Impact of 3,4-Dihydroxy-6-^{18}F-Fluoro-L-Phenylalanine PET/CT on Managing Patients with Brain Tumors: The Referring Physician's Perspective

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We investigated the impact of ^{18}F-DOPA brain PET/CT on the clinical management of patients with known or suspected brain tumors. **Methods:** A prospective survey of referring physicians was conducted. A pre-PET questionnaire inquired about indication, tumor histology or grade, level of suspicion for tumor recurrence, and planned management. Early post-PET questionnaires asked referring physicians to categorize PET findings as negative, equivocal, or positive; assessed the level of suspicion for primary or recurrent brain tumor; and recorded intended management changes prompted by PET findings. A late follow-up questionnaire 6 mo after the scan aimed at determining patient outcome (recurrence, survival). In addition, all referring physicians were contacted to determine whether management changes intended after ^{18}F-DOPA PET/CT were implemented. **Results:** Fifty-eight consecutive patients were included. The clinical suspicion for recurrence increased in 33%, remained unchanged in 50%, and decreased in 17% of patients after adding the PET/CT result to the available diagnostic data. The late post-PET questionnaire confirmed recurrence in 26 patients whereas 32 had stable disease or remained disease-free. ^{18}F-DOPA PET/CT resulted in intended management changes in 41% of patients. Changes in intended management from wait and watch to chemotherapy (6 patients [25%]) and from chemotherapy to wait and watch (4 patients [17%]) occurred most frequently. Clinical follow-up revealed that 75% of intended treatment changes were implemented. **Conclusion:** ^{18}F-DOPA PET/CT changed the intended management of 41% of patients with brain tumors, and intended management changes were implemented in 75% of these. These changes suggest a potentially important clinical role of imaging amino acid transport in the management of brain tumor patients.

Key Words: ^{18}F-DOPA PET/CT; glioma; glioblastoma; amino acid transport; management; outcome

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Primary brain tumors account for about 2% of all malignancies in adult patients. Approximately 80% of these are gliomas that arise from glial cells (*1*). The 5-y survival rates vary among histologic subtypes and range from 3.3% for glioblastoma multiforme to 70% for low-grade gliomas such as pilocytic astrocytoma or oligodendroglioma (*2*). Therapy includes chemotherapy, radiation treatment, and surgery.

The current brain tumor imaging modality of choice for diagnosing and monitoring the disease is contrast-enhanced, multiplanar MRI (*3*). However, the ability of MRI to differentiate between treatment-induced changes, such as radiation necrosis or edema, and residual or recurrent tumor is limited. Early detection of recurrence or disease progression, for instance, from low-grade to high-grade gliomas, is inaccurate by anatomic imaging (*4*). Moreover, determination of treatment responses is difficult (*5*). In addition, the intact blood–brain barrier of recurrent low-grade tumors precludes reliable detection with contrast-enhanced MRI (*6*).

Several PET tracers have been used to study various aspects of brain tumor metabolism and to detect primary or recurrent tumors. Among these are ^{18}F-FDG for imaging glucose metabolism and ^{11}C-methionine (*7*), ^{18}F-fluoroethyl-L-tyrosine (^{18}F-FET) (*8*), and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-DOPA) (*9*) for imaging amino acid transport. 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) (*10*) has been used to image cell proliferation at baseline (*10*) or in response to therapy (*11*). Probes of tissue hypoxia such as ^{18}F-fluoromisonidazole (*12*) have also been tested for PET brain tumor imaging.

Metabolic imaging of brain tumors with amino acid analogs has advantages over ^{18}F-FDG because tumor–to–normal-tissue background ratios are higher for these probes (*13*). The clinical utility of ^{11}C-methionine (*14*) is limited by its short physical half-life of 20 min. The amino acid analog ^{18}F-FET (*15*) provides clinical information that is comparable to that derived from ^{11}C-methionine (*16*) and can differentiate tumor recurrence from radiation necrosis (*17*).

^{18}F-DOPA has emerged as an accurate alternative to ^{11}C-methionine (*18*) and ^{18}F-FET. It is transported across tumor

cell membranes by L-amino acid transporters (*19,20*) that are overexpressed in most gliomas (*21*). The transport of ^{18}F-DOPA is independent of a blood–brain barrier breakdown (*22*).^{18}F-DOPA PET can be used for detecting primary and recurrent high- and low-grade brain tumors (*23,24*), and its tumor uptake correlates with the grade of newly diagnosed tumor.

^{18}F-DOPA PET has been used to image patients with neuroendocrine tumors (*25*) and movement disorders (*26–28*). We have also used it clinically for many years to image patients with recently diagnosed or recurrent brain tumors (*29*). We have demonstrated a high accuracy of this approach (*23*), and the number of requests for clinical ^{18}F-DOPA PET studies has been increasing.

The accuracy of ^{18}F-DOPA in imaging brain tumors has prompted us to determine prospectively the impact of ^{18}F-DOPA PET/CT studies on the intended management of patients with brain tumors. Moreover, we determined whether intended management changes were in fact implemented.

MATERIALS AND METHODS

We included patients of all ages with suspected or histologically proven brain tumors who were treated at the Division of Neuro-oncology at the UCLA Medical Center between July 2009 and October 2010 and were referred for a clinical ^{18}F-DOPA PET study. However, most of our patients had prior surgery and were imaged for suspected brain tumor recurrence, likely reflecting the preponderance of these patients in a tertiary care center.

The study was approved by the UCLA Los Angeles Institutional Review Board. All ^{18}F-DOPA scans were ordered clinically. Because referring physicians were surveyed on the impact of this test, which is routinely performed at our institution, the informed consent requirements were waived by the UCLA Institutional Review Board.

Image Acquisition and Reconstruction

^{18}F-DOPA was synthesized as described previously (*30*) and was injected intravenously at a dose of 129.5 MB (3.5 mCi). A tracer uptake time of 15 min was allowed (*29*) before PET/CT with a dual-detector system (Biograph Duo [Siemens]; $n = 12$) or a 64-detector system (Biograph 64 or Biograph mCT [Siemens]; $n = 46$) commenced.

A dedicated CT scan of the brain (120 kV, 80 mAs, 1-s tube rotation, 3-mm slice collimation) was acquired first. Fifteen minutes after tracer injection, a static PET scan was acquired in the 3-dimensional mode for a total of 20 min. PET images were reconstructed using an iterative algorithm (ordered-subset expectation maximization, 6 iterations, 8 subsets) as reported previously (*31*). The CT data were used for attenuation correction and lesion localization (*32*).

Image Interpretation

All ^{18}F-DOPA PET/CT studies were interpreted qualitatively during a clinical readout session. On the basis of a previous study (*23*), scans were classified as positive if tumors identified on CT or MRI regions exhibited tracer uptake above the level of the contralateral caudate nucleus. Scans were classified as negative if ^{18}F-DOPA uptake was lower than that of the contralateral caudate nucleus. Uptake at the level of the contralateral caudate was considered equivocal for malignancy.

Pertinent clinical information such as patient history, biopsy results, and reports from previous imaging tests were available at the time of image interpretation. Because referring physicians were surveyed about the impact on ^{18}F-DOPA PET (rather than evaluating the diagnostic accuracy of this test), the written reports of the imaging studies were reinterpreted by the referring physicians as positive, negative, or equivocal.

Survey

A set of 3 questionnaires per patient was mailed to the referring physicians as follows: a pre-PET scan questionnaire inquired about the indications for the study, tumor characteristics such as histology and grade, the level of clinical suspicion for primary brain tumor or recurrence, and the planned treatment approach.

The second, an early post-PET questionnaire, required referring physicians to categorize the ^{18}F-DOPA findings on the basis of the written PET reports as negative, equivocal, or positive for cancer. Furthermore, the questionnaire inquired about additional, previously unknown tumor sites in the brain. Moreover, referring physicians were asked to record their level of suspicion for recurrence and to indicate the type of intended management changes as a consequence of the ^{18}F-DOPA PET study.

A late follow-up questionnaire was aimed at determining patient outcome (recurrence, survival) and confirming the ^{18}F-DOPA findings. To verify whether intended management changes were indeed implemented, the referring physicians were contacted separately.

Statistical Analysis

The suggestion for recurrence or primary disease was qualified by referring physicians as ordinal values (1, low; 2, moderate; or 3, high) on the pre-PET and early post-PET questionnaires. The level of suspicion before and after ^{18}F-DOPA PET/CT was compared for each patient, and changes in level of suspicion were determined and classified as increasing, decreasing, or unchanged.

The intended treatment plan was recorded before and after ^{18}F-DOPA PET/CT and compared for each patient. The treatment options were radiation, chemotherapy, radiation and chemotherapy, surgery, wait and watch, no change, and supportive care. Changes from one modality to another were classified as change in treatment plan. Selection of the same modality before and after the scan, as well as changes from one treatment to no change, was categorized as no change.

A binary logistic regression model was applied to detect predictors for management changes after ^{18}F-DOPA PET/CT. Parameters included patient age, sex, histology, and tumor grade.

A survival analysis was done using the Kaplan–Meier method. A P value of less than 0.05 was considered significant.

RESULTS

Referring Physicians and Questionnaires

The 58 consecutive patients were referred from 5 different neurologic oncologists of our institution. One neurologic oncologist referred 44% of the patients, whereas the remaining 4 referred 19%, 17%, 10%, and 10% of patients. The entire set of questionnaires was completed for each of the 58 patients. Thus, the response rate was 100%.

The pre-PET questionnaires were completed within a maximum of 39 d before the PET scan. The early and late post-PET questionnaires were completed within 20 ± 22 and 203 ± 25 d after the scan, respectively.

Patient Population

Of the 58 patients, 7 had a suspected primary brain tumor and 51 had a suspected recurrent brain tumor.

The patient population consisted of 33 men and 25 women, with a mean age of 49 ± 13 y (age range, 23–81 y). The histologic subtypes and grades of the brain tumors are listed in Table 1. The indications for the clinical studies included new or changed contrast enhancement on MRI (31%), a new or changed T2 signal on MRI (28%), follow-up on a prior ^{18}F-DOPA scan (16%), baseline evaluation (7%), differentiation between tumor and nontumor (7%), and others (Table 2).

^{18}F-DOPA PET/CT Findings

^{18}F-DOPA PET/CT reports were interpreted by referring neurologists as negative for brain tumor in 20 (34%), as positive in 33 (57%), and as equivocal in 5 (9%) patients. ^{18}F-DOPA revealed additional unsuspected brain lesions in 5 patients (9%).

Changes in Suspicion of Recurrence or Primary Tumor

The pre-PET suspicion for primary or recurrent brain tumor was high in 10 patients (17%), moderate in 31 (54%), and low in 17 (29%). After PET, the level of suspicion changed in 50% of the patients. It increased in 19 (33%) and decreased in 10 patients (17%; Fig. 1).

Impact of ^{18}F-DOPA PET on Intended Patient Management

The treatment plan before ^{18}F-DOPA PET/CT was wait and watch in 36%, chemotherapy in 29%, no change in 14%, radiation and chemotherapy in 9%, surgery in 7%, radiation in 3%, and supportive care in 2% of patients.

^{18}F-DOPA PET/CT resulted in intended management changes in 24 of 58 (41%) patients. Three of these patients (12.5%) had suspected primary tumors, and 21 had recurrent disease (87.5%).

Intended treatments changed most frequently from wait and watch to chemotherapy (Fig. 2) and from chemotherapy to wait and watch. Intended treatment changes as a consequence of PET are listed in Table 3.

TABLE 1
Tumor Characteristics

Characteristic	*n*	%
Tumor histology		
Astrocytoma (grade I–IV)	28	48
Oligodendroglioma	7	12
Mixed histology	17	29
Unknown	6	11
Tumor grade		
WHO I	0	0
WHO II	15	26
WHO III	15	26
WHO IV	21	36
Unknown	7	12

TABLE 2
Indications for ^{18}F DOPA Scan

Indication	*n*	%
New or changed T2 signal on MRI	18	31
New or changed contrast enhancement on MRI	16	28
Follow-up on prior ^{18}F-DOPA scan	9	16
Baseline evaluation	4	7
Differentiation between tumor and nontumor	4	7
T2 signal on MRI and clinical symptoms	3	5
Contrast enhancement on MRI and clinical symptoms	2	3
Clinical symptoms suggestive of recurrence	2	3

The management plan before PET included a tissue biopsy in 7 patients. On the basis of PET, the biopsy was avoided in 4 of these 7 patients. However, a biopsy was intended in 9 additional patients because of positive PET findings. Seven of these biopsies were performed, all of which confirmed the presence of brain tumors. Histology revealed oligodendroglioma (n = 1), oligoastrocytoma (n = 1), anaplastic oligoastrocytoma (n = 1), anaplastic astrocytoma (n = 2), and glioblastoma (n = 2).

Eighteen additional intended diagnostic procedures including MRI (n = 8), CT (n = 1), and others that were not specified (n = 9) were avoided in 18 patients. However, as a consequence of PET, additional tests were planned in 16 patients (MRI, n = 14; CT, n = 1; and ^{18}F-DOPA PET, n = 1).

By binary logistic regression analysis, PET-based management changes were independent of age, sex, and histology or tumor grade.

Implemented Changes in Patient Management

Changes in management as a result of PET findings were planned in 24 of 58 (41%) and were implemented in 18 of these 24 patients (75%). One of the remaining 6 patients died before the change in treatment could be implemented, and treatment changes could not be verified in 2 other patients. Intended management changes had not been implemented in 3 patients at the time of the late follow-up.

DISCUSSION

To our knowledge, this is the first prospective study to determine the impact of amino acid transport PET on the management of patients with brain tumors. ^{18}F-DOPA PET/CT changed the intended management in 41% of the patients, and management changes were implemented in 75% of these patients.

Contrast-enhanced MRI is most frequently used to diagnose and monitor patients with brain tumors (*33*). However, after initial treatment, the assessment of recurrence by MRI can be difficult. Pseudoprogression, characterized by increasing contrast enhancement, a phenomenon resulting from transiently increased permeability of the tumor vasculature in response to treatment, can occur in 20%–30% of patients (*34,35*). Other limitations of MRI assessments include "the

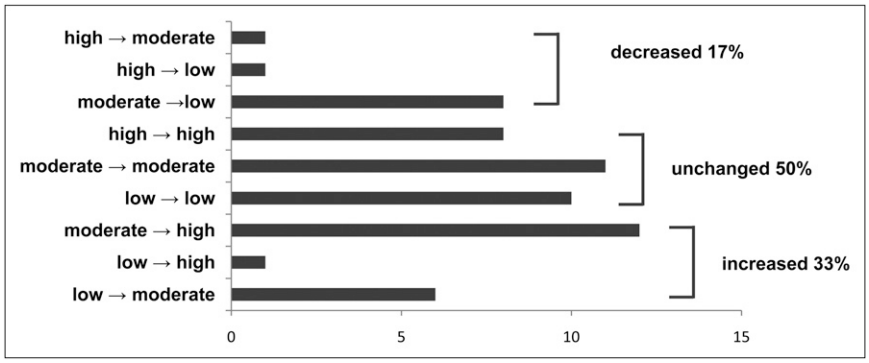

FIGURE 1. ^{18}F-DOPA PET–induced changes in degree to which primary or recurrent brain tumor was suspected.

difficulty of measuring tumor size, interobserver variability, the lack of assessment of the nonenhancing component of the tumor, lack of guidance for the assessment of multifocal tumors, and the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities" as recently discussed (*34*).

There is, therefore, a need to evaluate and validate imaging approaches that are unaffected by the integrity of the blood–brain barrier and tumor vasculature and that permit exact tumor assessments. PET of tumor metabolism could provide diagnostic and prognostic information independent of the integrity of the tumor vasculature, tumor morphology, and size. ^{18}F-FDG PET of brain tumors is limited by low target-to-background ratios especially in low-grade tumors. Nevertheless, a recent report from the National Oncology PET Registry reported a significant impact of ^{18}F-FDG PET on management of recently diagnosed, initially staged, or restaged patients (*36*). In this survey, intended management changes based on PET occurred in 36.6% of newly diagnosed or initially staged patients and in 38.7% of those who were restaged. Moreover, biopsies were performed in only 42% of those patients in whom a biopsy was intended before PET. However, the implementation of intended management changes was not reported in this study.

^{11}C-labeled methionine and ^{18}F-tyrosine are the most extensively studied amino acid tracers (*14,37*). We have focused on ^{18}F-DOPA brain tumor imaging for several reasons. First, ^{18}F-DOPA is versatile in that it can be used for imaging movement disorders, neuroendocrine tumors, and gliomas (*23,26,28*). Second, it can detect high- and low-grade tumors because tumor uptake is independent of the integrity of the blood–brain barrier (*22,23*). Third, it detects recurrent brain tumors with a high accuracy, and the degree of uptake in newly diagnosed tumors predicts tumor grade (*29*).

Although others (*18*) and we (*23*) have established a high accuracy of ^{18}F-DOPA brain tumor imaging, its impact on patient management has thus far not been investigated.

Two retrospective studies have reported a substantial impact of amino acid metabolism imaging on patient management. One study reported that PET with ^{11}C-methionine resulted in intended management changes in 40 of 80 of the patients (*38*). On the basis of clinical follow-up, management changes were considered beneficial in 36% of these patients but were detri-

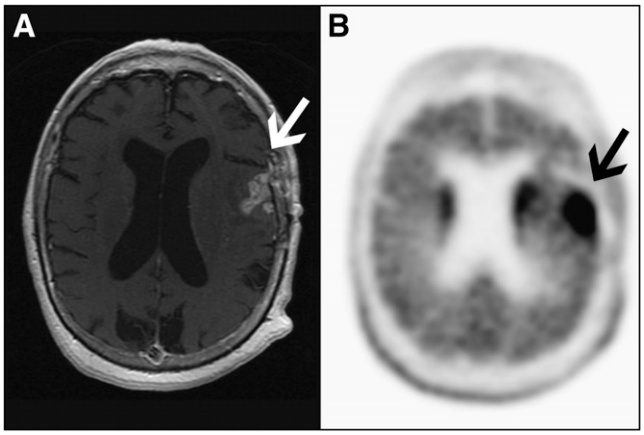

FIGURE 2. Management change after ^{18}F-DOPA PET. (A) Gadolinium-enhanced T1 MR image shows irregular nodular enhancement (arrow) in left frontal lobe in patient with glioblastoma, suggestive of recurrent disease. (B) ^{18}F-DOPA PET shows intense activity (arrow) at site of suspected recurrence. Suspicion of recurrence increased from moderate to high after ^{18}F-DOPA PET/CT. Accordingly, patient management was changed from wait and watch to chemotherapy.

TABLE 3
Changes in Patient Treatment

Treatment change	Planned (*n*)	Implemented (*n*)
Wait and watch → chemotherapy	6	4
Chemotherapy →wait and watch	4	1
Wait and watch → radiation and chemotherapy	2	2
Chemotherapy → surgery	2	2
Radiation and chemotherapy → chemotherapy	2	2
Wait and watch → radiation	1	1
Wait and watch → surgery	1	1
Chemotherapy → radiation	1	1
Radiation → wait and watch	1	1
Radiation and chemotherapy → surgery	1	0
Surgery →wait and watch	1	1
Surgery → radiation	1	1
Supportive care → wait and watch	1	1

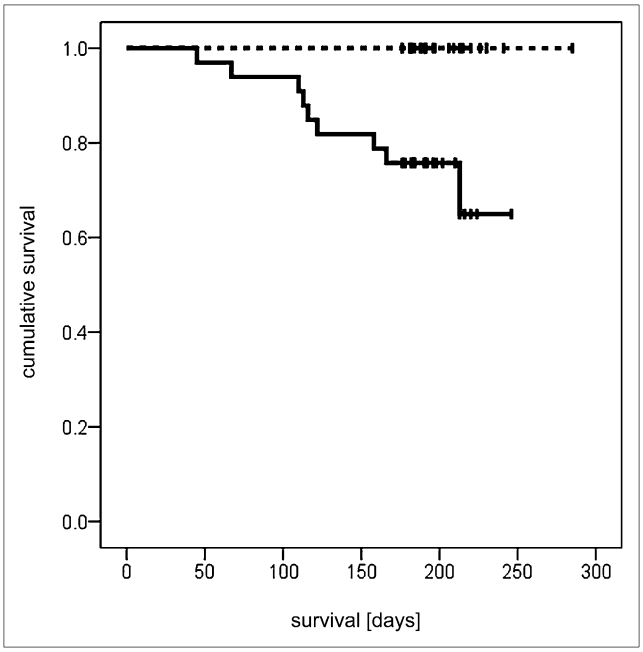

FIGURE 3. Kaplan–Meier survival curves. Survival was estimated for group of patients with positive (n = 33; solid line) vs. group of patient with negative (n = 20) or equivocal (n = 5; dashed line) ^{18}F-DOPA PET findings. Patients with negative or equivocal ^{18}F-DOPA findings had significantly longer survival than PET-positive patients (P = 0.02).

mental in 4.3%. The latter was explained by false-negative scan findings. Another study in 85 pediatric patients revealed a significant impact of ^{18}F-FDG or ^{11}C-methionine PET on surgical decisions in all patients (*39*).

Our study differs from these reports in that it was prospective, used ^{18}F-DOPA as a probe of amino acid transport, and determined whether intended management changes were in fact implemented. We demonstrate that intended management changes were implemented in 75% of the patients.

The study population consisted predominantly of patients who had prior brain tumor surgery. They were studied most frequently because of a moderate or high suspicion of recurrence. Thus, whereas ^{18}F-DOPA PET had a high impact on managing these patients, the results may not be applicable to patients undergoing initial or surgical brain tumor management.

We used a simple, straightforward survey with short and relatively few questions to determine the impact of PET on patient management. This approach has strengths and limitations. First, all scans were read during the routine clinical reading sessions. The use of the clinical routine setting increases the validity of our findings. Second, we had no drop-outs due to incomplete questionnaires, rendering a spectrum bias less likely (*40*). Yet, the surveyed physicians were all users of PET. The reported impact on management may therefore have been biased toward favoring PET. Finally, this was a single-center study, and the impact of PET on patient outcome was not evaluated.

This study did not assess the diagnostic accuracy of ^{18}F-DOPA imaging for detecting primary or recurrent brain tumors. However, in support of the previously reported high accuracy of ^{18}F-DOPA brain tumor imaging (*23*), we observed that 7 biopsies performed as a consequence of PET findings confirmed the PET results. Moreover, patients with ^{18}F-DOPA–positive tumors had significantly shorter survivals than those with negative ^{18}F-DOPA scans (Fig. 3). A similar observation was recently published by Hutterer et al. (*41*), who used ^{18}F-FET for imaging brain tumors.

CONCLUSION

Any novel diagnostic test needs to be accurate, needs to affect patient management, and should have a beneficial impact on patient outcome. We have previously established a high accuracy of ^{18}F-DOPA imaging for identifying primary or recurrent brain tumors. Here, we demonstrate a substantial impact of ^{18}F-DOPA PET on the management of these patients. Future studies will need to investigate the impact of ^{18}F-DOPA PET on outcome, defined as progression-free survival, and on overall survival and the actual cost-effectiveness of ^{18}F-DOPA PET. Such assessment would require a randomized trial in which one group of patients undergoes ^{18}F-DOPA PET while the other group does not.

DISCLOSURE STATEMENT

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734.

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