The use of 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-FDOPA) with positron emission tomography initially centered on studying central motor disorders and evaluating patients with Parkinsonian symptoms, based on its uptake into presynaptic dopaminergic terminals in the putamen and caudate nuclei of the brain. The roles of this tracer have since expanded to include monitoring disease progression, potentially contributing to drug development, and even questioning the current gold standard for making the diagnosis of Parkinson’s disease. As with some other amino acids, 18F-FDOPA has also been effective for visualizing brain tumors, either at time of diagnosis or when monitoring for recurrence, with high sensitivity and overall accuracy. 18F-FDOPA may be especially useful for imaging patients with low-grade gliomas, as well in the evaluation of patients with neuroendocrine tumors such as carcinoid and pheochromocytoma, in which its role as a precursor for amine neurotransmitter/neurohormones serves as a basis for its differential uptake.

Ahmanson Biological Imaging Division, UCLA Medical Center, Los Angeles, CA.
Address reprint requests to Daniel H.S. Silverman, MD, PhD, Ahmanson Biological Imaging Division, UCLA Medical Center, CHS AR-144, MC694215, Los Angeles, CA 90095-6942. E-mail: dsilver@ucla.edu

18F-FDOPA in the Evaluation of Central Motor Disorders
Pathophysiology and Treatment of Movement Disorders
In the nearly 200 years since the first modern clinical description of the spectrum of bradykinesia, tremor, and gait disturbance by James Parkinson, there has been tremendous progress in the understanding and clinical management of movement disorders. Neuroimaging methods, especially positron emission tomography (PET) and single-photon emission computed tomography (SPECT), have now assumed an important role in the refinement in understanding of differential diagnosis and clinical course by providing disease-relevant biomarkers that complement other clinical measures. The development of PET and SPECT imaging in movement disorders has been rooted in the early descriptions of the loss of dopamine neurons having cell bodies in the substantia nigra. This elucidation of a key pathophysiological feature of PD provided the impetus for rational therapies aimed at dopamine replacement and for neuroimaging...
agents. Moreover, with the development of radiopharmaceuticals that label specific dopaminergic targets in patients in vivo has come further refinement of our understanding of the pathophysiology with regard to differential diagnosis, and by extension, better informed strategies for use of current therapeutics.

Movement disorders comprise a spectrum of diseases with many common features but significant differences with regard to etiology, clinical course, and treatment, which may be generally divided into 4 major categories (Table 1); primary or idiopathic Parkinsonism, secondary Parkinsonism, Parkinson plus syndromes, and hereditary neurodegenerative disorders. Early in the disease course, idiopathic PD may be difficult to distinguish from the Parkinson-Plus syndromes and other processes. The latter disorders are less common than PD, but exhibit significant overlap of clinical symptoms, along with some clinical features which help to distinguish among them (Table 2). Perhaps the most effective tool in the clinician’s diagnostic armamentarium is time; for most patients the development and progression of symptoms will result in a clearer clinical diagnosis.

Levo-dopa (L-DOPA) in combination with carbidopa to inhibit peripheral drug metabolism has been the mainstay of PD treatment for several decades. L-DOPA dose must be increased over time because the drug becomes less potent. Many patients develop rapid cycling between severe bradykinesia and dyskinetic movements reflecting trough and peak levels of L-DOPA in brain. Slow-release versions of L-DOPA have been developed to accommodate the short half-life of the drug and produce longer response duration. Nonetheless, the occurrence of sometimes permanent motor side effects like dyskinesia and other nonmotor effects like hallucinations and paranoid ideation continues to plague treatment with L-DOPA.

The increasing use of dopamine agonists represents the second main pillar of dopamine-replacement approaches to PD treatment. Large clinical trials, including the CALM-PD study and the REAL-PET study in PD patients evaluating the effects of treatment with dopamine agonists, comparing with L-DOPA, the dopamine agonists pramipexole (CALM-PD) and ropinirole (REAL-PET), demonstrate significantly less wearing off, motor fluctuations and dyskinesias than occur with L-DOPA alone. Patients are not infrequently tried on combinations of dopaminergic replacement treatments to help prolong the effect of the “on” time and/or minimize side effects. Many movement disorder specialists advocate waiting a long as possible before the initiation of treatment because of the chronic nature of symptomatic therapy and the high likelihood of developing a treatment complication. During the last several years, therapeutic approaches to PD have expanded beyond aiming for symptomatic treatment to modifying the disease course. These new “disease-modifying” approaches are represented by treatments to either restore lost dopamine cell functions via cell transplantation or use of neural growth factors or neuroprotective therapies aimed at slowing down the inexorable loss of neuronal function. Neurprotective treatments derive from an improved understanding of the mechanisms of cell death pathways (apopto-

Table 1 Major Classification of Movement Disorders

<table>
<thead>
<tr>
<th>Primary Parkinson’s</th>
<th>Familial Parkinson’s Plus syndromes</th>
<th>Multiple system atrophy (MSA)</th>
<th>Shy-Drager syndrome</th>
<th>Olivopontocerebellar atrophy (OPCA)</th>
<th>Striatonigral degeneration (SNID)</th>
<th>Progressive supranuclear palsy (PSP)</th>
<th>Corticobasal degeneration (CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Drug-induced</td>
<td>Infectious</td>
<td>Metabolic</td>
<td>Toxic-induced</td>
<td>Structural/tumor</td>
<td>Psychogenic</td>
<td>Traumatic</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td></td>
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<td></td>
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<tr>
<td>Other disorders with altered motor function</td>
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<tr>
<td>Dementia with Lewy bodies (DLB)</td>
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<td></td>
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<tr>
<td>Alzheimer’s dementia</td>
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<tr>
<td>Huntington’s</td>
<td></td>
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<tr>
<td>Wilson’s disease</td>
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<tr>
<td>Lubag (Filipino x-linked dystonia)</td>
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<tr>
<td>Machado-Joseph disease</td>
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<tr>
<td>Pick’s disease</td>
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<tr>
<td>Hallervorden-Spatz</td>
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</tbody>
</table>

Table 2 Clinical Features of Common Movement Disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Idiopathic PD</th>
<th>Multiple System Atrophy</th>
<th>Progressive Supranuclear Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>In some</td>
<td>Atypical tremor</td>
<td>No</td>
</tr>
<tr>
<td>Symmetric symptom onset</td>
<td>Unusual</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Late feature</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Motor freezing</td>
<td>Late feature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>Late feature in some</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dysautonomias</td>
<td>Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olfaction</td>
<td>Diminished</td>
<td>Must</td>
<td></td>
</tr>
<tr>
<td>Response to L-DOPA</td>
<td>Good</td>
<td>Must early on</td>
<td>Minimal early on</td>
</tr>
<tr>
<td>Gaze palsy</td>
<td>No</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>Slow, variable</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
</tbody>
</table>
sis) and potential ways to interrupt these processes whereas neurorestorative approaches are based on the advancement of tissue transplant methods, identification and improvement in the brain delivery of neurotrophic factors, the possibility of gene therapies for enhancing the viability of brain neurons or encouraging neuronal proliferation and interconnection. These treatments remain experimental without current use in PD or other movement disorders based on well-controlled clinical trials (Table 3). 15–24 Nonetheless, the possibility of a disease-modifying therapy puts heightened emphasis on determining an early and accurate diagnosis to permit earlier intervention.

### Imaging Targets and Probes

Because of the first descriptions of postmortem PD brain indicating the reduction of pigmented neurons in the substantia nigra and elucidation of the nigrostriatal dopamine pathway and its implication in motor dysfunction, the development of imaging markers of the dopamine synapse was an early objective of PET and SPECT researchers. 25–29 Interest has been focused on imaging biomarkers directed at the presynaptic dopamine nerve terminals with specific targets including dopamine synthesis (18F-FDOPA PET), the dopamine transporter (DAT, multiple PET and SPECT agents), or vesicular transporter (11C VMAT2 PET).

18F-FDOPA is taken up into dopamine neurons and converted to 18F-dopamine by aromatic amino acid decarboxylase (AADC), where it remains trapped in the cell. Following release into the synapse, dopamine is taken back up into the presynaptic neuron through the dopamine transporter (DAT), a membrane-bound protein that is the site of action of drugs like cocaine. These presynaptic markers demonstrate high uptake in the striatum, an area representing the terminal projections of nigral dopaminergic neurons. Postmortem evaluations of PD brain demonstrate reductions in all these targets with more involvement in the putamen relative to the caudate. Hence, for all the presynaptic imaging markers of dopaminergic integrity, there is a highly specific pattern of loss of uptake in the striatum with asymmetry consistent with pathologic findings at post mortem as well as a clinical phenomenology (eg, left vs right asymmetry of symptoms corresponding with greatest reduction of radiotracer uptake occurring on the side of the brain contralateral to symptoms).

The largest patient experience with presynaptic imaging markers of dopaminergic neuronal function in PD is with 18F-FDOPA PET as a marker of dopamine neuronal metabolism, as well as DAT agents FP-CIT and β-CIT SPECT, and to a lesser extent 11C VMAT2, 99mTc TRODAT, and 123I altropane. 25–31 Despite these agents targeting different aspects of presynaptic dopamine function, studies in PD patients show remarkable similarity between these radiopharmaceuticals. For example, in newly diagnosed hemi-Parkinson’s patients who present with unilateral symptoms, all these radiopharmaceuticals demonstrate reduced uptake in the striatum on the side contralateral to the symptoms as expected, but also show smaller changes on the ipsilateral side to motor symptoms. These patients almost invariably go on to develop bilateral motor symptoms while maintaining a functional differential between the side contralateral to initial symptom presentation and the ipsilateral side. Investigators have taken this to suggest that imaging with presynaptic markers of dopaminergic function is sensitive to changes occurring in the brain even before symptom formation. 32

### Imaging for Differential Diagnosis of Movement Disorders

The diagnosis of PD and related disorders is based on clinical evaluation. The most widely accepted clinical definition of PD requires the presence of 2 of 3 cardinal motor signs (tremor, rigidity, and bradykinesia) and a response to L-DOPA. 33 At the onset of disease, accurate diagnosis is challenging because of the subtlety and nonspecificity of symptoms. The diagnoses most commonly mistaken for PD include vascular Parkinsonism, essential tremor, drug-induced Parkinsonism, and Alzheimer’s disease. Studies suggest that almost one third of patients are incorrectly diagnosed with Parkinson’s by primary care physicians initially.

Even among movement disorder specialists, the rate of misdiagnosis of Parkinson’s is reported to be 10% to 12%. 34,35 Movement disorder experts particularly misdiagnose PD early in its course when recruiting subjects for early PD clinical trials. For example, in the REAL-PET study, comparing ropinirole and L-DOPA as initial treatments in untreated patients, 11% (21/193) of enrolled subjects had scans without reduction in 18F-FDOPA striatal uptake at baseline and 2 years later. 32 Understanding that the diagnostic gold standard is currently considered to be clinical measures, studies that recruit the earliest PD patients with regard to disease onset consistently demonstrate the greatest percentage of 18F-FDOPA or 123I β-CIT normal scans. 9 Full characterization of these scans without evidence of dopaminergic deficits (SWEDD) is ongoing but highly suggestive that at least a significant proportion of these normal scan patients do not have PD. Later in the course of illness, the diagnoses commonly confused with Parkinson’s disease are progressive supranuclear palsy (PSP) and multiple systems atrophy (MSA). 36,37 The difficulties posed by diagnosis early in the illness course of PD are largely overcome by more protracted
periods of clinical observation of developing symptoms and response to dopaminergic therapy. The reported duration of observation for an accurate diagnosis in very early PD ranges from 3 to 12 months.

Delayed or misdiagnosed PD has several consequences. First, patients may be exposed to futile treatments with dopaminergic agents, often resulting in unnecessary side effects and cost. Many patients may undergo clinical testing with CT or MRI to rule out other less likely disorders again resulting in inconvenience for the patient and higher costs. One overlooked aspect of inaccurate or delayed diagnosis is the fact that patients and families want to know their diagnosis as soon as possible to better understand the short-term and long-term treatment options and prognosis. Imaging can distinguish patients with PD from those with drug induced Parkinsonism, gait disorders resembling PD, psychogenic parkinsonism, vascular parkinsonism, and dementia.

Interestingly, the concordance between the imaging results and the movement disorder specialists' diagnosis improves with longer periods of clinical assessment, suggesting the blinded movement disorder specialist changed his diagnostic impression more in line with the imaging diagnosis as additional clinical information became available, such as response to medication, the development of more characteristic symptoms, etc. Overall, this study indicates that it is feasible to improve the accuracy and timeliness of diagnosis using imaging assessments. This type of study design has been incorporated into clinical trials evaluating the diagnostic performance of other DAT imaging agents in the context of trials supporting clinical approval.

Some investigators have questioned the clinical impact of making an earlier diagnosis in patients because it could have limited influence on the actual clinical management of patients. Many clinicians prefer to maintain patients off medication as long as possible to minimize potential side effects, including dopaminergic side effects resultant from L-DOPA. Others have argued that it may be of some benefit to rethink this strategy and start patients on medication earlier in that some studies suggest that patients initiated early with dopamine replacement therapies have overall, a better clinical course than those for whom medications are withheld. Finally, the development of agents which might have actual disease modifying effects places a heavy onus on early and accurate diagnosis.

It is difficult to distinguish idiopathic PD from the Parkinson spectrum disorders including MSA and PSP, as all these disorders demonstrate deficits in striatal uptake. Some investigators have evaluated additional imaging measures including the relative asymmetry of the left and right striatal uptake (tends to be greater in idiopathic PD) or the caudate to putamen ratio (tends to be higher in idiopathic PD), with mild success due to overlap on these adjunct measures between PD and the other Parkinson spectrum disorders. In addition, some studies have evaluated the concomitant presynaptic and postsynaptic assessment of the dopamine terminal in the striatum using D2/D3 receptor agents combined with presynaptic DAT or 18F-FDOPA to improve accuracy in distinguishing between PD and Parkinsonism, although the practical use and need for these tests clinically remain to be clarified.

There has been recent interest in identifying dopaminergic system deficits in patients with cognitive impairment in the context of movement abnormalities. A number of studies have shown the feasibility of distinguishing dementia with Lewy bodies from Alzheimer's dementia by identifying a dopaminergic deficit in the former.

**Monitoring Disease Progression and Drug Development**

A number of clinical studies have used PET and SPECT to monitor the progression of PD as well as assess the effect of drugs that have putative neuroprotective effects. These studies, using different imaging agents, have consistently demonstrated a loss of imaging signal on the order of 6% to 13% per year. The slowly insidious progression of PD makes it challenging to evaluate imaging signal loss, usually expressed as a percent reduction per year in individual subjects. Most studies of disease progression that have incorporated imaging measures have relied on large subject numbers. This is especially true for evaluating differences in disease progression in cohorts of subjects who are undergoing treatment with agents purported to engender reduction of an already small imaging signal loss. For such studies, a combination of adequate subject number and appropriate duration of evaluation are required based on the projected impact of the disease-modifying treatment. Other factors that are important in the application of imaging biomarkers for assessing disease progression include (1) effects of symptomatic drugs on imaging measures, (2) requirement for robust quantitative algorithms with high degree of reproducibility, and (3) understanding factors unrelated to the density of target sites or dopamine nerve terminal integrity which influence the quantitative signal described in Table 4.

There have been a number of recent studies using PET and SPECT evaluation of disease progression and long-term monitoring in PD patients. Two important studies were designed to evaluate the hypothesis that dopamine agonist drugs have

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**Table 4 Factors Affecting Measurement of Striatal Binding Ratios**

<table>
<thead>
<tr>
<th>Neuronal Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Allelic variants of dopamine transporter</td>
</tr>
<tr>
<td>Pharmacokinetic factors of the radiopharmaceutical, metabolism, protein binding of parent compound</td>
</tr>
<tr>
<td>Patient hydration</td>
</tr>
<tr>
<td>Drugs competing with the radioligand for binding at the target site</td>
</tr>
<tr>
<td>Patient cooperation, ability to remain motionless</td>
</tr>
<tr>
<td>Equipment: Resolution and sensitivity of selected camera, collimator</td>
</tr>
<tr>
<td>Performance drifts in cameras over time</td>
</tr>
<tr>
<td>Photon flux counts in image</td>
</tr>
<tr>
<td>Reconstruction/filtration</td>
</tr>
<tr>
<td>Size and placement of regions of interest</td>
</tr>
</tbody>
</table>
neuroprotective effects in preclinical models. One of these trials, the CALM-PD study, was performed by the Parkinson’s Study Group in the United States to evaluate clinical outcomes in approximately 300 patients initially treated with the dopamine agonist pramipexole compared with those started on L-DOPA. A study of very similar design to the CALM-PD trial was reported about the same time in a similar cohort of PD subjects, with very similar findings. The REAL-PET study used 18F-FDOPA in a multicenter trial to assess the effects of ropinirole, a dopamine agonist versus L-DOPA on both clinical and imaging measures. Forty-five PD patients were imaged at baseline and followed for 2 years after randomization and imaged again at 2 years. Patients treated with ropinirole for 2 years had about a 13% loss of uptake on the 18F-FDOPA scan, whereas the patients treated with L-DOPA showed a 20% loss for a relative difference of 35%. There was no correlation between the percent loss of signal on 18F-FDOPA PET and UPDRS clinical ratings.

Although the imaging findings from the CALM-PD and REAL-PET studies are consistent with the original hypothesis, that dopamine agonists are neuroprotective, they do not prove this to be the case. Since neither of these studies had a placebo control group, it is not possible to determine whether the imaging differences were due to slowing of the rate of progression by the dopamine agonists, or hastening of the progression by L-DOPA, some combination of these factors, or another explanation.

How are we to understand a SWEDD or normal scan in subjects who meet diagnostic criteria for PD by movement disorder specialists? Some possibilities include (1) the patient may not have Parkinson’s disease, (2) the patient may have Parkinson’s disease, but without a dopamine transporter or F-dopa deficit, or (3) imaging is not sensitive to alterations found in early disease. Data from large 18F-FDOPA PET and DAT PET and SPECT PD disease progression trials argues against the possibility that imaging is insensitive in early disease. When SWEDD patients identified at baseline imaging are followed for 2 or more years, there is no change between the baseline and repeat scans, that is, the imaging does not become abnormal in the patients. Specifically in the ELL-DOPA (19/19) and REAL-PET (19/19) studies, patient scans that were normal at baseline remained normal at follow-up. Other cross-sectional studies in patients with early Parkinson’s support the notion that imaging is exquisitely sensitive to changes in brain which may be manifest before the development of clinical symptoms. In every 18F-FDOPA and DAT imaging study reported involving early PD patients, the great majority of these patients are hemiparkinsonian with symptoms detectable only on one side of the body. Both qualitative and quantitative imaging measures demonstrate bilateral changes. The side contralateral to symptoms shows the greatest abnormality. Because these patients go on to develop bilateral disease with time and the progression of disease, this suggests imaging is sensitive to changes before the manifestation of symptoms. The final resolution of this controversy of normal scans among operationally-diagnosed PD patients awaits the data from on-going, long-term clinical follow-up of these patients. Nonetheless the incorporation using PET or SPECT imaging of dopaminergic function as a screening criterion for enrollment into long-term disease-modification trials has been suggested. If the SWEDD scan ultimately proves to be a good means to separate PD from other diagnostic entities without detectable dopaminergic abnormality, then trial sizes could be smaller, and the population for whom the treatment is intended would be enrolled. This is especially important given the long-duration and high costs of disease modification therapeutic trials in PD.

**New Targets, New Directions**

PD is not singularly and exclusively a disease of the degenerating dopamine neuron alone. Other neurochemical systems are known to be involved, either directly or in response to dopaminergic functional loss. Recently, this concept has been expanded into a more fully articulated model by Braak and colleagues in reviewing pathological brain specimens from PD, AD, and other neurodegenerative disorders. The theory proposes a serial evolution of changes, occurring in multiple neuronal systems in susceptible nerve types, which begins in the more primitive brain structures including brain stem and progresses over time to involve anteromedial temporal mesocortex, then neocortex from prefrontal and high order sensory association areas to first order sensory association and premotor areas along with primary sensory and motor fields. These investigations and others suggest the utility of evaluating a range of newer brain targets, potentially accessible with in vivo imaging modalities like PET, to directly explore newer pathophysiologic hypotheses in PD as well as the mechanism for progression.

**18F-FDOPA in the Evaluation of Brain Tumors**

Malignant brain tumors are a heterogeneous group of diseases, each with its own biology, prognosis, and treatment. The most common tumor types are metastatic tumors and malignant gliomas. In 2005, American Cancer Society estimated that primary brain tumor was the cause of death in approximately 12,760 people. Metastatic tumors are more common in that more than 100,000 people die per year with symptomatic intracranial metastases. The initial presentation and diagnostic approaches are similar but the natural courses of diseases are different. PET imaging of such tumors initially focused on scans acquired with FDG, but the high background uptake of this tracer has limited its utility for imaging many brain tumors. PET imaging of malignant gliomas and metastatic tumors with other kinds of tracers, including 18F-labeled amino acids such as 18F-FDOPA has thus been of great interest. In what follows, we will focus on this latter class of tracers, following a consideration of the clinical issues pertinent to neuroimaging, and the benefits and limitations of the more commonly available neuroimages acquired using MRI and FDG-PET.

**Epidemiology and Classification of Gliomas**

According to World Health Organization (WHO) classification, there are 3 main types of gliomas: astrocytomas, oligo-
dendroglomas, and mixed oligoastrocytomas, which can usually be distinguished by their histological features. These tumors are typically heterogeneous in nature that different levels of malignant degeneration can occur in different regions within the same tumor. Analysis of the most malignant region of the tumors establishes grading: low-grade or WHO grades I and II, and high-grade or WHO grades III and IV. Grading is based on the degree of nuclear atypia, mitosis, microvascular proliferation and necrosis, with increasing anaplasia as tumor grade increases. The histological features of the tumor and the patient’s age and performance status are major prognostic factors on outcome.59

There are three subtypes of low-grade gliomas, pilocytic astrocytoma (grade-I), astrocytoma (grade-II) and oligodendroglioma (grade-II). High-grade gliomas include anaplastic tumors (grade III, astrocytoma and oligodendroglioma) and glioblastoma (grade IV). Glioblastoma is the most malignant and most common glioma, accounting for 45 to 50% of all gliomas.60 The mean age at onset for glioblastoma is 61 years, and the mean age for anaplastic astrocytoma is 40 years.61 Men are more frequently affected than women with a sex ratio of 3:2. Low-grade tumors typically affect patients at a younger age than high-grade gliomas (fourth vs sixth decade of life).

**Imaging Modalities**

**Conventional Imaging Studies**

Clinical gold standard imaging procedure MRI provides excellent anatomic details. Standard T1- and T2-weighted MRIs detect brain tumors with high sensitivity with regard to size and localization, as well as mass effect, edema, hemorrhage, necrosis, and signs of increased intracranial pressure. Most high-grade tumors such as glioblastoma lead to the destruction of the blood-brain barrier (BBB) with subsequent leakage of contrast media. In contrast, low-grade tumors usually have no or minimal enhancement. A high-grade glioma normally presents as an irregular hypodense lesion on T1-weighted MRI with various degrees of contrast enhancement and edema. Ring-like enhancement surrounding irregularly shaped foci of presumed necrosis is suggestive of glioblastoma. However, anaplastic tumors can often present as non-enhancing tumors and even glioblastoma may present initially as a nonenhancing lesion especially in older patients. Likewise, some low-grade appearing tumors may contain areas of anaplastic tumor. In addition, the specificity of MRI in distinguishing neoplastic disease from vascular or inflammatory processes can be a problem in some cases.

It is clinically challenging to evaluate disease status with MRI in patients who have been treated. First, treatment-induced changes, such as radiation necrosis, can be difficult to distinguish from recurrent tumor.52,60 This is becoming a more critical issue clinically now that concurrent chemoradiation and stereotactic radiosurgery have been used more extensively, as both treatment processes increase the prevalence of necrosis. Second, dexamethasone has been shown to induce reductions in tumor size by MRI.64 It should be mentioned that a large portion of glioma patients are under treatment with corticosteroids and that withholding this drug for the purpose of an imaging study would ethically not be feasible. Finally, it is challenging with MRI to evaluate recurrent low-grade tumors without anaplastic transformation as changes on MRI can often be indistinguishable from treatment-induced changes.

**Amino Acid PET Tracers**

Amino acid and amino acid analog PET tracers constitute another class of tumor imaging agents.65,66 They are particularly attractive for imaging brain tumors due to the high uptake in tumor tissue and low uptake in normal brain tissue, thus higher tumor to normal tissue contrast. The best studied amino acid tracer is 11C-methionine.67 Because of the short half-life of 11C (t1/2 = 20 minute), 18F-labeled amino acid analogues have been developed for tumor imaging.68 Tumor uptake of O-(2-[18F]fluoroethyl-L-tyrosine (FET) and 18F-FDOPA have been reported to be similar to MET.69,70 18F-FDOPA metabolite 3-O-methyl-6-[18F]fluoro-L-DOPA (OMFD) has also been investigated for brain tumor imaging with PET.71 Superior diagnostic accuracy of 18F-FDOPA to FDG in evaluating recurrent low-grade and high-grade gliomas was reported recently.72

Amino acids are transported into the cell via carrier-mediated processes.73 Amino acid imaging is based on the observation that amino acid transport is generally increased in malignant transformation.74,75 In animal models, it has been demonstrated that up-regulation of the amino acid transporter in the supporting vasculature of brain tumor tissue is responsible for increased facilitated amino acid transport into the tumor cell.76 Factors involved in this active transport have been reviewed: flux of the amino acid to the tissue, the intrinsic activity of the amino acid transporter, and the rate of the intracellular amino acid metabolism.77 It is generally accepted that the rate-limiting step is the amino acid transport even for the few amino acid tracers that are incorporated into protein. The relationship between proliferative activity and amino acid transport was investigated in three glioma cell lines.78 The authors demonstrated by using nonmetabolized amino acid that there is increased amino acid transport in tumor cells regardless of the phases of cell cycle and this up-regulation of transport does not depend on the breakdown of the BBB. In an earlier study, it was shown that amino acid transport into brain tumors does not require breakdown of the BBB but a broken down BBB may enhance transport.79 11C-methionine had significant uptake in low-grade astrocytoma but not as high as in glioblastoma. However, 11C-methionine uptake was even higher in meningioma (lack of BBB) than in glioblastoma. In contrary, FDG uptake is higher in glioblastoma than in meningioma. Therefore, while transport across the BBB is not the rate-limiting step for FDG, this transport does appear to be the rate-limiting process for amino acid tracers.80

**Evaluation of Disease Status**

**Radiation Necrosis**

The actual incidence of radiation necrosis is difficult to establish because few authors have studied patients treated with
radiation exclusively, and chemotherapy is known to increase the risk of radiation necrosis when both modalities are used. What is clear is that now that stereotactic radiosurgery is used more extensively and the combination of chemotherapy with radiation for high-grade gliomas has become the standard practice, the incidence of radiation necrosis is likely to increase. Several types of radiation injury may occur. Acute injury involves tumor swelling and occurs hours to weeks after the completion of radiation. This acute injury usually is reversible and has good prognosis. Early delayed injury involves demyelination and occurs weeks to months after the completion of radiation, which is also reversible. Late injury involves liquefactive or coagulative necrosis, which usually is irreversible. Late injury can occur months to years after the completion of radiation. The pattern of radiation injury may vary from lesions located diffusely in periventricular white matter to local (or multifocal) lesions. It may also occur at sites distant from the sites of the original treatment. Radiation necrosis is difficult to differentiate from tumor growth on MRI. It is especially challenging in early delayed and late injuries as recurring tumor can occur along the same time lines.

Early studies reported sensitivities of 81% to 86% and specificities of 40 to 94% for FDG-PET to distinguish between radiation necrosis and tumor. Amino acid tracers have the potential to improve diagnostic performance in evaluating radiation necrosis. In a report of 21 patients with brain metastases treated by stereotactic radiosurgery, MET correctly identified 7 of 9 recurrences and 10 of 12 radiation injuries. Levels of uptake of FET, FDG, and 18F-choline (FCH) were compared in acute cerebral radiation injury lesions (inflammatory cells) as well as acute cryolesions (disruption of BBB) in rat. Both FDG and FCH were accumulated in macrophages, a common inflammatory mediator in radiation necrosis, but FET uptake was absent in macrophages. Moreover, FET uptake ratio in radiation necrosis versus normal cortex was much lower than that of FDG and FCH, suggesting that FET is promising for differentiating radiation necrosis from tumor recurrence. The complete lack of FET uptake in a case of radiation necrosis was reported. In a recently reported study with FDOPA, lesion to normal brain ratio of less than 1.6 or lesion to striatum ratio of less than 1.0 was demonstrated in all 4 radiation necrosis cases from metastatic lung cancer, metastatic melanoma, glioblastoma, and grade III astrocytoma. Although these results appear promising, larger systematic studies are needed to evaluate the diagnostic accuracies of these amino acid tracers in differentiating radiation necrosis from recurrent tumor.

**Evaluation of Recurrent Tumors**

High FDG uptake in a previously diagnosed low-grade glioma with low FDG uptake is diagnostic of anaplastic transformation. This high FDG uptake is strongly prognostic. For example, 28 patients with low-grade glioma were studied with FDG PET and followed for a mean of 27 months. All 19 patients with tumors that were hypometabolic on PET were alive, whereas 6 of 9 patients with hypermetabolic patterns on PET died.

FDG PET, however, is not sensitive in identifying recurrent low-grade tumors without anaplastic transformation. In contrast to FDG, amino acid uptake has been shown to be increased relative to normal brain tissue in most low- and high-grade tumors (Fig. 1). Initial research focused on 11C-labeled amino acids, particularly MET. However, due to the short half-life of 11C, the applicability of this tracer is limited to sites with on-site cyclotrons and the demand for 18F-labeled analogues has been increasing.

18F-FDOPA imaging of a glioma was initially reported as an incidental finding in a patient undergoing evaluation of movement disorders. Subsequently, 18F-FDOPA PET and MET PET imaging of brain tumors was compared in 19 patients. No significant difference in uptakes of 18F-FDOPA and MET in both low- and high-grade tumors was demonstrated.

In the most comprehensive study of 18F-FDOPA in brain tumors yet published, 18F-FDOPA was compared with FDG in 30 patients with brain tumors and the diagnostic accuracy of 18F-FDOPA was evaluated in a subsequently expanded study to additional 51 patients. Initially, 30 patients with brain tumors, newly diagnosed (n = 7) or previously treated (n = 23) were prospectively studied. All patients were studied with 18F-FDOPA and FDG-PET within the same week. MRI studies of the brain were acquired in all patients within 1 week before the PET scans. The accuracies of the imaging data were validated by histology or subsequent clinical follow up.

Time-activity curves demonstrated that the highest tracer uptake in tumor and cerebellum generally occurred between 10 minute and 30 minute after injection. Tracer activity in the striatum did not reach peak until 50 minutes after injection. Thus, tumor uptake from 10 to 30 minute post injection is near maximum and occurs sufficiently early to avoid peak uptake in the striatum.

With the criterion that any tracer activity above the background in the adjacent brain be considered abnormal, 22 of 23 high- and low-grade tumors were visualized with FDOPA (96% sensitivity; Fig. 1), with 1 false negative in a patient with residual low-grade tumor. All 3 patients without active disease (in long-term remission) or radiation necrosis on MRI lacked any visible uptake in 18F-FDOPA PET scans, and all 4 patients with radiation necrosis had very low but visible 18F-FDOPA uptake. Using the same visual criterion, only 14 of 23 tumors were visualized using FDG-PET (sensitivity: 61%). Similarly to FDOPA, there was no visible FDG uptake in 3 stable patients in long-term remission and there was low level FDG uptake in 4 patients with radiation necrosis.

Thus, 18F-FDOPA was more sensitive in identifying tumors overall than FDG at comparable specificity. 18F-FDOPA PET in gliomas demonstrated lower SUV values than did FDG. However, the tumor to normal tissue contrast was higher than that with FDG, due to the low normal brain tissue uptake in 18F-FDOPA PET scans. This proved useful in detecting low-grade as well as recurrent tumors (Fig. 2). ROC analysis was also used to identify the FDOPA tumor to normal tissue uptake ratios that would give the best sensitivity...
and specificity, T/N (tumor to normal contra-lateral hemisphere), T/S (tumor to striatum), and T/W (tumor to white matter). The specificity of \(^{18}\text{F-FDOPA}\) brain tumor imaging was relatively high using thresholds of tumor to striatum ratio T/S of 0.75 or 1.0, tumor to normal hemispheric brain ratio T/N of 1.3 or tumor to normal white matter ratio T/W of 1.6.

\(^{18}\text{F-FDOPA}\) PET imaging was subsequently expanded to a larger population of 51 patients to test these thresholds generated from ROC analysis of the first group of 30 patients studied. The previously established tumor to normal tissue thresholds T/S of 0.75, 1.0, T/N of 1.3, and T/W of 1.6 were used to test the sensitivity, specificity, positive predictive value, and negative predictive value, and were validated. Overall, although tumor/striatum ratio T/S of 0.75 resulted in a slightly higher accuracy of 95% and sensitivity of 98%, ratios of 1.0 provided slightly lower sensitivity of 92% but higher specificity of 95%. The latter is clinically practical as it is readily visually approximated, and still has high overall accuracy (93%).

Tumor grade did not significantly affect tracer uptake in the 81 lesions in FDOPA PET studies, a finding that is consistent with most studies using amino acid tracers.\(^{69-71}\) Likewise, no statistically significant difference in uptake levels between tumors which were contrast-enhancing and non-enhancing was seen, in agreement with the notion that similar to that of other amino acid tracers, tumor accumulation of FDOPA activity is most likely mediated through a specific transport system, rather than requiring the breakdown of BBB.\(^{76}\)

### Other Tumors

In addition to the roles \(^{18}\text{F-FDOPA}\) PET has played in the evaluation of patients with central motor disorders and brain tumors, a growing literature has focused on the potential utility of imaging with \(^{18}\text{F-FDOPA}\) in the assessment of a number of conditions in which neuroendocrine tumors are suspected or known to be involved.

The neuroendocrine condition for which the role of \(^{18}\text{F-FDOPA}\) PET has been most extensively documented is carcinoid. For example, in a recent prospective study of the diagnostic accuracy in 53 patients with metastatic carcinoids, the use of \(^{18}\text{F-FDOPA}\) PET enabled researchers to find metastases in all of the patients: it detected 96% of the lesions, compared with 46% of the lesions identified with the use of somatostatin-receptor scintigraphy (SRS), and 65% of the lesions found with combined SRS and CT imaging.\(^{89}\) Another recent study describing results of 33 \(^{18}\text{F-FDOPA}\) PET scans in 30 neuroendocrine tumor patients, found a sensitivity of 93% for carcinoid tumors, compared with a sensitivity of 81% with...
SRS imaging. For the noncarcinoid tumors examined, however, \(^{18}\text{F}-\text{FDOPA}\) PET sensitivity decreased to 25%.\(^{90}\)

A number of studies have pointed to a role for \(^{18}\text{F}-\text{FDOPA}\) PET in evaluation of other neuroendocrine conditions. These include hyperinsulinism in adults\(^{91}\) and infants,\(^{92}\) gastrointestinal tumors in patients with negative or inconclusive structural and SRS imaging,\(^{93}\) glomus tumors in patients genetically predisposed to develop paragangliomas,\(^{94}\) and medullary thyroid carcinoma in patients with elevated calcitonin levels,\(^{95}\) among others. Strikingly, in a consecutive series of 14 patients with suspected pheochromocytoma in whom 17 tumors were found by MR, \(^{18}\text{F}-\text{FDOPA}\) PET demonstrated 100% sensitivity and 100% specificity relative to the MR reference standard, while four tumors were missed by metaiodobenzylguanidine (MIBG) scintigraphy.\(^{96}\) Although more and larger studies are needed to better delineate the most appropriate roles for \(^{18}\text{F}-\text{FDOPA}\) PET imaging in each of these settings, the ability to gain diagnostically useful information with this modality in patients with a variety of neuroendocrine conditions has become increasingly evident.

**Conclusions**

The rapid elaboration of imaging biomarkers for PET and SPECT has resulted in significant changes in the potential approach to diagnosis and symptom management in the movement disorders, especially PD. The proliferation of readily available radiopharmaceuticals for assessing dopamine deficits raises the possibility of earlier and more accurate diagnosis with an algorithm which includes a rule-in diagnostic imaging examination, though there remain significant unanswered questions with regard to the place of neuroimaging in such algorithms for at-risk screening and differential diagnosis. Originally incidentally noted, \(^{18}\text{F}-\text{FDOPA}\) has turned out to also provide excellent visualization of high- and low-grade tumors. It is more sensitive and specific for evaluating recurrent tumors than FDG. It may prove particularly valuable for examining recurrent low-grade gliomas since these tumors are difficult to evaluate by MRI and are usually not visible on FDG PET. FDOPA might also be valuable for distinguishing recurrent tumor from radiation necrosis, although a larger series of radiation necrosis cases is

![Figure 2](https://example.com/figure2.jpg)
needed to confirm this, and may play an increasing role in a variety of neuroendocrine tumors, especially in previously image-negative patients, such as carcinoid and pheochromocytoma.

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