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European Journal of Radiology xxx (2008) xxx–xxx

EJR
EUROPEAN JOURNAL OF RADIOLOGY

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^{18}F-FDOPA PET/MRI fusion in patients with primary/recurrent gliomas: Initial experience

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Received 15 November 2007; received in revised form 5 March 2008; accepted 21 April 2008

Abstract

Background and purpose: ^{18}F-FDOPA PET demonstrates higher sensitivity and specificity for gliomas than traditional [^{18}F] FDG PET imaging. However, PET provides limited anatomic localization. The purpose of this study was to determine whether ^{18}F-FDOPA PET/MRI fusion can provide precise anatomic localization of abnormal tracer uptake and how this activity corresponds to MR signal abnormality.
Methods: Two groups of patients were analyzed. Group I consisted of 21 patients who underwent ^{18}F-FDOPA PET and MRI followed by craniotomy for tumor resection. Group II consisted of 70 patients with a pathological diagnosis of glioma that had ^{18}F-FDOPA PET and MRI but lacked additional pathologic follow-up. Fused ^{18}F-FDOPA PET and MRI images were analyzed for concordance and correlated with histopathologic data.
Results: Fusion technology facilitated precise anatomical localization of ^{18}F-FDOPA activity. In group I, all 21 cases showed pathology-confirmed tumor. Of these, ^{18}F-FDOPA scans were positive in 9/10 (90%) previously unresected tumors, and 11/11 (100%) of recurrent tumors. Of the 70 patients in group II, concordance between MRI and ^{18}F-FDOPA was found in 49/54 (90.1%) of patients with sufficient follow-up; in the remaining 16 patients concordance could not be determined due to lack of follow-up. ^{18}F-FDOPA labeling was comparable in both high- and low-grade gliomas and identified both enhancing and non-enhancing tumor equally well. In some cases, ^{18}F-FDOPA activity preceded tumor detection on MRI.
Conclusion: ^{18}F-FDOPA PET/MRI fusion provides precise anatomic localization of tracer uptake and labels enhancing and non-enhancing tumor well. In a small minority of cases, ^{18}F-FDOPA activity may identify tumor not visible on MRI.

Keywords: Positron emission tomography (PET); Magnetic resonance imaging (MRI); PET/MRI; ^{18}F-FDOPA; Image registration; Image fusion; Glioma

1. Introduction

CT and MRI are the standard anatomic imaging modalities used for the evaluation of brain tumor patients. Following treatment, the differentiation between treatment-related changes and residual or recurrent tumor can be challenging.

Given these limitations of anatomic imaging, post-treatment positron emission tomography (PET) has been advocated as a clinically useful imaging modality to differentiate treatment-related changes from recurrent tumor For these reasons, PET imaging with the glucose analogue 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F] FDG), has proven useful as a metabolic tracer in tumor imaging [1–3].

Several important limitations of [^{18}F] FDG PET imaging have been found, however, particularly for brain lesions

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doi:10.1016/j.ejrad.2008.04.018

[4,5]. First of all, normal brain exhibits high background glucose metabolism, particularly in the cortex, limiting both the sensitivity and specificity of FDG-PET in differentiating brain tumor from normal brain. Secondly, since [^{18}F] FDG PET measures increased glucose metabolism, tumors with low glucose metabolism such as low-grade gliomas may not be well visualized, thereby limiting its role in evaluating these lesions. Lastly [^{18}F] FDG uptake is not tumor specific as false-positives occur with inflammatory and granulomatous diseases [4,6,7].

For these reasons, alternative PET tracers with low background brain uptake, such as the ^{18}F-labeled amino acid 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-FDOPA), have been investigated for brain tumor imaging than [^{18}F] FDG. ^{18}F-FDOPA, a dopamine precursor, has been extensively used to assess the integrity of the dopaminergic system in movement disorders such as Parkinson's disease [8–10], but it has only recently shown promise in brain tumor imaging [11,12]. As an analog to DOPA, FDOPA normally accumulates in the basal ganglia. Little FDOPA activity is present in the normal cerebral cortex or white matter. PET imaging with ^{18}F-FDOPA has been shown to have higher sensitivity (96%) for gliomas than traditional [^{18}F] FDG PET imaging [12]. Furthermore, unlike contrast-enhanced MRI, tumor visualization using ^{18}F-FDOPA PET does not depend on blood–brain barrier (BBB) breakdown as this agent is believed to utilize active transport mechanisms for tissue uptake.

Metabolic imaging has increasingly been combined with anatomical imaging modalities (i.e. CT and MRI) to improve the diagnosis, treatment, and follow-up of tumors. However, no prior studies have examined ^{18}F-FDOPA PET/MRI fusion for brain tumor assessment. In the current study, we reviewed fused ^{18}F-FDOPA PET/MRI images and qualitatively assessed the correspondence between increased tracer uptake and evidence of tumor on MRI, and correlated these results with pathologic data.

2. Materials and methods

2.1. Patients

All patients with a pathological diagnosis of glioma who also received ^{18}F-FDOPA scans and brain MRI or brain autopsy were selected from the UCLA brain tumor database, which has been approved by the institutional review board. All patients provided informed consent. Ninety-one patients (55 men, 36 women; mean age at time ^{18}F-FDOPA scan of 44.9 ± 13.1 years (standard deviation, S.D.); age range, 21–79 years) with an initial or subsequent pathological diagnosis of glioma who underwent ^{18}F-FDOPA between January 2003 and September 2007 were studied.

Patients were retrospectively divided into two groups: group I patients had pathology to confirm ^{18}F-FDOPA results as a gold standard whereas group II patients were followed with serial MRI scans. Group I consisted of 21 patients who had craniotomy for tumor resection within 3 months of ^{18}F-FDOPA and MRI scanning. Of these, 10 had previously unresected brain lesions that were suspicious for tumor based upon MRI and clinical data. Of these 10, seven were treatment naive, whereas the other three had either biopsy, or biopsy followed by chemotherapy and radiation treatment. Diagnoses for these 10 were subsequently established as GBM ($n = 4$), anaplastic oligodendroglioma ($n = 2$), anaplastic mixed glioma ($n = 1$), oligodendroglioma ($n = 2$) and grade II astrocytoma ($n = 1$). For the 11 patients with recurrent tumor, initial diagnoses were GBM ($n = 6$), anaplastic oligodendroglioma ($n = 1$) and oligodendroglioma ($n = 4$).

Group II consisted of 70 patients all of whom had a pathologic diagnosis of glioma based on the histopathological World Health Organization (WHO) classification for brain tumors. Sixty-two patients received complete resection of the primary tumor, and eight patients underwent biopsy only. All biopsies were performed prior to ^{18}F-FDOPA PET. In 61 patients, ^{18}F-FDOPA scanning was performed between 6 months and 2 years after initial resection or biopsy to limit the effects of immediate surgical changes; follow-up MRI performed within 2 weeks of ^{18}F-FDOPA. The remainder of the patients underwent ^{18}F-FDOPA PET within half a year post-resection. The distribution of tumor types for group II was grade II astrocytoma ($n = 7$), oligodendroglioma ($n = 13$), low grade mixed glioma ($n = 6$), anaplastic astrocytoma ($n = 8$), anaplastic oligodendroglioma ($n = 6$), mixed anaplastic glioma ($n = 6$) and glioblastoma multiforme (GBM, $n = 24$). All GBM patients in this group received radiation therapy, and the majority were also treated with chemotherapy. Most WHO grade III gliomas also were treated with radiation therapy.

2.2. Image protocol

All MR sequences were acquired on a 1.5-T scanner. Sequences obtained generally included sagittal T1-weighted (T1W; TR 400-550, TE14, slice thickness 5 mm), axial T1W (TR 400, TE 15, slice thickness 3 mm), T2-weighted (T2W) fast spin-echo (TR 4000, TE 126-130, slice thickness 3 mm), proton density (TR 4000, TE 13-15, slice thickness 3 mm), and contrast-enhanced (Gd-diethylenetriaminepentaacetic acid [Gd-DTPA]; 0.1 mmol/kg body weight), enhanced axial and coronal T1W images (TR 400, TE 15, slice thickness 3 mm), with a field of view of 24 cm and a matrix size of 256×256. All scans contained at least T1 pre- and post-contrast and T2W images.

The preparation of ^{18}F-FDOPA and the PET acquisition was performed following a previously reported protocol [13]. Briefly, ^{18}F-FDOPA PET scans were performed with a high-resolution full-ring ECAT HR or ECAT HR+ PET scanner. The resulting images contained either 47 contiguous transaxial slices with a slice thickness of 3.4 mm (with the ECAT HR) or 63 contiguous transaxial slices with a slice thickness of 2.4 mm (axial field of view 15 cm, with the EXACT HR+). ^{18}F-FDOPA preparation took place in a cyclotron laboratory, and total radioactivity was assayed by ionization chamber. After an intravenous injection of a total of 3.5 mCi ^{18}F-FDOPA, ^{18}F-FDOPA-PET images were acquired immediately with a 30-min emission and 5 min transmission scan. Carbidopa was not given for tumor imaging.

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2.3. ^{18}F-FDOPA PET/MRI image fusion and image interpretation

Interpretation of the ^{18}F-FDOPA PET scans was performed independently by a nuclear medicine physician using standard visual image interpretation. Any tracer uptake above background levels, including minor uptake around resection cavities, was considered positive. Clinical information was available to the physician. MRI scans were interpreted independently by two neuroradiologists and any discrepancies were resolved by consensus review. MRI scans were graded as positive for tumor, negative for tumor, or indeterminate. Again, clinical information was available to the physicians. If both the MRI and ^{18}F-FDOPA PET images were interpreted as positive or both interpreted as negative, then the studies were scored as concordant. All other combinations, including all patients with MRI scans that were graded as indeterminate for tumor, were scored as not concordant. ^{18}F-FDOPA PET and MRI images were transferred to a Vitrea2 workstation. The images were automatically co-registered using a commercially available software package (Mirada Fusion7D, Vital Images, Inc., Minnetonka, MN, USA). ^{18}F-FDOPA PET scans were fused to T1W contrast-enhanced and T2W pulse sequences

3. Results

3.1. ^{18}F-FDOPA PET detects most gliomas

For group I patients who had no prior resection, 9/10 tumors were positive on ^{18}F-FDOPA, and all had tumor identified by MRI and by subsequent histopathologic analysis (with pathologic diagnosis as the gold standard). For group I patients with suspected recurrent tumor, 11/11 were positive on ^{18}F-FDOPA scans confirmed by subsequent histopathology. On MRI, 9/11 were found to be positive, 1/11 was indeterminate, and 1/11 was negative. Thus for this group of patients ($n = 21$), the sensitivity of ^{18}F-FDOPA was 95.2% and that of MRI was 90.5%. The specificity cannot be estimated, as none of the lesions were negative for tumor at pathology.

For group II patients, there was concordance between the MRI and ^{18}F-FDOPA findings for 49/54 (90.1%) of cases with sufficient follow-up. Concordance in the remaining 16 patients could not be determined due to lack of follow-up. Of the 49 concordant cases, 43 were positive on both ^{18}F-FDOPA and MRI, and 6 were negative on both. Of the five non-concordant cases, three cases were presumed to be false positive ^{18}F-FDOPA scans given stable clinical follow-up; the other two cases were presumed to be false negative ^{18}F-FDOPA scans given MRI findings highly suspicious for tumor.

3.2. ^{18}F-FDOPA activity correlates well with non-enhancing tumor

Fig. 1 illustrates a well-defined, non-enhancing, T2W hyperintense mass that demonstrated increased uptake on ^{18}F-FDOPA PET. Note how the abnormal ^{18}F-FDOPA PET activity closely corresponds to the region of T2W signal abnormality. This mass was resected and determined to be a low-grade oligodendroglioma.

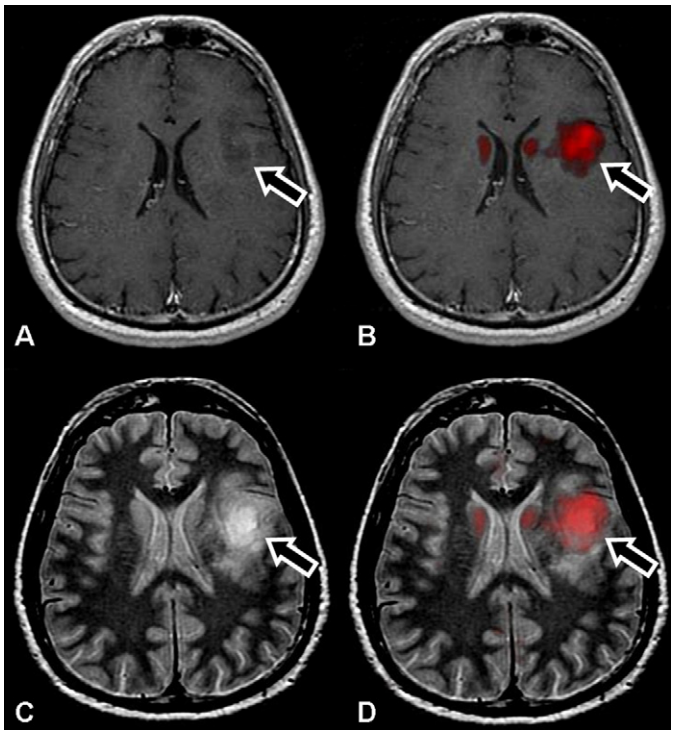

Fig. 1. Non-enhancing tumor (grade II oligodendroglioma) on contrast-enhanced T1W MRI (A, arrow) shows high ^{18}F-FDOPA activity as seen on the ^{18}F-FDOPA PET-MRI fusion image (B, arrow). T2W signal abnormality (C, arrow) corresponds well with the region of elevated ^{18}F-FDOPA activity (D, arrow).

Fig. 2 is an example of a patient with history of resected grade II oligodendroglioma with T2W signal change around the resection cavity. ^{18}F-FDOPA-MRI fusion showed increased activity along the posterior, but not anterior margin of the cavity, even though both areas exhibited T2W signal change. Subsequent resection of the region of ^{18}F-FDOPA activity demonstrated recurrent tumor. This raises the possibility that FDOPA PET may have utility in distinguishing non-enhancing tumor from other causes of T2W signal change such as gliosis, edema, etc.

3.3. ^{18}F-FDOPA activity is also increased in enhancing and non-enhancing high-grade gliomas

^{18}F-FDOPA labeling of non-enhancing areas of GBM also was identified, as can be seen in Fig. 3. This patient had a recurrent GBM that enhanced on MRI and also demonstrated ^{18}F-FDOPA uptake that corresponded to regions of abnormal enhancement (not shown). More superiorly, there was a separate focus of non-enhancing tumor, which subtly expanded the cortex in the parasagittal frontal lobe. Increased ^{18}F-FDOPA activity in this region clearly detected the presence of non-enhancing tumor, a finding that may have been missed if MRI had been used alone. Subsequently, 7-month follow-up demonstrated significant interval tumor growth in this region, which also developed contrast enhancement. Thus, in this case, ^{18}F-FDOPA

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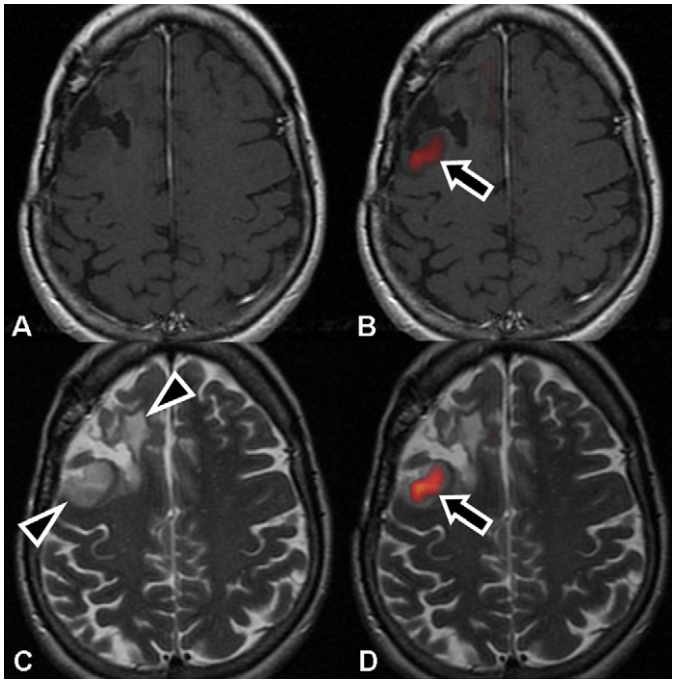

Fig. 2. Non-enhancing tumor regions on contrast-enhanced T1W MRI (A) show high ^{18}F-FDOPA activity on the fused images (B, arrow) posterior to the resection cavity, without associated contrast enhancement. There is T2W signal abnormality anterior and posterior to the resection cavity (C, arrowheads), but only the region of T2W signal posterior to the resection cavity demonstrates abnormal ^{18}F-FDOPA activity (D, arrow). This region was resected and confirmed to be recurrent tumor.

uptake delineated a region of tumor that was inconspicuous on MRI and which preceded abnormal contrast-enhancement on MRI.

3.4. ^{18}F-FDOPA activity is sometimes seen in regions of subsequent tumor recurrence

^{18}F-FDOPA also appeared to identify residual tumor not clearly seen on MRI alone. Fig. 4 shows a case that demonstrated a small amount of contrast enhancement adjacent to a neurosurgical resection cavity. On MRI the appearance could be attributable to either post-surgical change or residual tumor. However, ^{18}F-FDOPA PET scanning showed extensive ^{18}F-FDOPA activity corresponding to not only the region of contrast enhancement, but also to the surrounding non-contrast enhancing tissue as well. Follow-up MRI 3 months later showed extensive contrast enhancement consistent with tumor recurrence at the previous site of ^{18}F-FDOPA activity. In this case, the metabolic abnormality on ^{18}F-FDOPA PET preceded the local tumor recurrence on MRI, suggesting that ^{18}F-FDOPA may detect residual tumor not clearly defined by MRI alone.

3.5. Mild ^{18}F-FDOPA labeling is seen along margins of resection cavities

We noted several cases in which mild ^{18}F-FDOPA activity was present along the margin of resection cavities. This

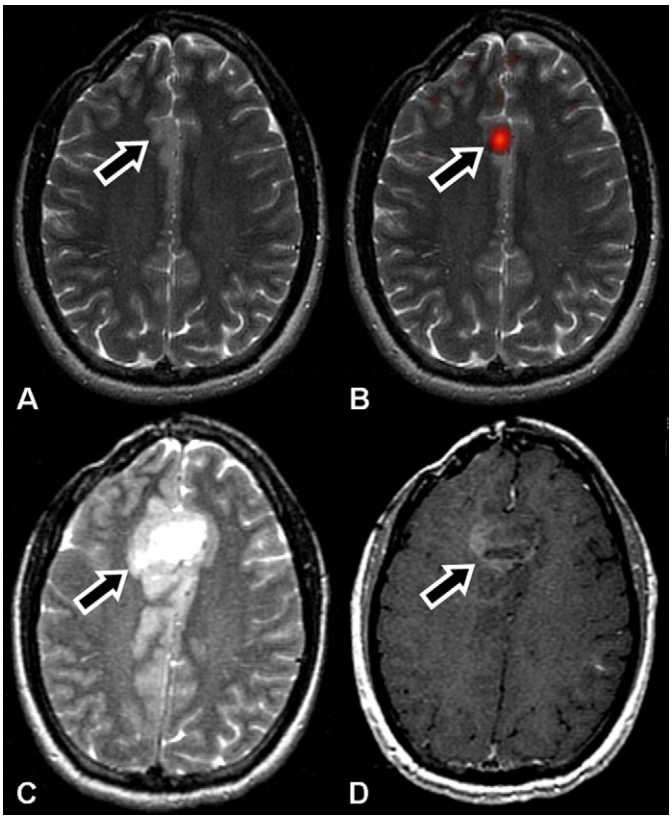

Fig. 3. In this patient, elevated ^{18}F-FDOPA activity is seen at the margins of the resection cavity corresponding to a region of abnormal contrast enhancement (not shown). More superiorly, a non-enhancing area subtly expands the cortex in the parasagittal frontal lobe as shown on axial T2W MRI (A, arrow) also exhibits increased ^{18}F-FDOPA activity (B, arrow). There was significant interval tumor growth into this previously PET-delineated tumor region on 7-month follow-up MRI scan (T2W MRI (C, arrow) and contrasted-enhanced T1W MRI (D, arrow)).

activity could persist for several months, but often would fade on follow-up exams. Increasing activity along resection margins was predictive of tumor re-growth visible on MRI, however.

3.6. Presumed false-negative ^{18}F-FDOPA cases

In addition to the ^{18}F-FDOPA negative GBM case from group I mentioned above, there were three presumed false negative cases in group II, in which tumor did not show ^{18}F-FDOPA uptake but was evident on MRI. Fig. 5 illustrates the ^{18}F-FDOPA and MRI scans of a patient with recurrent/residual WHO grade II oligodendroglioma. In this case, recurrent/residual tumor is clearly evident on MRI, but no activity in the region of T2W signal abnormality was found. The presence of ^{18}F-FDOPA activity in the basal ganglia served as an internal control and confirmed that the ^{18}F-FDOPA labeling protocol had been performed successfully in this patient. Interestingly, this tumor shrank following the negative ^{18}F-FDOPA scan, only to resume growth approximately 3 years later. Thus the metabolic activity of this tumor may have been reduced by treatment, accounting for the negative ^{18}F-FDOPA scan. Another case of presumed false negative ^{18}F-FDOPA scan was a highly

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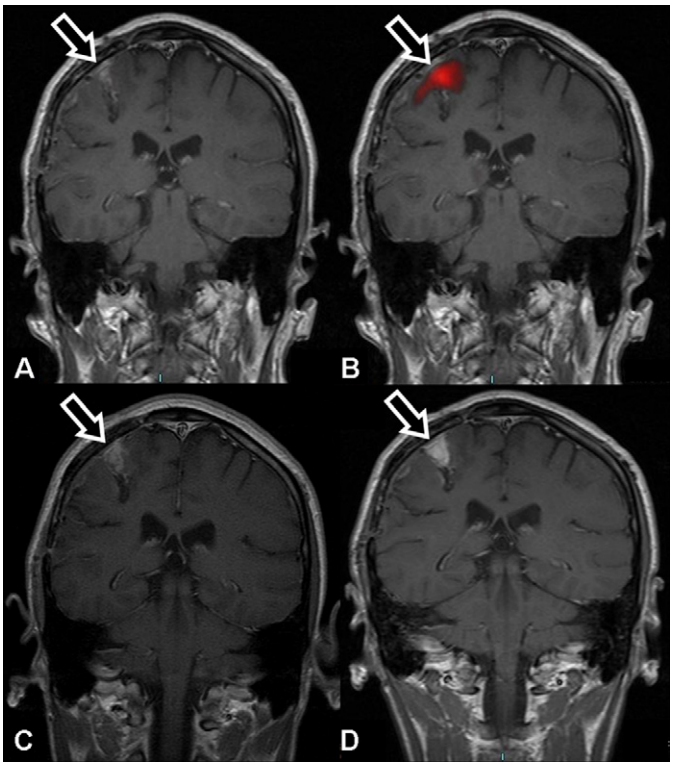

Fig. 4. ^{18}F-FDOPA labeling differentiates post-surgical changes from recurrent tumor. Seven month follow-up MRI for a resected grade III oligodendroglioma exhibits contrast-enhanced areas (A, arrow) that might represent either post-surgical change or recurrent tumor; however ^{18}F-FDOPA activity on PET-MRI fusion (B, arrow) suggests the possibility of tumor recurrence. A subsequent follow-up MRI 2 months (C, arrow) and 3 months (D, arrow) later shows increased enhancement into the area previously delineated by ^{18}F-FDOPA activity.

infiltrative WHO grade II astrocytoma that showed evidence of tumor on MRI but none on ^{18}F-FDOPA (not shown). The third potential false negative was a grade II oligodendroglioma with spread of non-enhancing tumor into the left frontal lobe. This was confirmed with spectroscopy, which showed abnormally high choline and reduced NAA metabolic peaks, consistent with tumor. However, no ^{18}F-FDOPA uptake was present (not shown).

4. Discussion

To our knowledge, this is the first clinical study to systematically investigate the use of ^{18}F-FDOPA PET/MRI fusion for brain tumor assessment. In this preliminary investigation, we show that ^{18}F-FDOPA PET/MRI fusion works well technically, and that there is good correlation between both enhancing and non-enhancing tumor on MRI and increased ^{18}F-FDOPA uptake.

Amino acids and their analogs are attractive for imaging brain tumors because of the high uptake in tumor tissue and low uptake in normal brain tissue. The best-studied amino acid tracer is methyl-^{11}C-L-methionine (^{11}C-methionine), which has shown to be effective in delineating tumor [11]. ^{11}C-methionine has also recently been found to have higher sensitivity than FDG PET and 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) PET [14,15]. The major drawback of ^{11}C-methionine, however, is the short half-life of ^{11}C (20 min) and the rapid catabolism of methionine, which limits its widespread utilization. Because of this, ^{18}F-labeled amino acid analogs with longer half-lives such as *O*-(2-[^{18}F]fluoroethyl)-l-tyrosine (FET) and ^{18}F-FDOPA have recently been used to assess brain tumors [16]. These tracers have half-lives of 110 min and thus can be used without an on-site cyclotron. Studies have shown ^{18}F-FDOPA to have similar tumor uptake compared to ^{11}C-methionine [17,18]. The diagnostic accuracy of ^{18}F-FDOPA appears to be superior to that of ^{18}F-FDG in evaluating recurrent low-grade and high-grade gliomas [12].

The tumor uptake of ^{18}F-FDOPA is dependent on the tumor cells' ability to transport radiolabeled amino acids into the cell rather than on BBB breakdown. ^{18}F-FDOPA crosses the BBB via a carrier-mediated transport mechanism commonly referred to as the large neutral amino acid (LNAA) transport system [19,20]. The ^{18}F label in position 6 of the aromatic ring is believed to provide primary transport information since it has been shown to be removed immediately following membrane transport [21].

Studies using the amino acid tracer ^{11}C-methionine have shown that the intensity of amino acid uptake correlates, in general, with the grade of malignancy [13]. However, some low-grade gliomas such as oligodendrogliomas can exhibit elevated

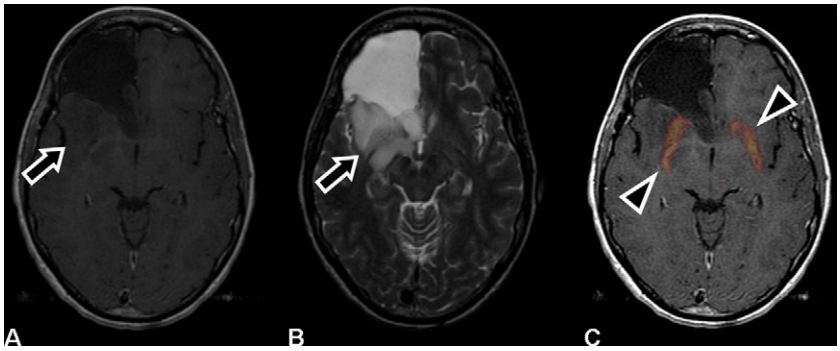

Fig. 5. T1W MRI (A) shows area of non-enhancing tumor posterior to the resection cavity (arrow), which can be more clearly seen on T2W MRI (B) (arrow). ^{18}F-FDOPA-MRI fusion (C) shows no ^{18}F-FDOPA PET activity in this area of tumor recurrence. The presence of ^{18}F-FDOPA activity in the basal ganglia (arrowhead) serves as an internal control and confirms that the ^{18}F-FDOPA labeling protocol had been carried out successfully.

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amino acid transport. Therefore, amino acid tracers that are useful in detecting tumor presence may be limited in determining tumor grade. For tumor grade assessment, other tracers such as markers of cellular proliferation, tumor hypoxia, or tumor angiogenesis are needed.

One of the advantages of ^{18}F-FDOPA imaging is independence of blood–brain barrier breakdown, allowing ^{18}F-FDOPA uptake to occur in both enhancing and non-enhancing tumor. For patients with gliomas who have undergone treatment, conventional MRI follow-up can be limited in its ability to distinguish treatment-related effects from tumor residual or recurrence, as both can result in T2W signal abnormality. Of particular concern are regions of active tumor that do not enhance [22,23]. These areas may also escape detection by [^{18}F] FDG PET secondary to the high-energy metabolism of normal gray matter which obscures subtle increases of [^{18}F] FDG uptake in tumor-bearing tissue with low cellular density as in low grade gliomas [24]. Thus, the ability of ^{18}F-FDOPA to distinguish non-enhancing tumor from other causes of T2W signal abnormality merits further investigation.Although we report a high sensitivity for the detection of pathologically confirmed tumors by ^{18}F-FDOPA PET, its specificity for tumor versus other lesion has not been established. Examples in the literature include reports of increased ^{18}F-FDOPA uptake in demyelinating lesions [11,25]. Additional research will be required to determine what role, if any, ^{18}F-FDOPA PET has in distinguishing tumor from other mass lesions. In our series we identified four cases of ^{18}F-FDOPA negative tumors, including one GBM and three grade II tumors. Each of these lesions had been treated with chemotherapy and radiation, which could have had an impact on the metabolic activity of the tumor. However, there were also many cases of ^{18}F-FDOPA positive tumors (both low and high grade) that had been similarly treated. Additional research will be required to determine what effects, if any, chemotherapy and radiation have on ^{18}F-FDOPA activity, and how this corresponds to tumor response identified by MRI.

One problem in the diagnosis of residual tumor using ^{18}F-FDOPA is the differentiation between tumor and granulation tissue after surgery. High levels of amino acid transport into cells are also described for macrophages, which are activated after surgery. This might explain the mild ^{18}F-FDOPA tracer uptake that was sometimes present around resection cavities. Alternately leakage of ^{18}F-FDOPA due to BBB disruption could account for this finding.

For these reasons a small amount of labeling by ^{18}F-FDOPA around resection margins should be interpreted with caution, as this could represent post-surgical change rather than residual tumor. This is similar to studies using FET, which find that patients without clinical signs of recurrence nonetheless show low and homogeneous FET uptake at the margins of the resection cavity [26]. Previously it has been shown with ^{18}F-FDOPA that using a tumor:striatum activity ratio >1.0 increases specificity with only a small sacrifice in sensitivity [12]. Thus the best interpretation of the data may depend on the clinical question to be answered, depending on which is more important, positive or negative predictive value. Regardless of this consideration, follow-up ^{18}F-FDOPA-PET that shows increasing ^{18}F-FDOPA activity at the resection margins over time should be considered highly suspicious for tumor recurrence. More broadly, it is possible that change in tracer activity over time may be the best indicator of treatment response/recurrence.

Given the limitations of conventional MRI in assessing glioma recurrence, ^{18}F-FDOPA shows potential for use as a complementary tool for detecting gliomas since 1) there may be cases in which ^{18}F-FDOPA detects recurrence earlier than that of MRI and 2) ^{18}F-FDOPA may be better at differentiating non-enhancing tumor from other causes of MRI T2-weighted signal change such asgliosis and edema. Further investigation will be required to determine in what specific clinical settings is ^{18}F-FDOPA potentially useful in expediting therapeutic decisions to improve patient management.

5. Conclusion

This study demonstrates the feasibility of fusing ^{18}F-FDOPA PET and MR images for precise anatomical localization of abnormal ^{18}F-FDOPA PET activity. ^{18}F-FDOPA PET labeling appears to be highly sensitive for gliomas, irrespective of tumor grade, labeling both enhancing and non-enhancing tumor equally well. In general ^{18}F-FDOPA PET confirmed the presence of tumor apparent on MRI, although we found several examples where ^{18}F-FDOPA PET detected tumor that was inconspicuous or not visible on MRI. Our results suggest that assessing the ability of ^{18}F-FDOPA PET to distinguish recurrent non-enhancing tumor from other causes of T2W signal change on MRI merits further investigation.

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