poor prognosis of patients with gliomas, particularly with high-grade lesions, the overall clinical utility of single photon emission computed tomography (SPECT) and PET in characterizing recurrent lesions remains dependent on the availability of effective treatments. These tools are thus mostly suited to the evaluation of treatment response in experimental protocols designed to improve the patients' outcome.

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BRAIN TUMORS ARE typically diagnosed when they produce symptoms such as headache, nausea, personality change or seizure, or when they produce focal neurologic impairments. Although historically nuclear medicine techniques once played a significant role for diagnosing brain tumors, the $^{99\text{m}}\text{Tc}$ pertechnetate, diethylenetriamine pentaxetic acid (DTPA) or glucoheptanate brain scans are now obsolete. Magnetic Resonance Imaging (MRI) has now been established as the preferred diagnostic modality for detecting suspected primary brain tumors, with an exquisite ability to localize brain tumors in relationship to normal structures, evaluate edema, hemorrhage, and hydrocephalus.

The estimated number of new cases of central nervous system malignancies in the United States

is 17,000 for 2002.¹ Most of these malignancies involve the brain, with a high rate of mortality despite significant advances in early diagnosis brought about by computed tomography (CT) and MRI since the 1980s. Spinal cord tumors are much less frequent, with an incidence ratio relative to brain tumors of approximately 15%.

According to the 1993 World Health Organization (WHO) classification, primary brain tumors are classified according to their presumed cell of origin.² For example, tumors derived from astrocytes are called astrocytomas or gliomas, while tumors derived from ependymocytes are called ependymomas. A nonexhaustive list is presented in Table 1. Gliomas constitute approximately 45% of all brain tumors.³ Other common tumors include meningiomas (27%), pituitary tumors (10%) and nerve sheath tumors (7%). Central nervous system (CNS) lymphomas constitute less than 4% of primary brain tumors. Although many benign tumors such as meningiomas and neuromas are cured by surgery, even low-grade glial cell tumors are notoriously challenging to treat, with a very high relapse and mortality rate. Since most nuclear imaging techniques have been targeted at characterizing primary or recurrent gliomas, this review will focus on that particular group of tumors.

Gliomas are typically subdivided in astrocytic

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Table 1. Primary Tumors of the Central Nervous System

Neuroepithelial Tumors:
Astrocytic tumors
Pilocytic astrocytoma (grade I)
Astrocytoma (grade II)
Anaplastic astrocytoma (grade III)
Glioblastoma multiforme (grade IV)
Oligodendroglial tumors
Oligodendroglioma
Anaplastic oligodendroglioma
Ependymal cell tumors
Ependymoma
Anaplastic ependymoma
Myxopapillary ependymoma
Subependymoma
Mixed gliomas
Mixed oligoastrocytomas
Malignant oligoastrocytomas
Neuroepithelial tumors of uncertain origin
Gliomatosis cerebri, astroblastoma, others
Tumors of the choroid plexus
Choroid plexus papilloma and carcinoma
Neuronal and mixed neuronal-glioma tumors
Pineal Parenchyma Tumors
Pineocytoma, pineoblastoma, mixed
Tumors with neuroblastic or glioblastic elements
(embryonal tumors)
Medulloepithelioma
Primitive neuroectodermal tumors medulloblastoma and others
Neuroblastoma
Retinoblastoma
Ependymblastoma
Other CNS Neoplasms:
Tumors of the sellar region
Pituitary adenoma, craniopharyngioma
Hematopoietic tumors
Primary malignant lymphomas and others
Meningiomas and mesenchymal tumors
Tumors of cranial and spinal nerves
Schwannoma, neurofibroma

tumors, oligodendroglial tumors, ependymal tumors, and mixed gliomas. Astrocytic tumors are further graded into grade I (pilocytic astrocytoma) to grade IV (glioblastoma multiforme) according to specific pathologic criteria that include cellular atypia, mitotic activity, necrosis, endothelial proliferation, etc. The tumor grade is established depending on the number of criteria found in the histopathologic specimen.⁴

Surgery remains the primary therapeutic approach for most brain tumors, generally with a curative intent. However, except for pilocytic astrocytomas, the extent of necessary surgical resection beyond obtaining a tissue diagnosis remains controversial.⁵ In completely or partially resected

low-grade astrocytomas, radiation therapy can often be deferred until there are signs of progressive recurrence or malignant transformation. Although the 5-year progression-free survival is improved with immediate irradiation, the overall 5-year survival is unchanged. Since radiation therapy can cause significant cognitive and pituitary dysfunction in longer term survivors, well-differentiated astrocytomas can be treated with a lower dose. In infiltrative glial tumors, the goal of primary surgery is to provide a histological diagnosis while reducing tumor bulk and brain compression as much as possible. These tumors typically infiltrate apparently normal brain tissues quite deeply, and complete surgical resection is usually impossible. Patients with higher grade gliomas have a survival benefit with radiation therapy compared to chemotherapy alone. However, glioblastoma multiforme is highly radioresistant and has a dismal prognosis, with a median survival time of 10 months. The efficacy of chemotherapy is limited, and agents such as carmustine, carboplatin, procarbazine, tamoxifen, and several others have been used in clinical trials, with varying but relatively limited success. Temozolomide, an orally administered alkylating agent, is used with modest results in anaplastic astrocytomas and glioblastomas and is relatively well tolerated.⁶

Because of the relative ineffectiveness of conventional chemotherapy, multiple trials are ongoing at several institutions to search for more effective approaches, for instance gene therapy or antiangiogenic agents.⁶ The superiority of these approaches over traditional multimodality treatments that include surgery, radiation therapy and chemotherapy has yet to be demonstrated in well-designed randomized trials.

CT and MRI with contrast (to assess the integrity of the blood brain barrier) are excellent tools for tumor localization. These methods are however often unable to characterize the underlying histopathology. Particular areas of difficulty include defining tumor extension and grade, as well as differentiating tumor recurrence from necrosis or scar.⁷ Radiation necrosis is particularly problematic, as this entity can produce disruption in the blood-brain barrier by vascular and astrocytic damage, and thus contrast enhancement, edema, and cortical dysfunction that are indistinguishable from recurrent tumor on conventional CT or MRI.⁸ Several attempts have been made to circumvent

these limitations with the use of functional imaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Brain SPECT tracers have a long history predating the development of more anatomically orientated modalities such as CT and MRI, which have developed into the clinical workhorses in the primary assessment of brain tumors. There is however an appreciation of the limitations of these techniques, as mentioned above. SPECT tracers have long been used in an attempt to answer some of these questions, beginning with ^{201}Tl and MIBI, and more recently 3-[I-123]Iodo-alpha-methyl-L-tyrosine (IMT). SPECT tracers also have the distinct advantages (as compared to PET tracers) of being widely available and significantly less expensive. This section will focus on three of the most researched tracers (^{201}Tl , MIBI, and IMT).

Thallium-201

Thallium-201 (^{201}Tl) is cyclotron produced from ^{201}Pb , with a T1/2 of 73 hours. ^{201}Tl decays by electron capture to Hg-201, which then emits characteristic x-rays in the 68-80 KeV range mainly. It is classed as a group IIIA element, though it behaves chemically similar to potassium (monovalent, similar ionic radii). Thus, it is usually administered as a chloride and is rapidly distributed and cleared from the body. Most brain imaging protocols generally require IV doses ranging from ~2-4 mCi with early imaging at ~15 min and possible delayed images up to 2 hours later.

^{201}Tl was in fairly wide usage in the 1970s as a myocardial tracer. It was also known from various other clinical applications that it had very low cerebral uptake. Ancrì et al⁹ in an early study attempted to exploit some of these properties to image a group of patients with miscellaneous cerebral lesions (gliomas, meningiomas, metastases, infarction, hematomas, pituitary adenomas) as compared to normals. The patients were studied with 1.5-2 mCi of ^{201}Tl and compared to scans with 10-15 mCi of $^{99\text{m}}\text{Tc}$ pertechnetate. It was found that in the ^{201}Tl patients there was relatively good visualization of the brain including the temporal fossa and subtentorial regions (ie, low uptake). Normal areas of hyperactivity included the

orbital region, the base of the skull, and the hypophyseal region. ^{201}Tl easily identified the lesions and was felt to be superior to $^{99\text{m}}\text{Tc}$ pertechnetate because of improved contrast, discrimination between multiple lesions, and shorter time to scanning.⁹

Subsequently, in the mid 1980s Kaplan et al.¹⁰ again noting the disparity between CT brain scans and performance scores performed a study on 29 subjects with pathological correlation for seven. Patients with grade III/IV gliomas were evaluated with ^{201}Tl , $^{99\text{m}}\text{Tc}$ gluceptate, and ^{67}Ga as well as CT scans. In the seven patients with pathological follow-up, ^{201}Tl was found to be the best modality for identifying viable tumor. ^{67}Ga gave similar results in those patients not taking steroids. Gluceptate and CT were routinely unable to differentiate fibrosis, necrosis and non-fibrotic change from viable tumor. In the patients without pathologic correlation ^{201}Tl was routinely found to display smaller and more focal abnormalities than either ^{67}Ga or gluceptate. It was proposed that ^{201}Tl uptake may have been related to a combination of factors including alterations in the blood brain barrier, variability in the expression of the Na/K ATPase pump (viable cell having intact uptake mechanisms), and blood flow.

Kim et al¹¹ in the late 1980s looked at a mixed group of 45 patients most with primary brain tumors, some with metastatic lesions, hematoma or toxoplasmosis. Twenty-five patients had available autopsy information. Using ratios of regions of interest (ROI) of the tumor site compared to apparently normal contralateral hemispheric ROIs, various indices were calculated. There was a correlation between ^{201}Tl uptake and tumor grade. They were able, using a threshold ratio (tumor/non-tumor) of 1.5, to distinguish low grade from high grade lesions with an accuracy of 89%. This was not a perfect indicator of grade however, as some low grade lesions had high uptake ratios and vice versa. Partial volume effects as well as non-uniformity in the tumor ROIs (necrosis or edema) were felt to be in part responsible for these findings.

The idea of non-invasively predicting tumor grade spurred on further study by various research groups worldwide. Oriuchi et al¹² in 1993 looked at 28 presurgical patients. Postoperative tumor histology and cellular proliferation (using a thymidine analogue BUdR-bromodeoxyuridine) were

correlated. ROIs of tumor to normal contralateral brain were able to differentiate grade IV gliomas from lower grade tumors with some success. Furthermore, there was a good correlation between the ^{201}Tl index and cellular proliferation. There were, however, some false-positives (high ROIs and low proliferative indices) including a pilocytic astrocytoma. An attempt was also made to predict malignant degeneration in low grade gliomas as well as with prognosis with some success.

In an effort to further improve the specificity of ^{201}Tl brain imaging, Jinnouchi et al¹³ looked at a group of 13 meningioma patients. Meningiomas are hypervascular tumors and based on the increased blood flow they have significant ^{201}Tl uptake. By comparing the initial uptake index (early UI) to the delayed uptake index (delayed UI), a retention index (RI) was calculated. As expected the early UIs were elevated for all types of meningiomas, however delayed UIs varied somewhat between the various histologies, with the RI being lowest in meningothelial meningiomas. Based on these findings it was concluded that a high RI identifies those meningiomas with malignant potential. Ishibashi et al¹⁴ studied a group of 34 patients with various brain tumor histologies using monoclonal antibody Ki-67 and proliferating cell nuclear antigen (PCNA) as cell proliferating indices and compared these results to ^{201}Tl uptake indices (early and delayed). Astrocytomas were distinguished from glioblastomas on both early and delayed ^{201}Tl imaging, however neither tumor could be significantly distinguished from anaplastic astrocytomas. The PCNA indices correlated well with the ^{201}Tl early uptake index in astrocytomas but not for the other tumors. Ki-67 on the other hand correlated only with the delayed ^{201}Tl indices in astrocytomas, anaplastic astrocytomas and glioblastoma. Interestingly, although benign hypervascular tumors displayed increased early uptake indices, their washout rates were not statistically different from those of normo/hypovascular tumors. In effect this study showed some correlation, though not always consistently, between ^{201}Tl uptake and malignancy as well as cellular proliferation.

Dierckx et al¹⁵ conducted a large retrospective study of 90 patients comparing ^{201}Tl brain SPECT in the differential diagnosis of various brain tumors. Overall, in a population fairly representative of what might be seen in many centers, the

sensitivity was found to be 71.7% and the specificity 80.9%. False positives included a skull metastasis, hemorrhagic strokes, an angioma, and an epidural hematoma. False negatives occurred in tumors located in the posterior fossa, the temporal regions or in deep locations. Tumors of small volumes were also problematic. The comments were made that delayed imaging with retention indices as well as close clinical correlation may have helped improve the sensitivity and specificity. Ricci et al¹⁶ in a MRI/ ^{201}Tl comparison of 13 patients with histologically proven glioblastomas found that the main limiting property of ^{201}Tl was its poor resolution. It was shown that necrosis (a marker of high grade activity) was a common cause of underestimation of tumor grade. On the other hand, perilesional edema was not an important factor.

More recently, Sun et al¹⁷ described in a study of 41 patients with primary and secondary brain tumors the utility of delayed imaging and calculating retained indices. Using these tools they were able to separate low grade or benign tumor groups from high grade or metastatic tumor groups. However, in some cases there was overlap between groups.

Staffen et al¹⁸ in 1998 published a study comprising 40 patients with either a suspected brain tumor or with a recurrence of a previously treated brain tumor. As a group, low grade and high grade gliomas could be separated from each other. However, there was significant overlap with other disease entities such as scars, strokes, metastases and meningioma, limiting the clinical utility of the scans.

^{99m}Tc -MIBI (MIBI)

MIBI's utilization as a brain tumor imaging agent began well after ^{201}Tl . MIBI has several similarities to ^{201}Tl in terms of its exclusion from the brain by the BBB and its similarities as a myocardial perfusion agent. MIBI is a cationic compound and accumulates in cytoplasm and mitochondria as a result of passive diffusion across the negative cellular/organelle membrane. Uptake is nonspecific, but is driven by metabolic demand. Additionally, it has much better imaging properties (140 KeV) and larger doses can be given intravenously (10-30 mCi). O'Tuama et al¹⁹ compared ^{201}Tl to MIBI in 19 children with brain tumors and found that both modalities were fairly similar

(sensitivity of 67% for both ^{201}Tl and MIBI, specificity of 91% for ^{201}Tl vs. 100% for MIBI). Lesion boundaries were better defined by MIBI, however, they generally paralleled those of thallium. Problem areas for MIBI were in the regions of choroid plexus, uptake that wasn't prevented by the administration of potassium perchlorate. Both modalities were felt to complement MRI by providing functional information.

Using a 4-point visual grading scale (tumor MIBI uptake compared to normal brain background) Bagni et al.²⁰ looked at 27 patients presurgically. Normal MIBI distribution was observed in the choroid plexus, scalp, and pituitary gland but not in normal brain parenchyma. Among the findings a trend between MIBI uptake and astrocytoma grade was identified. Meningiomas appeared to have uptake proportional to their vascularity. Glioblastomas had variable uptake. Furthermore, lesions in the fronto-parietal regions were more easily identified as compared to those in the temporal regions or the posterior fossa.

Another study by Soler et al.²¹ looked retrospectively at a group of 35 malignant glioma patients with clinical deterioration to assess MIBI's usefulness as an indicator of tumor recurrence. Tumor uptake was compared to pituitary gland activity. Although only 6 patients had biopsies, the others were followed clinically and with conventional imaging for at least another 6 months. There was 100% sensitivity and specificity in those patients in whom a biopsy had been performed. In the other cases the SPECT findings correlated well with the clinical outcome. Thus, it was concluded that MIBI is an effective tool in differentiating tumor recurrence from radiation necrosis.

One of the interesting properties of MIBI is its efflux from cells by P-glycoprotein (Pgp), which also acts as energy-driven efflux pump for several antineoplastic agents. In a study by Yokogami et al.²² MIBI and thallium were assessed for their uptake in malignant brain tumors. The MIBI findings were also compared to the expression of the MDR-1 gene and its product Pgp. In the 19 patients studied, it was found that MIBI had sharper image definition as compared to ^{201}Tl ; however, choroid plexus uptake interfered with paraventricular lesions detection, a finding similar to previous studies. The early uptake indices for MIBI correlated better with degree of malignancy than the late uptake indices. This finding was reversed for ^{201}Tl .

MDR-1 gene expression was found to be inversely related to grade of malignancy in gliomas, thus indicating that its expression is not likely related to chemoresistance for gliomas. A further finding of note was that neither MIBI nor ^{201}Tl appeared better than MRI for determining the distribution of tumor cells.

Most recently, yet another study comparing ^{201}Tl and MIBI was published. Nishiyama et al.,²³ in a series of 25 patients with malignant brain tumors, found that uptake ratios (early and delayed) were elevated in malignant tumors for both MIBI and ^{201}Tl . The retention index was determined to be less useful. Once again, neither ^{201}Tl nor MIBI showed tumor beyond the contrast enhanced lesions on MRI, and thus likely did not accurately delineate the full tumor extension. ^{201}Tl and MIBI were found to be relatively equivalent as imaging agents.

$^{99\text{m}}\text{Tc}$ -Tetrofosmin has several features in common with $^{99\text{m}}\text{Tc}$ -MIBI, and theoretically could be used as a brain tumor imaging agent. However to date research with this radiopharmaceutical has been too sparse to draw any conclusions.²⁴

^{123}I -Alpha-Methyl Tyrosine (IMT)

An area of recent interest is that of iodine-123-alpha-methyl tyrosine (IMT). IMT is seen as a possible SPECT alternative to less available/more expensive PET tracers such as ^{11}C -methyl-methimide (MET).

Initial work on this tracer began in the late 1980s when Biersack et al.²⁵ showed that in 9 of 10 patients with brain tumors demonstrated uptake significantly above background. Further study indicated that IMT is taken up in the brain by carrier mediated, stereoselective active transport systems. These systems involve transport across both the blood brain barrier (BBB) and brain cell membranes. IMT is not incorporated into cellular proteins, however uptake does bear a relationship to cellular proliferation, at least in human glioma cells.²⁶

Clinical work has focussed on evaluating gliomas. Kuwert et al.²⁷ in 1996 analysed IMT uptake in 53 patients with various grades of gliomas (40 patients) and non-neoplastic lesions (13 patients). They reported a diagnostic sensitivity of 71% and specificity of 83% for differentiating high from low grade gliomas. High grade gliomas were separated from non-neoplastic lesions with a sen-

sitivity of 82% and specificity of 100%. Unfortunately, non-neoplastic lesions could not accurately be differentiated from low-grade gliomas. Interestingly, some marked overlap between low and high grade groups did occur, most notably with an oligodendroglioma recurrence and an oligo-astrocytoma, presumably because of the high cellularity of these tumors.

IMT imaging was performed in another study by Kuwert et al²⁸ in an effort to address the important clinical question of identification of glioma recurrence in a post primary therapy patient population. Twenty-seven patients were imaged with IMT and followed clinicopathologically. Histologic diagnosis was obtained in 11 of the patients. Using a specified uptake ratio as a cutoff between recurrence and benign post-therapeutic change, the investigators were able to achieve a sensitivity of 78% and a specificity of 100%.

The role of IMT SPECT in the non-invasive evaluation of tumor grade and prognosis has been researched. Schmidt et al²⁹ reviewed the files of patients investigated over a 10 year period with IMT. The 58 patients comprised a mixed group of primary and recurrent gliomas of various grades. No relationship between IMT tumor to background ratios and histologic grade or survival could be established. The only identified prognostic imaging feature was the absence of contrast enhancement on CT or MRI. These results were paralleled by Weber et al³⁰ who in a study of 114 patients were unable to differentiate tumor grade on the basis of IMT uptake. However, not surprisingly the presence of significant IMT uptake post tumor resection was found to be an important prognostic factor, implying the importance of IMT as a marker of residual tumor.

In a small comparative study between SPECT with IMT and PET with MET, 11 patients with cerebral gliomas were evaluated by Langen et al.³¹ In all cases both tracers showed significant uptake in the gliomas above baseline with no discrepant results between imaging agents. IMT was, however, found to have a faster washout from the tumors than MET, presumably because IMT isn't involved in intracellular metabolism as opposed to MET. Disruption of the BBB did not appear to be a critical factor for IMT or MET uptake, as two non-enhancing tumors on CT both displayed increased amino acid accumulation.

Several comparisons of IMT SPECT with FDG

PET have also been performed. Weber et al.,³² demonstrated that in a series of 19 patients IMT was more reliable than FDG at detecting tumor with less interobserver variability and was better at delineating tumor extent. IMT uptake was not related to grade, although FDG uptake did appear proportional to histologic grade. Woesler et al.,³³ in another study of 23 histologically proven brain tumors found that IMT and FDG were equally good at differentiating low grade and high grade tumors with accuracies of 83% and 91% respectively. In yet another study Bader et al.,³⁴ examined 30 patients who were being assessed post primary therapy for either tumor recurrence or for determination of upgrading. IMT scanning was true positive in 26 of 29 patients for recurrence. IMT identified the one true negative patient. IMT was not successful in noninvasively grading the recurrence. FDG was true positive in 23 of the 29 patients, and also identified the one true negative. As would be expected, IMT was better than FDG for detecting low grade recurrences, but FDG on the other hand was able to grade recurrence. Sasaki et al.³⁵ evaluated ²⁰¹Tl, MET and FDG PET in 23 patients with newly diagnosed astrocytic tumors. They found that ²⁰¹Tl was better than either FDG or MET for evaluating histologic grade. MET was the most effective agent for defining the limits of astrocytomas. Two examples of IMT scans are shown in Figs 1 and 2.

A new SPECT tracer is *p*-[I-123]iodo-L-phenylalanine. Only very preliminary work has been performed on this agent. It appears to be similar to IMT in many respects, however may be somewhat more specific for brain tumors and has a longer retention time, allowing for more flexibility in imaging.³⁶

POSITRON EMISSION TOMOGRAPHY (PET)

The first attempts to visualize brain tumors with positron emission tomography (PET) were published in 1951 by Wrenn and colleagues, followed closely by Brownell and Sweet in 1953.^{37,38} Since then, several radioisotopes and radiopharmaceuticals have been used in clinical research studies. ¹³N-ammonia was unsuccessful in visualizing primary brain tumors.³⁹ ¹⁵O-water was used to measure tumor blood flow⁴⁰ and ¹⁵O₂ to measure oxygen utilization.⁴¹ Nucleoside analogues such as ¹¹C-thymidine have been utilized with mixed success to detect cell division rates.⁴² Few reports

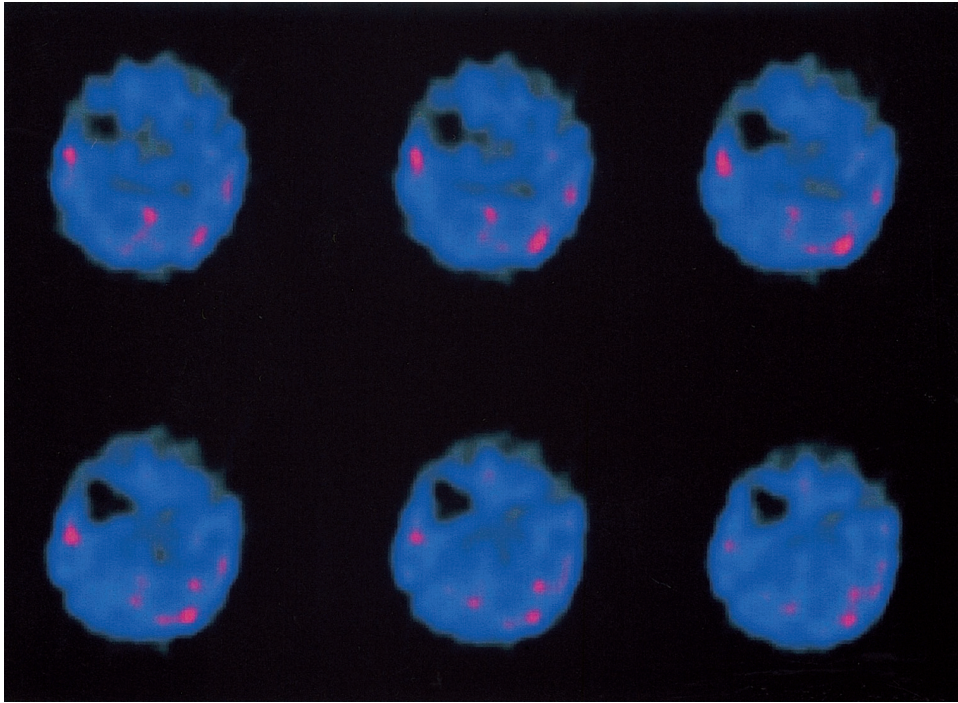


Fig 1. Fifty-year-old patient reevaluated after radiotherapy for a suspected recurrent multifocal oligoastrocytoma grade III initially located in the right fronto-parietal area. There was no evidence of recurrence on the IMT scan, which only showed a photopenic area. Follow-up confirmed these findings. (Courtesy of Dr H. Everaert, AZ-VUB, Brussels).

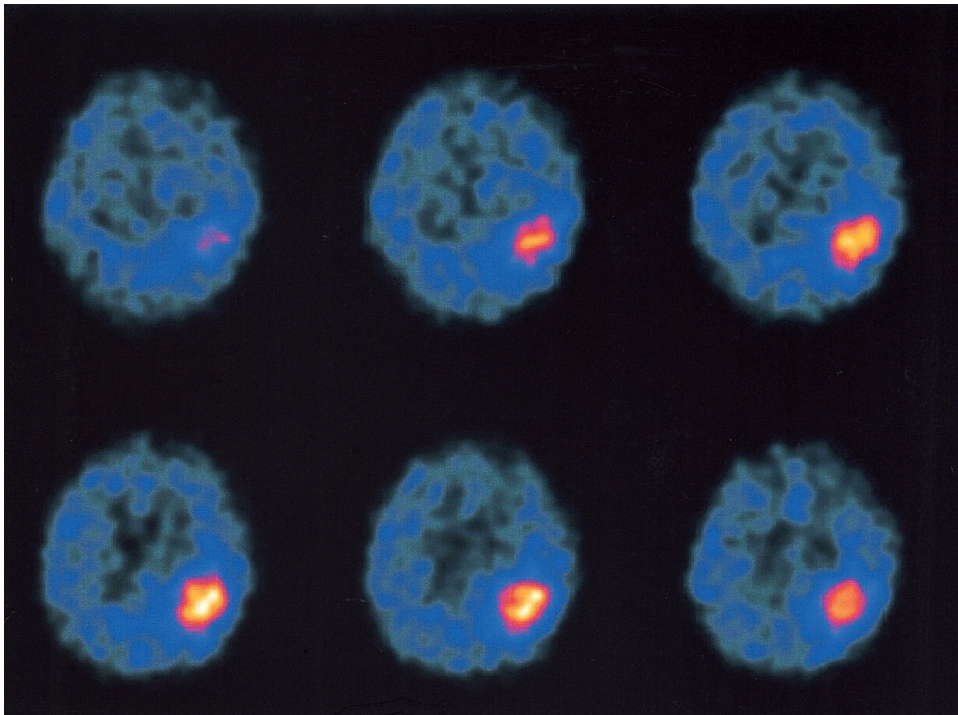


Fig 2. Reevaluation after surgery, chemo- and radiotherapy for a glioblastoma multiforme. There is an intense IMT accumulation in the left temporo-occipital region consistent with recurrent tumor. (Courtesy of Dr H. Everaert, AZ-VUB, Brussels).

have been published with this tracer for brain tumor imaging. Thymidine analogues are not transported well across the blood-brain barrier (BBB). Initial reports suggested the feasibility of imaging brain tumors with ^{11}C -thymidine.⁴³ However, BBB disruptions appear to account for a significant proportion of the uptake when the label is attached to the methyl carbon.⁴⁴ With 2- ^{11}C thymidine and kinetic analysis, Eary and colleagues were able to resolve DNA synthesis from passive BBB disruption.⁴⁵ Other nucleoside analogues, such as ^{124}I iododeoxyuridine-5-fluoro-2'-deoxyuridine have also been considered for PET imaging of brain tumors.⁴⁶ Fluorothymidine has recently been proposed to measure tumor proliferation rate,⁴⁷ but uses of this tracer for brain tumor imaging have not yet been published. Putrescine has also been labeled to evaluate polyamine metabolism.⁴⁸

Therapeutic agents such as carmustine⁴⁹ have been labeled with positron emitters for imaging tumors as well as for performing in vivo pharmacokinetic studies. Another interesting area of research is the development of ^{18}F labeled compounds for imaging tumor hypoxia for correlation with the response to radiation therapy.⁵⁰

Although these radiopharmaceuticals present definite research interest, no clear practical clinical utility has yet been defined for these tracers. Most clinical researchers have focused their efforts on metabolic substrates such as choline, amino acids and ^{18}F fluoro-2-deoxy-2-glucose (FDG).

Radio-Labeled Choline Analogues

Choline, a phospholipid precursor, has been shown by magnetic resonance spectroscopy to be present in increased concentration in brain tumors, particularly high-grade lesions.⁵¹ Shinoura and colleagues evaluated 20 patients with brain tumors using ^{11}C -choline PET. They observed progressive uptake over time in brain tumors with negligible normal brain uptake, and a high tumor-to-background ratio. ^{11}C -choline uptake was not related to blood flow in tumor tissue.⁵² Ohtani et al.⁵³ compared ^{11}C -choline PET with FDG PET and MR imaging in 22 patients. There was higher uptake of choline in high-grade brain tumors, except for very high uptake in a case of pilocytic astrocytoma. ^{11}C -choline PET showed greater tumor extent than MRI, could differentiate high-grade from low-grade lesions, but not low-grade lesions from 2 non-neoplastic lesions. Fluorinated analogs of cho-

line have been recently synthesized.⁵⁴ These tracers could be promising agents for brain tumor imaging.

Amino Acids

Many amino acids have been proposed as tumor imaging agents.⁵⁵ Increased amino acid transport across the cell membrane and incorporation into proteins are the main mechanisms by which these agents accumulate in tumor cells. The uptake of radio-labeled amino acids reflect protein synthesis rate (PSR) to some extent, although this may be quite variable according to the amino acid being studied.⁵⁶ ^{11}C -methyl-methionine (MET) has been frequently utilized, and its usefulness has been demonstrated in imaging brain tumors.⁵⁷⁻⁶⁰ This agent is easily synthesized,⁶¹ but its main drawback relates to the short half-life of the carbon-11. MET is an imperfect marker of protein synthesis rate, and a significant fraction seems to be incorporated into phospholipids through the S-adenylmethionine pathway.⁶² MET has been shown to be a good marker of tumor response to radiation therapy and this agent does not seem to be taken up as avidly in inflammatory tissues as FDG.⁶³ The absolute tumor uptake is generally high, and MET might reflect response to therapy better than FDG.⁶⁴ MET uptake in brain tumors appears to be partly related to tumor grade,^{60,65} but this does not hold true for all tumor types.⁶⁶ Even in low grade gliomas, this agent offers much better contrast than FDG relative to surrounding gray matter activity. It also delineates the extent of tumors better than other imaging techniques, and therefore may help in planning therapy, as showed in Fig 3.⁶⁷⁻⁶⁹ These benefits are offset by a potentially lower specificity of MET for tumor tissues. The uptake is partly related to passive diffusion in tumors with significant breakdown of the blood-brain barrier (BBB)⁷⁰ and this may limit the specificity of MET in diagnosing recurrence in areas of high contrast enhancement on CT or MRI.

Ogawa et al.⁷¹ studied 50 glioma patients with MET PET. They observed MET uptake in nearly all high-grade gliomas (31/32) and approximately 60% of low-grade tumors. These authors also observed that the tumor extent delineated with MET corresponded more closely to pathology results than CT. Voges et al.⁷² imaged 46 patients with gliomas before and after brachytherapy. Tumor extent on MET PET was greater than MRI in

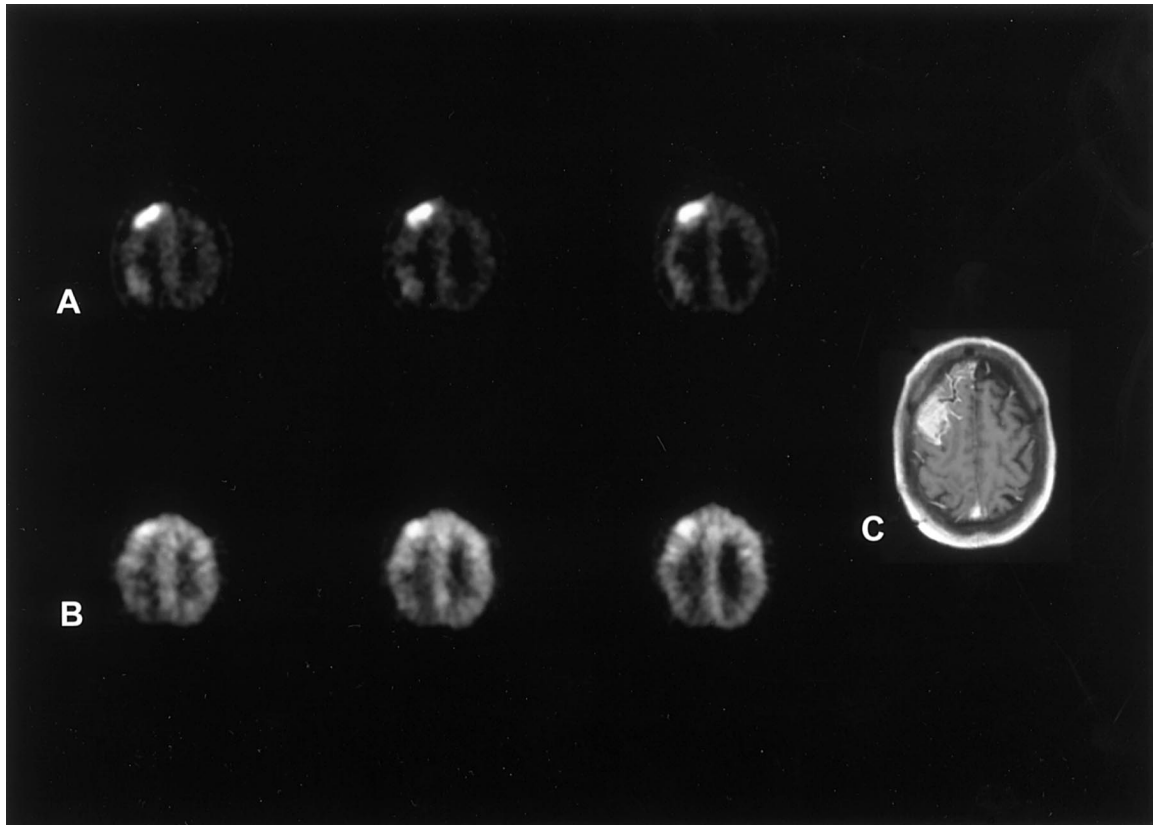


Fig 3. Right frontal lobe glioblastoma. Although the tumor is hypermetabolic on both MET (A) and FDG PET scans (B), its extent is better delineated using the former than with the latter; The corresponding contrast-enhanced MRI is also shown (C). (Courtesy of Dr B. Kaschten, CHU Liège).

2/3 of patients, and similar in the others. MET was valuable in assessing response to therapy, particularly in low-grade tumors, where FDG was ineffective in their study. De Witte et al.⁷³ recently reported their experience with MET PET. In a large retrospective study of 85 patients, they observed a good relationship between MET uptake and primary tumor grade, and MET uptake in nearly all gliomas. Pirotte et al.⁶⁹ also used MET in combination with FDG to guide stereotactic brain biopsies. MET PET had an accuracy of 79% in a large series of 196 patients for differentiating low-grade gliomas from non-tumoral lesions.⁷⁴

Other amino acids, such as ¹¹C-tyrosine and ¹¹C-leucine have been proposed as better PSR imaging agents,⁶¹ but the clinical experience with these radiotracers is still limited. Carbon-11 labeling is a limiting factor for routine clinical use and for regional distribution. Tyrosine can also be labelled with ¹⁸F, with high yields and specific activity.⁷⁵ L-[2-¹⁸F]Fluorotyrosine holds promises

to replace MET and complement FDG in tumor diagnosis, as illustrated in Fig 4.⁷⁶

¹⁸F-fluorodeoxyglucose (FDG)

FDG remains the keystone of PET imaging in oncology. Warburg demonstrated more than six decades ago that malignant cells have highly elevated rates of glucose uptake and metabolism compared to non malignant cells.⁷⁷ Tumor cells with high glycolytic rates have high levels of enzymes that control glycolysis such as hexokinase, phosphofructokinase and pyruvate dehydrogenase.⁷⁸ Changes in glucose transport rate are not simply related to the accelerated growth rate but are transformation specific.⁷⁹ Although the mechanism for this biochemical alteration remains unclear at this time, increased membrane glucose transport capability has been shown to occur with neoplastic transformation.⁸⁰ There is a significant increase in the number of functional glucose transporters at the transformed cell's surface, and nearly

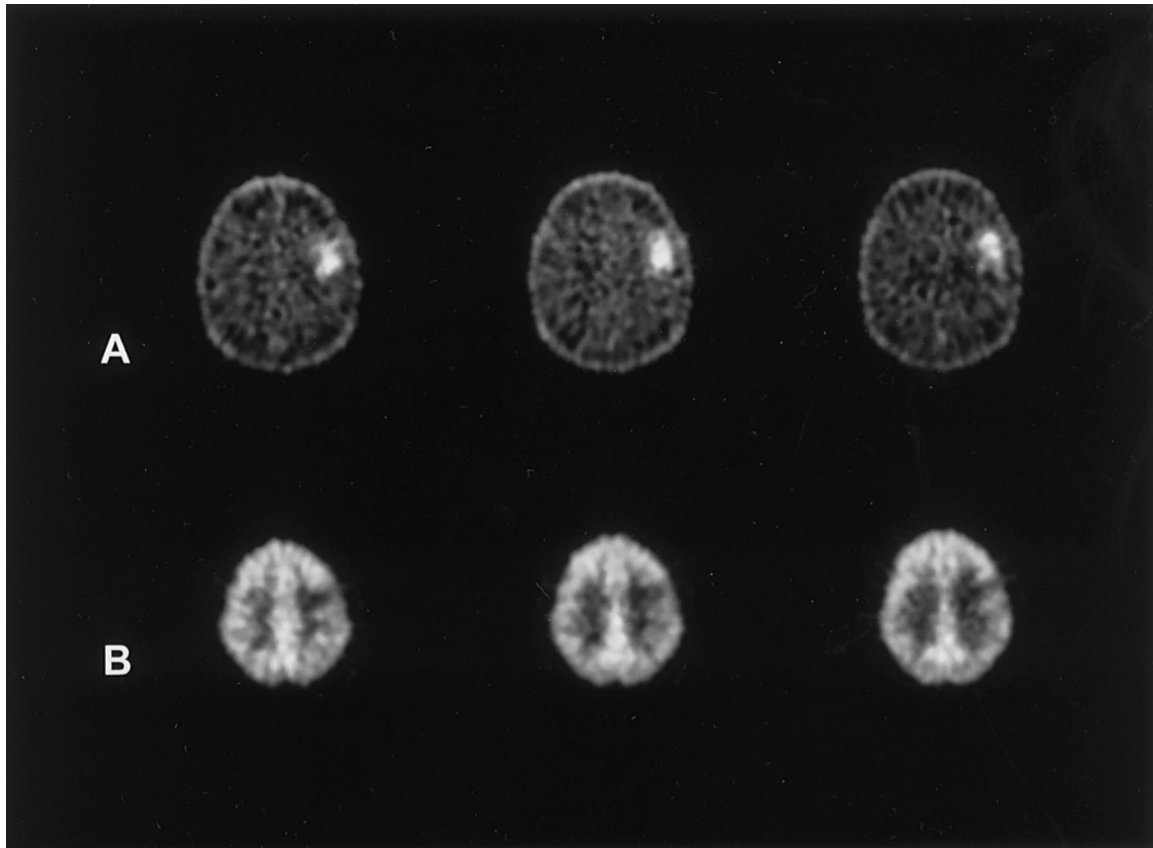


Fig 4. Recurrent low-grade oligodendroglioma. Only the F-TYR PET study shows the lesion, with a high tumor to background ratio (A). There is no significant uptake on the FDG scan (B). (Courtesy of Dr B. Kaschten, CHU Liège).

all mitogens and cellular oncogenes activate glucose transport.⁸¹ Six mammalian glucose transporters have been identified and overexpression of both GLUT-1 and GLUT-3 mRNA has been demonstrated in brain tumors, with a higher ratio of GLUT-3 in more aggressive lesions.⁸² PET can capitalize on this increased capacity for glucose transport observed in malignant glial cells to image brain tumors with FDG. In a group of 10 patients with astrocytomas (WHO grade 2 and 3), Herholz et al⁸³ found that cell density, but not nuclear polymorphism, correlated significantly with FDG uptake.

Di Chiro et al^{84,85} reported the successful use of FDG-PET imaging in evaluating primary brain tumors and radiation necrosis in 1982. In studies of primary brain tumors, PET-FDG imaging has been able to determine the degree of malignancy at the time of imaging.⁸⁵ While low grade tumors reveal low levels of metabolism, those with high grade appear hypermetabolic compared to normal brain

tissue (Figs 4 and 5). Both quantitative and qualitative analysis can be used to demonstrate these findings, although simple approaches such as the tumor/whole-brain ratio seem to work quite well. Either approach shows a significant difference between the low grade and high grade tumors.⁸⁶ However, low-grade oligodendrogliomas and pilocytic astrocytomas can be quite FDG avid, so FDG uptake in such lesion does not necessarily imply a poorly differentiated histology.⁶⁶ Meyer and colleagues compared several quantitative indices using receiver operating characteristic (ROC) curves and found that a 6-score visual grade system was more effective and reproducible to separate high grade (WHO grade III-IV) from low grade (II) lesions. Their visual grading cutoff was set at a level of tumor uptake much greater than white matter activity, but less than grey matter.⁸⁷ Standardized uptake values (SUV) in the brain do not correlate well with regional metabolic rates of glucose utilization (MRGlu), and are less effective

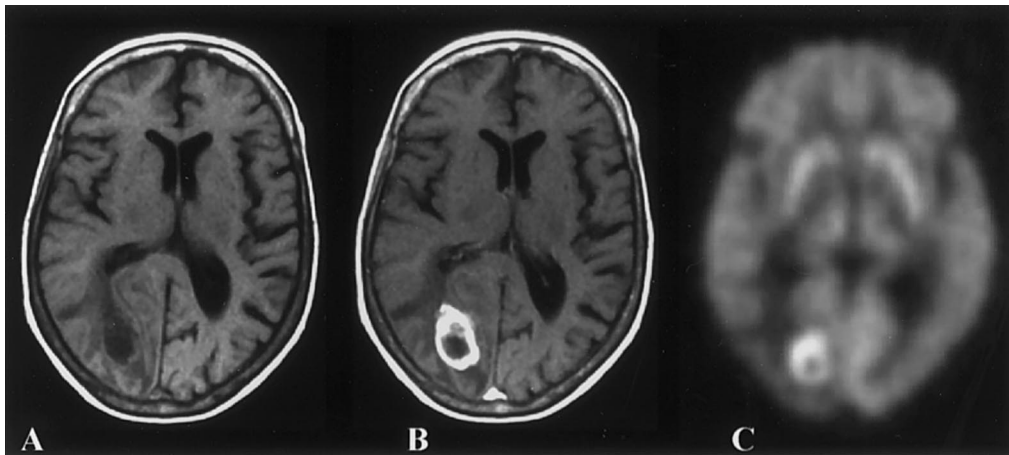


Fig 5. Right occipital lobe glioblastoma. The lesion visualized on the MR images non-enhanced (A) and contrast-enhanced (B) is highly hypermetabolic on the PET study (C).

in characterizing primary brain tumors than tumor-to-white matter or tumor-to-cortex ratios.⁸⁸ In pediatric tumors, FDG also appears to be accurate in grading tumors⁸⁹ and assessing response to treatments.⁹⁰

Metabolic activity of the tumor as shown by the PET-FDG method is a good indicator of the prognosis in patients with primary brain tumors.^{91,92} Persistent uptake of FDG-PET also has prognostic significance after surgery for glioblastoma.⁹³ Patients with hypermetabolic tumors have a significantly worse prognosis than those with hypometabolic lesions. However, De Witte et al.⁹⁴ found that histological grade remains a more important predictor of survival than FDG as the uptake of FDG in glioblastomas did not appear to

have an independent prognostic significance given its correlation with tumor grade.

PET-FDG has been used to differentiate recurrent brain tumors from necrosis after radiation and/or chemotherapy (Fig 6).⁹⁵⁻⁹⁷ The areas of necrosis reveal significantly reduced metabolism while recurrent tumors are identified having increased metabolism. Kim and colleagues from the M.D. Anderson Cancer Center evaluated 33 patients with brain tumors after radiation therapy (15 gliomas, 7 metastases and a mixture of other lesions), and found a sensitivity of 80% and a specificity of 94% for tumor recurrence.⁹⁸ Some studies report the use of FDG-PET to determine the response to therapy. In a pilot study, Brock and colleagues demonstrated that MRGlu measured

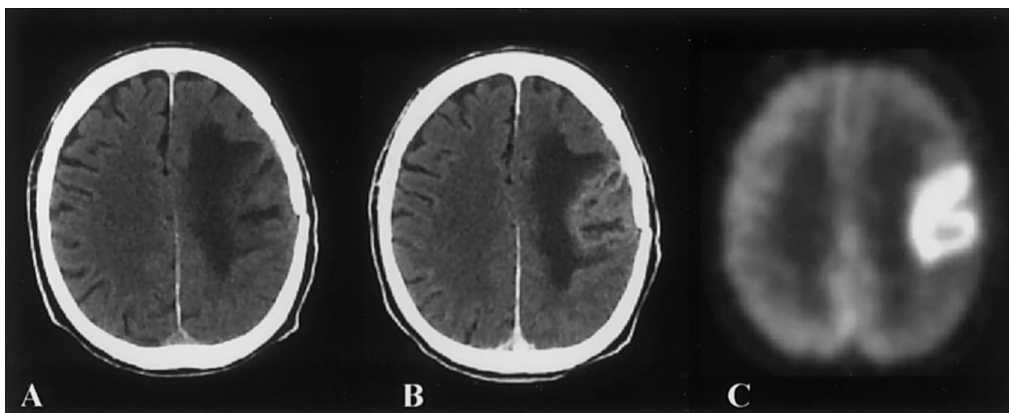


Fig 6. Recurrent left parietal lobe glioblastoma. CT images are shown before (A) and after contrast enhancement (B). The very high FDG uptake leaves no doubts as regard to the malignant nature of the lesion (C).

with FDG-PET could differentiate responders (25% reduction in the region of highest uptake) from non responders after one cycle of temozolomide. They found the SUV ineffective in assessing treatment response of brain tumors.⁹⁹ Rozenal found that secondary to both chemotherapy and stereotactic radiotherapy there was an acute increase of MRGlu 24 hours after treatment, followed by a progressive decline.^{100,101} FDG uptake is not increased after initial resection of CNS tumors, and can document the extent of resection.⁹⁶

PET-FDG imaging can identify malignant degeneration of low grade gliomas. While low-grade tumors are noted to have low levels of FDG uptake, areas of malignant degeneration show increased metabolic activity,¹⁰² confirming the findings of tumor grade mentioned earlier. De Witte also associated increased uptake in low-grade tumors with an unfavorable prognosis.¹⁰³ Hanson initially published case reports on the use of FDG-PET to guide stereotactic biopsies.¹⁰⁴ Pirotte and colleagues found in 38 patients that PET guided biopsies always yielded a tissue-diagnosis, unlike those guided by CT only, and that the use of FDG-PET information in biopsy planning could reduce the number of trajectories needed for a successful diagnosis.⁶⁹

In clinical practice, FDG-PET imaging works

reasonably well in differentiating radiation necrosis from recurrent tumors for high-grade gliomas. In most cases, this assessment is readily made. However, the activity in very thin rims of recurrent highly necrotic tumors can be underestimated due to partial-volume averaging effects.¹⁰⁵ Small areas of recurrent lesions visualized on MRI can be difficult to differentiate from normal grey matter if they involve only part of a gyrus without causing significant edema. Primary low-grade tumors can be less active than the contralateral white matter, and amino acids such as MET may be preferable for this group of lesions.⁶⁶

PET AS AN INDICATOR OF GENE EXPRESSION IN GLIOMAS

Recently, studies have begun assessing gene therapy in recurrent gliomas. Transduction of the herpes simplex virus type-1 thymidine kinase (HSV-1-*tk*) followed by subsequent activation of the prodrug gancyclovir may be beneficial as adjuvant therapy. The level of expression of this gene may predict response to therapy. One of the promising substrate/markers is the I-124-labelled 2'-fluoro-2'-deoxy-1 β -D-arabino-furanosyl-5-iodouracil (FIAU). This probe may prove to be a convenient imaging marker for gene therapy.¹⁰⁶⁻¹⁰⁸

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