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Image in endocrinology. Localization of an adrenocorticotropic-producing pheochromocytoma using 18F-dihydroxyphenylalanine positron emission tomography.

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Elevated striatal dopamine function linked to prodromal signs of schizophrenia.


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CONTEXT: A major limitation on the development of biomarkers and novel interventions for schizophrenia is that its pathogenesis is unknown. Although elevated striatal dopamine activity is thought to be fundamental to schizophrenia, it is unclear when this neurochemical abnormality develops in relation to the onset of illness and how this relates to the symptoms and neurocognitive impairment seen in individuals with prodromal symptoms of schizophrenia. OBJECTIVES: To determine whether striatal dopamine function is elevated in individuals with prodromal symptoms of schizophrenia before the onset of psychosis and to assess how this relates to the symptoms and neurocognitive impairment. DESIGN: Case-control study of in vivo striatal dopaminergic function. SETTING: Academic research. Patients Patients were recruited from a community mental health service. Twenty-four patients having prodromal symptoms of schizophrenia were compared with 7 patients with schizophrenia and with 12 matched healthy control subjects from the same community. Main Outcome Measure Striatal 6-fluoro-l-dopa F 18-dopa uptake measured using positron emission tomographic (18)F-dopa imaging. RESULTS: Striatal (18)F-dopa uptake was elevated in patients with prodromal symptoms of schizophrenia (effect size, 0.75) to an intermediate degree compared with that in patients with schizophrenia (effect size, 1.25). The elevation was localized in the associative striatum in both groups. Moreover, striatal (18)F-dopa uptake in patients with prodromal symptoms of schizophrenia was correlated with the severity of prodromal psychopathologic and neuropsychological impairment but not with the severity of anxiety or depressive symptoms. CONCLUSIONS: These findings indicate that dopamine overactivity predates the onset of schizophrenia in individuals with prodromal psychotic symptoms, is predominantly localized in the associative striatum, and is correlated with the severity of symptoms and neurocognitive dysfunction.

Relationship of striatal dopamine synthesis capacity to age and cognition.


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Past research has demonstrated that performance on frontal lobe-dependent tasks is associated with dopamine system integrity and that various dopamine system deficits occur with aging. The positron emission tomography (PET) radiotracer 6-[(18)F]fluoro-l-m-tyrosine (FMT) is a substrate of the dopamine-synthesizing enzyme, aromatic amino acid decarboxylase (AADC). Studies using 6-[(18)F]fluorodopa (FDOPA) (another AADC substrate) to measure how striatal PET signal and age relate have had inconsistent outcomes. The varying results occur in part from tracer processing that renders FDOPA signal subject to aspects of postrelease metabolism, which may themselves change with aging. In contrast, FMT remains a purer measure of AADC function. We used partial volume-corrected FMT PET scans to measure age-related striatal dopamine synthesis capacity in 21 older (mean, 66.9) and 16 younger (mean, 22.8) healthy adults. We also investigated how striatal FMT signal related to a cognitive measure of frontal lobe function. Older adults showed significantly greater striatal FMT signal than younger adults. Within the older group, FMT signal in dorsal caudate (DCA) and dorsal putamen was greater with age, suggesting compensation for deficits elsewhere in the dopamine system. In younger adults, FMT signal in DCA was lower with age, likely related to ongoing developmental processes. adults who performed worse on tests of frontal lobe function showed greater FMT signal in right DCA, independent of age effects. Our data suggest that higher striatal FMT signal represents nonoptimal dopamine processing. They further support a relationship between striatal dopamine processing and frontal lobe cognitive function.
Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study.

Goldstein DS.

Progression of dopaminergic dysfunction in a LRRK2 kindred: a multitracer PET study.


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OBJECTIVE: Little is known about the progression of dopaminergic dysfunction in LRRK2-associated Parkinson disease (PD). We sought to characterize the neurochemical progression with multitracer PET in asymptomatic members of parkinsonian kindred (family D, Western Nebraska) carrying LRRK2 (R1441C) mutation. METHOD: Thirteen family D subjects underwent PET scans of presynaptic dopaminergic integrity and five subjects were rescanned 2 to 3 years later. RESULTS: In subjects 8, 9 (mutation carriers), and 13 (genealogically at risk subject), there was a decline in PET markers over the course of the study that was significantly greater than the expected rate of decline in healthy controls. Reduced dopamine transporter binding was the earliest indication of subclinical dopaminergic dysfunction and progression to clinical disease was generally associated with the emergence of abnormal fluorodopa uptake. CONCLUSION: PET study of presymptomatic members of our LRRK2 kindred revealed dopaminergic dysfunction that progressed over time. This represents an ideal group to study the natural history of early disease and the potential effects of neuroprotective interventions.

Dopamine in amygdala gates limbic processing of aversive stimuli in humans.


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Dopamine is released under stress and modulates processing of aversive stimuli. We found that dopamine storage capacity in human amygdala, measured with 6-(18)Ffluoro-L-DOPA positron emission tomography, was positively correlated with functional magnetic resonance imaging blood oxygen level-dependent signal changes in amygdala and dorsal anterior cingulate cortex that were evoked by aversive stimuli. Furthermore, functional connectivity between these two regions was inversely related to trait anxiety. Our results suggest that individual dopamine storage capacity in amygdala subserves modulation of emotional processing in amygdala and dorsal cingulate, thereby contributing to individual differences in anxious temperament.

Classification of schizophrenic patients and healthy controls using [18F] fluorodopa PET imaging.

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Striatal dopaminergic overactivity has been implicated in the pathophysiology of schizophrenia on the basis of in vivo neuroimaging studies. In particular, elevated striatal dopamine synthesis and storage has been repeatedly demonstrated in schizophrenia using the radiotracer 6-[18F]fluoro-L-DOPA ([18F] DOPA) and positron emission tomography (PET). Conventionally analysed [18F] DOPA PET imaging lacks the sensitivity or specificity to be used diagnostically. The aim of this study was to determine if the application of an Artificial Neural Network (ANN) would improve classification of images, and increase the sensitivity and specificity of [18F] DOPA as a potential diagnostic test for schizophrenia. We tested an ANN model in the discrimination of schizophrenic patients from normal controls using [18F] DOPA rate constants within the anterior-posterior subdivisions of the striatum, and compared the model with a general linear analysis of the same data. Participating in the study were 19 patients diagnosed with paranoid schizophrenia and 31 healthy subjects. Maximum classification was achieved using laterality quotients, - the ANN model correctly identified 94% of the controls and 89% of the patients, equivalent to 89% sensitivity and 94% specificity. Using all bilateral striatal regions correctly categorised 74% of the controls and 84% of the patients, equivalent to 84% sensitivity and 74% specificity. In comparison, the general linear analysis performed poorly, correctly classifying only 58% of the controls and 63% of the patients. Overall, these analyses have shown the potential utility of pattern recognition tools in the classification of psychiatric patients based upon molecular imaging of a single target.
**Functional nuclear medicine imaging of medullary thyroid cancer.**

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Medullary thyroid cancer (MTC) originates from parafollicular C cells of the thyroid and accounts for 3-12% of all thyroid cancers. As opposed to other types of dedifferentiated thyroid tumours, MTC cells are highly functional, producing and secreting high amounts of calcitonin and carcinoembryonic antigen. As parafollicular C cells are of neural crest origin, MTC acts as a neuroendocrine tumour also and expresses somatostatin receptors. Although conventional radiological methods such as ultrasonography, computed tomography and magnetic resonance imaging are widely used in the primary diagnosis and staging, they often fail to localize the residual or recurrent disease because the majority of MTC recurrence presents as occult disease. Thus, owing to functional characteristics of MTC, functional imaging modalities of nuclear medicine play a major role in the diagnostic and therapeutic strategies for MTC. Among nuclear medicine modalities, Tc(V) -dimercaptosuccinic acid, In-octreotide and I/I-meta-iodobenzylguanidine are commonly used in the diagnostic and even more in postoperative work-up of MTC. Alternatively, F-fluorodeoxyglucose and other positron emission tomography radiopharmaceuticals such as F-fluorodopa or F-fluorodopamine as well as radiolabelled antibodies such as Tc/I/I anticarcinoembryonic antigen, anti gastrin, and anticholecystokinin-B have promising results. Functional imaging has a great advantage for nuclear medicine techniques in the routine work-up of MTC patients and also has a wide use in experimental studies.

**Age-related changes in midbrain dopaminergic regulation of the human reward system.**

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The dopamine system, which plays a crucial role in reward processing, is particularly vulnerable to aging. Significant losses over a normal lifespan have been reported for dopamine receptors and transporters, but very little is known about the neurofunctional consequences of this age-related dopaminergic decline. In animals, a substantial body of data indicates that dopamine activity in the midbrain is tightly associated with reward processing. In humans, although indirect evidence from pharmacological and clinical studies also supports such an association, there has been no direct demonstration of a link between midbrain dopamine and reward-related neural response. Moreover, there are no in vivo data for alterations in this relationship in older humans. Here, by using 6-{[(18)F]FluoroDOPA (FDOPA) positron emission tomography (PET) and event-related 3T functional magnetic resonance imaging (fMRI) in the same subjects, we directly demonstrate a link between midbrain dopamine synthesis and reward-related prefrontal activity in humans, show that healthy aging induces functional alterations in the reward system, and identify an age-related change in the direction of the relationship (from a positive to a negative correlation) between midbrain dopamine synthesis and prefrontal activity. These results indicate an age-dependent dopaminergic tuning mechanism for cortical reward processing and provide system-level information about alteration of a key neural circuit in healthy aging. Taken together, our findings provide an important characterization of the interactions between midbrain dopamine function and the reward system in healthy young humans and older subjects, and identify the changes in this regulatory circuit that accompany aging.

**Sedation of infants with congenital hyperinsulinism during PET CAT scanning. A case collection**

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Infants with congenital hyperinsulinism may require a positron emission tomography examination with 18F-labeled L-DOPA for the evaluation and planning of surgical interventions. To obtain optimal results it is important for the child to be in a stress-free situation because a stable glucose homoeostasis must be maintained by intravenous glucose infusion. The infant needs to lie calm over a long period of time to obtain optimal results. Sedation for this purpose can be achieved with a continuous infusion of propofol and should be carried out by an anaesthesiologist. Additionally blood glucose measurements must be regularly carried out and the glucose infusion must be adjusted to prevent hypoglycemia.
Hyperinsulinism is a rare disorder, affecting one in more than 50,000 births. It was initially thought to be due to a diffuse anomaly called nesidioblastosis, but interventional radiology-based studies demonstrated the existence of two separate forms, one diffuse and the other focal. These invasive techniques have now been replaced by PET studies with 18F fluorodopa. Focal forms can be cured by surgical removal of the lesion, while the diffuse form can be treated medically or by subtotal resection of the pancreas. Biochemical and genetic studies show that focal and diffuse forms are due to various mutations of chromosome 11.

PET imaging of brain tumors

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Effect of age on caudate dopaminergic function in idiopathic Parkinsonism.

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Aging has long been implicated in the pathogenesis of Idiopathic Parkinsonism (IP). However, postmortem studies have demonstrated that the pathological changes in aging and IP affect the dopaminergic function in putamen and caudate nuclei differently. This has been considered by some authors as evidence against the role of aging in IP. We performed fluorodopa (FD) positron emission tomography (PET) in 36 patients with IP and 25 normal controls to test the hypothesis that the effect of aging on the striatal dopaminergic function in IP differs from the effect of aging in normal controls. We found that the FD uptake constant (Ki) in the caudate nucleus of patients with IP declines with both age (p = 0.002) and duration (p = 0.05) of symptoms. This effect was over and above that of normal aging (p = 0.007). We did not find a similar superimposed effect of age in the putamen. We conclude that the effect of aging on the dopaminergic function in the caudate nucleus in IP differs from that in normal aging. Whether this abnormal aging precedes and even predisposes to IP or is triggered by pathogenetic factors in IP is unclear.

Whole body 18fluoro-L-dopa PET-CT: a useful tool for location and surgical guidance in primary carcinoid tumours.


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Bilateral symptoms and signs of Parkinson's disease (PD) are often improved by unilateral subthalamic nucleus deep brain stimulation (STN-DBS). However, the mechanism for such bilateral effects is unknown. This study was intended to examine effects of unilateral STN-DBS using positron emission computed tomography (PET) and to elucidate mechanisms for bilateral improvement achieved by unilateral stimulation. We conducted (18)F-fluorodeoxyglucose ((18)FDG) and (18)F-fluorodopa ((18)F-DOPA) PET...
scans in PD patients whose bilateral limb symptoms and axial symptoms were improved by unilateral DBS. Two scans were performed in each PET study: when DBS was on and off. We compared those images using statistic parametric mapping (SPM) 99. The significant clinical improvement obtained by unilateral DBS was shown as improvements in bilateral motor limb, axial, and gait sub-scores of the Unified PD Rating Scale (UPDRS). Moreover, (18)FDG PET revealed significant metabolic increases in the ipsilateral ventrolateral thalamic areas and metabolic decrease at the contralateral globus pallidus interna (GPI). In contrast, (18)F-DOPA PET showed no significant differences between DBS on and off. Ipsilateral thalamic activation might induce ipsilateral motor cortical activation, which explains the improvement of contralateral limb symptoms. Furthermore, deactivation of the contralateral GPI might disinhibit the thalamus and contralateral motor cortex, which explains reduction of ipsilateral limb symptoms. These results suggest the mechanisms for bilateral improvement achieved by unilateral DBS.

Positron emission tomography (PET) is a recent and expanding functional nuclear imaging technique. Its extensive development is related to the radiophysical properties fluorine 18 (18F) weak energy of positron, sufficiently long physical half-life and to the simple production and labeling procedures for 18F. [18F]fluorodesoxyglucose was the first licensed radiopharmaceutical in France in 1998. [18F]fluoroDOPA was registered in 2006. Introduction of automated chemistry modules enable development of new fluorinated tracers.

Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in Parkinson disease: PET studies with [11C]NNC 112 and [18F]FDOPA.


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Frontostriatal cognitive dysfunction is common in Parkinson disease (PD), but the explanation for its heterogeneous expressions remains unclear. This study examined the dopamine system within the frontostriatal circuitry with positron emission tomography (PET) to investigate pre- and post-synaptic dopamine function in relation to the executive processes in PD. Fifteen non-demented PD patients and 14 healthy controls underwent [(18)F]FDOPA (for dopamine synthesis) and [(11)C]NNC 112 (for D(1) receptors) PET scans and cognitive testing. Parametric images of [(18)F]FDOPA uptake (K(i)) and [(11)C]NNC 112 binding potential (BP(ND)) were calculated using reference tissue models. Group differences in K(i) and BP(ND) were assessed with both volume of interest and statistical parametric mapping, and were correlated with cognitive tests. Measurement of [(18)F]FDOPA uptake in cerebral cortex was questionable because of higher K(i) values in white than adjacent gray matter. These paradoxical results were likely to be caused by violations of the reference tissue model assumption rendering interpretation of cortical [(18)F]FDOPA uptake in PD difficult. We found no regional differences in D(1) receptor density between controls and PD, and no overall differences in frontostriatal performance. Although D(1) receptor density did not relate to frontostriatal cognition, K(i) decreases in the putamen predicted performance on the Wisconsin Card Sorting Test in PD only. These results suggest that striatal dopamine denervation may contribute to some frontostriatal cognitive impairments in moderate stage PD.

Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuroendocrine tumours.


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PURPOSE: (18)F-FDG positron emission tomography (PET) value for the assessment of neuroendocrine tumours (NET) is limited. Preliminary studies indicate that (18)F-DOPA and (68)Ga-DOTA-NOC are more accurate for disease assessment and (68)Ga-DOTA peptides provide additional data on receptor status that are crucial for targeted radionuclide therapy. At present, there are no comparative studies investigating their role in NET. AIM: The aim of this study was to compare (68)Ga-DOTA-NOC and (18)F-DOPA for the evaluation of gastro-entero-pancreatic and lung neuroendocrine tumours. MATERIALS AND METHODS: Thirteen patients with biopsy-proven NET (gastro-entero-pancreatic or pulmonary) were prospectively enrolled and scheduled for (18)F-DOPA and (68)Ga-DOTA-NOC PET. PET results obtained with both tracers were compared with each other, with other
conventional diagnostic procedures (CT, ultrasound) and with follow-up (clinical, imaging). RESULTS: The most common primary tumour site was the pancreas (8/13) followed by the ileum (2/13), the lung (2/13) and the duodenum (1/13). The carcinoma was well differentiated in 10/13 and poorly differentiated in 3/13 cases. (68)Ga-DOTA-NOC PET was positive, showing at least one lesion, in 13/13 cases while (18)F-DOPA PET was positive in 9/13. On a lesions basis, (68)Ga-DOTA-NOC identified more lesions than (18)F-DOPA (71 vs 45), especially at liver, lung and lymph node level. (68)Ga-DOTA-NOC correctly identified the primary site in six of eight non-operated cases (in five cases, the primary was surgically removed before PET), while (18)F-DOPA identified the primary only in two of eight cases. CONCLUSIONS: Although the patients studied are few and heterogeneous, our data show that (68)Ga-DOTA-NOC is accurate for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours in either the primary or metastatic site and that it offers several advantages over (18)F-DOPA.


68Ga-DOTA-peptides versus 18F-DOPA PET for the assessment of NET patients.

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Central dopamine deficiency in pure autonomic failure.


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OBJECTIVE: Pure autonomic failure (PAF) and Parkinson’s disease (PD) share several clinical laboratory abnormalities; however, PAF is not associated with parkinsonism. In this study, we tested the hypothesis that preservation of nigrostriatal dopaminergic innervation explains the absence of motor dysfunction in PAF. MMETHODS: Patients with PAF (N = 5) or PD (N = 21) and control subjects (N= 14) had brain 6-[18F]fluorodopa positron emission tomographic scanning and cerebrospinal fluid catechol measurements. A patient with PAF and another with PD had rapid postmortem striatal, nigral, and sympathetic ganglion sampling, with assays of catechols and tyrosine hydroxylase activity. RESULTS: The PAF and PD groups had similarly low mean substantia nigra (SN):occipital (OCC) ratios of 6-[18F]fluorodopa-derived radioactivity and similarly low cerebrospinal fluid dihydroxyphenylacetic acid and DOPA levels. Only the PD group, however, had low PUT:OCC, caudate:OCC, or PUT:SN ratios. The PAF and PD cases had similarly low SN tissue concentrations of dopamine and tyrosine hydroxylase activity, but the PD patient had tenfold lower PUT dopamine and the PAF patient 15-fold lower myocardial norepinephrine concentrations. CONCLUSIONS: Surprisingly, PAF and PD entail similarly severe nigral and overall central dopaminergic denervation. There is more severe loss of striatal dopaminergic terminals in PD than in PAF and more severe loss of sympathetic noradrenergic terminals in PAF than in PD. These differences explain the distinctive clinical manifestations of the two Lewy body diseases. Parkinsonism appears to reflect striatal dopamine deficiency rather than loss of nigral dopaminergic neurons per se.


6-L-18F-fluorodihydroxyphenylalanine PET in neuroendocrine tumors: basic aspects and emerging clinical applications.

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In recent years, 6-L-18F-fluorodihydroxyphenylalanine (18F-DOPA) PET has emerged as a new diagnostic tool for the imaging of neuroendocrine tumors. This application is based on the unique property of neuroendocrine tumors to produce and secrete various substances, a process that requires the uptake of metabolic precursors, which leads to the uptake of 18F-DOPA. This nonsystematic review first describes basic aspects of 18F-DOPA imaging, including radiochemistry, factors involved in tracer uptake, and various aspects of metabolism and imaging. Subsequently, this review provides an overview of current clinical applications in neuroendocrine tumors, including carcinoid tumors, pancreatic islet cell tumors, pheochromocytoma, parangangioma, medullary thyroid cancer, hyperinsulinism, and various other clinical entities. The application of PET/CT in carcinoid tumors has unsurpassed sensitivity. In medullary thyroid cancer, pheochromocytoma, and hyperinsulinism, results are also excellent and contribute significantly to clinical management. In the remaining conditions, the initial experience with 18F-DOPA PET indicates that it seems to be less valuable, but further study is required.
Striatal FDOPA uptake and cognition in advanced non-demented Parkinson’s disease: a clinical and FDOPA-PET study.

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This study sought to determine the nature of the relationship between cognition and striatal dopaminergic functioning in 28 patients with advanced Parkinson’s disease (PD) using fluorodopa Positron emission tomography (FDOPA-PET) and neuropsychological test scores. Mental flexibility was related to putamen activity while mental organization (executive memory and fluency) was related to caudate FDOPA uptake. Interestingly, the caudate may be more important in the mental components of executive functioning, while the putamen may be more important in the motor components of executive functioning.


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[F-18] fluorodopa ([F-18] DOPA) accumulates in the synaptic terminal of the dopaminergic neuron depending on the enzyme activity converting dopa into dopamine. The enzyme activity can be up/down-regulated by disease conditions, while the number of dopamine transporter is thought to be defined by the number of the synapse. There are four major pathways of dopaminergic projection systems. The nigrostriatal pathway is particularly involved in the production of movement, as part of a system called the basal ganglia motor loop. The mesocortical/limbic pathway is be involved in cognitive function and motivation and emotional response. Dopaminergic functions in the extrastralatal area in addition to the striatum in vivo have been visualized with the combination of [F-18] DOPA PET and statistical image analyses. Ito K found the significant differences of influx rate (Ki) calculated with voxel-by-voxel Patlak analysis among Parkinson’s disease (PD), PD with dementia (PDD), and normal control. Compared with the normal group, SPM localized declines of the [F-18] DOPA Ki bilaterally in the putamen, the right caudate nucleus and the left ventral midbrain for the PD group. Compared with the normal group, the PDD group showed reduced [F-18] DOPA Ki bilaterally in the striatum, midbrain and anterior cingulate. A relative difference in 18F-dopa uptake between PD and PDD was the bilateral decline in the anterior cingulate area and ventral striatum and in the right caudate nucleus in the PDD group. Accordingly, we conclude that dementia in PD is associated with impaired mesolimbic and caudate dopaminergic function. The next question is whether the corresponding dopaminergic change exists in the neural ganglia in the midbrain. We developed a method optimized for the statistical analysis of the brain stem. PD showed slight increase of Ki in the raphe nucleus and the locus ceruleus. In contrast, PDD demonstrated decline tendency of Ki in the raphe and the locus ceruleus. These suggest cognitive impairment in PDD is caused by the affected the mesolimbic dopaminergic system which originates in the ventral tegmental area. This finding corresponds to Braak’s staging of the intracerebral inclusion body pathology associated with PD.
Basal ganglia involvement in temporal lobe epilepsy: a functional and morphologic study.

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OBJECTIVES: A decrease of [(18)F]fluoro-l-dopa uptake in basal ganglia was recently reported in medically refractory epilepsy. The purpose of this study was to assess the involvement of dopaminergic neurotransmission in refractory temporal lobe epilepsy (TLE) and its relationship to glucose metabolism and morphologic changes. METHODS: Twelve TLE patients were studied using [(18)F]fluorodeoxyglucose PET, [(18)F]fluoro-l-dopa PET, and MRI and compared with healthy control volunteers. Morphologic cerebral changes were assessed using voxel-based morphometry. Student t test statistical maps of functional and morphologic differences between patients and controls were obtained using a general linear model. RESULTS: In TLE patients, [(18)F]fluoro-l-dopa uptake was reduced to the same extent in caudate and putamen in both cerebral hemispheres as well as in the substantia nigra (SN). These dopaminergic functional alterations occurred without any glucose metabolism changes in these areas. The only mild morphologic abnormality was found in striatal regions without any changes in the SN. CONCLUSION: The present study provides support for dopaminergic neurotransmission involvement in temporal lobe epilepsy. The discrepancies between gray matter volume atrophy and the pattern of [(18)F]fluoro-l-dopa suggest that basal ganglia involvement is not related to structural subcortical abnormalities. A functional decrease can be ruled out because there was no change of the glycolytic pathway metabolism in these areas.

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Evaluation of [18F]fluoro-L-DOPA positron emission tomography-computed tomography for surgery in focal congenital hyperinsulinism.

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CONTEXT: In congenital hyperinsulinism (CHI), the identification and precise localization of a focal lesion is essential for successful surgery. OBJECTIVE: Our objective was to evaluate the predictive value and accuracy of integrated [18F]fluoro-L-DOPA ([18F]FDOPA) positron emission tomography (PET)-computed tomography (CT) for the surgical therapy of CHI. DESIGN: This was an observational study. SETTING: The study was performed in the Department of Pediatric Surgery at a university hospital. PATIENTS: From February 2005 to September 2007, 10 children with the clinical signs of CHI and an increased radiotracer uptake in a circumscribed area of the pancreas in the [18F]FDOPA PET-CT were evaluated. INTERVENTIONS: Guided by the [18F]FDOPA PET-CT report, all children underwent partial pancreatic resection, in two cases twice. MAIN OUTCOME MEASURES: Correlation of the anatomical findings at surgery with the report of the [18F]FDOPA PET-CT, and the results of surgery and clinical outcome were determined. RESULTS: In nine children the intraoperative situation corresponded exactly to the description of the [18F]FDOPA PET-CT. A limited resection of the pancreas was curative in eight cases at the first surgery, in one case at the second intervention. We observed no diabetes mellitus or exocrine insufficiency in the follow up so far. In one child, hypoglycemia persisted even after two partial resections of the pancreatic head. Histological analysis finally revealed an atypical intermediate form of CHI. CONCLUSIONS: The integrated [18F]FDOPA PET-CT is accurate to localize the lesion in focal CHI and is a valuable tool to guide the surgeon in limited pancreatic resection.


PET and digestive cancers


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In digestive oncology, the most frequent indication for FDG PET, in our experience and as reported in the literature, is the localisation of recurrent colorectal cancer. This molecular imaging method has also been shown to be clinically useful in various other settings, especially for preoperative staging, for colorectal, esophageal, gastric, pancreatic, hepatic and biliary cancers. We also report on current PET practice in two particular cancers: hepatocellular carcinoma, for which other tracers, including fluoromethylcholine-(18F), are being currently evaluated, and gastrointestinal endocrine tumours, which are included in the recent French marketing authorisation of fluoroDOPA-(18F) and which are also potential targets for radio-labelled somatostatin analogues for PET imaging.


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Congenital hyperinsulinism (HI) of infancy, the most frequent cause of hypoglycaemia in young children, is a neuro-endocrine disease secondary to either focal adenomatous hyperplasia or a diffuse abnormal pancreatic insulin secretion. This inappropriate secretion of insulin induces severe hypoglycaemias that require aggressive treatment to prevent the high risk of irreversible brain damage. Focal and diffuse forms of HI share a similar clinical presentation, but their treatment is dramatically different. Selective surgical resection can cure focal HI whilst diffuse forms require near-total pancreatectomy if resistant to medical treatment. Until recently, preoperative differential diagnosis was based on pancreatic venous sampling, an invasive method, technically difficult to perform, which requires general anaesthesia. The pancreas is one of the most heavily innervated peripheral organs in the body, and its functional imaging with positron emission tomography (PET) is difficult to perform, in part because of the vast number of physiological roles and cell types that characterize this organ. However, HI, as all neuro-endocrine diseases, is notable for the ability to take up amine precursors and to convert them into biogenic amines. Therefore, we have evaluated the use of PET with [18F]fluoro-L-DOPA, a precursor of catecholamines, to image the pancreas and distinguish focal from diffuse HI.


(18)F-labeled positron emission tomographic radiopharmaceuticals in oncology: an overview of radiochemistry and mechanisms of tumor localization.

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Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in a living system. At present, positron emission tomography/computed tomography (PET/CT) is one of the most rapidly growing areas of medical imaging, with many applications in the clinical management of patients with cancer. Although [(18)F]fluorodeoxyglucose (FDG)-PET/CT imaging provides high specificity and sensitivity in several kinds of cancer and has many applications, it is important to recognize that FDG is not a "specific" radiotracer for imaging malignant disease. Highly "tumor-specific" and "tumor cell signal-specific" PET radiopharmaceuticals are essential to meet the growing demand of radioisotope-based molecular imaging technology. In the last 15 years, many alternative PET tracers have been proposed and evaluated in preclinical and clinical studies to characterize the tumor biology more appropriately. The potential clinical utility of several (18)F-labeled radiotracers (eg, fluoride, FDOPA, FLT, FMISO, FES, and FCH) is being reviewed by several investigators in this issue. An overview of design and development of (18)F-labeled PET radiopharmaceuticals, radiochemistry, and mechanism(s) of tumor cell uptake and localization of radiotracers are presented here. The approval of clinical indications for FDG-PET in the year 2000 by the Food and Drug Administration, based on a review of literature, was a major breakthrough to the rapid incorporation of PET into nuclear medicine practice, particularly in oncology. Approval of a radiopharmaceutical typically involves submission of a "New Drug Application" by a manufacturer or a company clearly documenting 2 major aspects of the drug: (1) manufacturing of PET drug using current good manufacturing practices and (2) the safety and effectiveness of a drug with specific indications. The potential routine clinical utility of (18)F-labeled PET radiopharmaceuticals depends also on regulatory compliance in addition to documentation of potential safety and efficacy by various investigators.


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[18F]Fluoro-L-dopa PET/CT in congenital hyperinsulinism.

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Congenital hyperinsulinism can be divided into diffuse or focal form. The treatment and outcome depend on distinguishing between the 2 forms. Pancreatic venous sampling was the only method available to localize the insulin secretion. [F]Fluoro-levodopa, 3,4-dihydroxy-L-phenylalanine positron emission tomography/computed tomography is a noninvasive imaging investigation and increasingly used to determine the type of hyperinsulinism preoperatively. We present a case of diffuse form of congenital hyperinsulinism demonstrated by the [F]levodopa, 3,4-dihydroxy-L-phenylalanine positron emission tomography/computed tomography preoperatively and review the literature.

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Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism.

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OBJECTIVES: Focal lesions in infants with congenital hyperinsulinism (HI) represent areas of adenomatosis that express a paternally derived ATP-sensitive potassium channel mutation due to embryonic loss of heterozygosity for the maternal 11p region. This study evaluated the accuracy of 18F-fluoro-l-dihydroxyphenylalanine ([18F]DOPA) positron emission tomography (PET) scans in diagnosing focal vs. diffuse disease and identifying the location of focal lesions. DESIGN: A total of 50 infants with HI unresponsive to medical therapy were studied. Patients were injected iv with [18F]DOPA, and PET scans were obtained for 50-60 min. Images were coregistered with abdominal computed tomography scans. PET scan interpretations were compared with histological diagnoses. RESULTS: The diagnosis of focal or diffuse HI was correct in 44 of the 50 cases (88%). [18F]DOPA PET identified focal areas of high uptake of radiopharmaceutical in 18 of 24 patients with focal disease. The locations of these lesions matched the areas of increased [18F]DOPA uptake on the PET scans in all of the cases. PET scan correctly located five lesions that could not be visualized at surgery. The positive predictive value of [18F]DOPA in diagnosing focal adenomatosis was 100%, and the negative predictive value was 81%. CONCLUSIONS: [18F]DOPA PET scans correctly diagnosed 75% of focal cases and were 100% accurate in identifying the location of the lesion. These results suggest that [18F]DOPA PET imaging provides a useful guide to surgical resection of focal adenomatosis and should be considered as a guide to surgery in all infants with congenital HI who have medically uncontrollable disease.


The use of 18-fluoro-dihydroxyphenylalanine and 18-fluorodeoxyglucose positron emission tomography scanning in the assessment of metaiodobenzylguanidine-negative pheochromocytoma.

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123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy is commonly used in the imaging of pheochromocytoma (and paraganglioma) to confirm the site of disease and whether any spread has occurred. However, 123I-MIBG imaging is negative in 15% of cases of benign pheochromocytoma and around 50% of cases of malignant pheochromocytoma. In recent years, positron emission tomography (PET) scanning using various different radiotracers has been shown to be a good alternative or supplementary investigation in pheochromocytoma. We present the cases of four patients with symptoms and signs suggestive of pheochromocytoma, but who had negative 123I-MIBG scans, and illustrate the usefulness of 18-fluoro-dihydroxyphenylalanine PET scanning in their assessment. In one of the patients, we illustrate how fluorodeoxyglucose PET scanning can provide useful information about the extent of malignant disease. These illustrative cases lend further support for the use of PET scanning in the assessment of pheochromocytoma and suggest that it may have a particularly important role in the investigation of patients in whom 123I-MIBG scanning is negative.


The effects of carbidopa on uptake of 6-18F-Fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma.


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6-(18)F-fluoro-L-3,4-dihydroxyphenylalanine ([18F]-DOPA) PET is a useful tool for the detection of certain neuroendocrine tumors, especially with the preadministration of carbidopa, an inhibitor of DOPA decarboxylase. Whether carbidopa also improves (18)F-
DOPA PET of adrenal pheochromocytomas and extraadrenal paragangliomas is unknown. The aim of this study was to investigate the sensitivity of (18)F-DOPA PET in the detection of paraganglioma and its metastatic lesions and to evaluate whether tracer uptake by the tumors is enhanced by carbidopa. METHODS: Two patients with nonmetastatic adrenal pheochromocytoma, and 9 patients with extraadrenal abdominal paraganglioma (1 nonmetastatic, 8 metastatic), underwent whole-body CT, MRI, baseline (18)F-DOPA PET, and (18)F-DOPA PET with oral preadministration of 200 mg of carbidopa. The dynamics of tracer uptake by these lesions and the physiologic distribution of (18)F-DOPA in normal tissues were recorded. RESULTS: Seventy-eight lesions were detected by CT or MRI, 54 by baseline (18)F-DOPA PET (P = 0.0022 vs. CT/MRI), and 57 by (18)F-DOPA PET plus carbidopa (P = 0.0075 vs. CT/MRI, not statistically significant vs. baseline). In reference to findings on CT and MRI, the sensitivities of baseline (18)F-DOPA PET were 47.4% for lesions and 55.6% for positive body regions, versus 50.0% (lesions) and 66.7% (regions) for (18)F-DOPA PET plus carbidopa (neither is statistically significant vs. baseline). Compared with baseline, carbidopa detected additional lesions in 3 (27%) of 11 patients. Carbidopa increased the mean (+/-SD) peak standardized uptake value in index tumor lesions from 6.4 +/- 3.9 to 9.1 +/- 5.6 (P = 0.037). Pancreatic physiologic (18)F-DOPA uptake, which may mask adrenal pheochromocytoma, is blocked by carbidopa. CONCLUSION: Carbidopa enhances the sensitivity of (18)F-DOPA PET for adrenal pheochromocytomas and extraadrenal abdominal paragangliomas by increasing the tumor-to-background ratio of tracer uptake. The sensitivity of (18)F-DOPA PET for metastases of paraganglioma appears to be limited.


18F-FDOPA kinetics in brain tumors.

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L-3,4-Dihydroxy-6-(18)F-fluoro-phenyl-alanine ((18)F-FDOPA) is an amino acid analog used to evaluate presynaptic dopaminergic neuronal function. Evaluation of tumor recurrence in neurooncology is another application. Here, the kinetics of (18)F-FDOPA in brain tumors were investigated. METHODS: A total of 37 patients underwent 45 studies; 10 had grade IV, 10 had grade III, and 13 had grade II brain tumors; 2 had metastases; and 2 had benign lesions. After (18)F-DOPA was administered at 1.5-5 MBq/kg, dynamic PET images were acquired for 75 min. Images were reconstructed with iterative algorithms, and corrections for attenuation and scatter were applied. Images representing venous structures, the striatum, and tumors were generated with factor analysis, and from these, input and output functions were derived with simple threshold techniques. Compartmental modeling was applied to estimate rate constants. RESULTS: A 2-compartment model was able to describe (18)F-FDOPA kinetics in tumors and the cerebellum but not the striatum. A 3-compartment model with corrections for tissue blood volume, metabolites, and partial volume appeared to be superior for describing (18)F-FDOPA kinetics in tumors and the striatum. A significant correlation was found between influx rate constant K and late uptake (standardized uptake value from 65 to 75 min), whereas the correlation of K with early uptake was weak. High-grade tumors had significantly higher transport rate constant k(1), equilibrium distribution volumes, and influx rate constant K than did low-grade tumors (P < 0.01). Tumor uptake showed a maximum at about 15 min, whereas the striatum typically showed a plateau-shaped curve. Patlak graphical analysis did not provide accurate parameter estimates. Logan graphical analysis yielded reliable estimates of the distribution volume and could separate newly diagnosed high-grade tumors from low-grade tumors. CONCLUSION: A 2-compartment model was able to describe (18)F-FDOPA kinetics in tumors in a first approximation. A 3-compartment model with corrections for metabolites and partial volume could adequately describe (18)F-FDOPA kinetics in tumors, the striatum, and the cerebellum. This model suggests that (18)F-FDOPA was transported but not trapped in tumors, unlike in the striatum. The shape of the uptake curve appeared to be related to tumor grade. After an early maximum, high-grade tumors had a steep descending branch, whereas low-grade tumors had a slowly declining curve, like that for the cerebellum but on a higher scale.

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Non-[18F]FDG PET in clinical oncology.

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PET is an exquisitely sensitive molecular imaging technique using positron-emitting radioisotopes coupled to specific ligands. Many biological targets of great interest can be imaged with these radiolabelled ligands. This review describes the current status of non-18-fluorodeoxyglucose PET tracers that have a potential clinical effect in oncology. With the help of these tracers, knowledge is being acquired on the molecular characterisation of specific tumours, their biological signature, and postinterventional response. The potential role of these imaging probes for tumour detection and monitoring is progressively being recognised by clinical oncologists, biologists, and pharmacologists.
The added value of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy: a retrospective study involving 49 children.


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PURPOSE: Neuroendocrine diseases are a heterogeneous group of entities with the ability to take up amine precursors, such as L-DOPA, and convert them into biogenic amines, such as dopamine. Congenital hyperinsulinism of infancy (HI) is a neuroendocrine disease secondary to either focal adenomatous hyperplasia or a diffuse abnormal pancreatic insulin secretion. While focal hyperinsulinism may be reversed by selective surgical resection, diffuse forms require near-total pancreatectomy when resistant to medical treatment. Here, we report the diagnostic value of PET with [18F]fluoro-L-DOPA in distinguishing focal from diffuse HI.

METHODS: Forty-nine children were studied with [18F]fluoro-L-DOPA. A thoraco-abdominal scan was acquired 45-65 min after the injection of 4.2 +/- 1.0 MBq/kg of [18F]fluoro-L-DOPA. Additionally, 12 of the 49 children were submitted to pancreatic venous catheterisation for blood samples (PVS) and 31 were also investigated using MRI. RESULTS: We identified abnormal focal pancreatic uptake of [18F]fluoro-L-DOPA in 15 children, whereas diffuse radiotracer uptake was observed in the pancreatic area in the other 34 patients. In children studied with both PET and PVS, the results were concordant in 11/12 cases. All patients with focal radiotracer uptake and nine of the patients with diffuse pancreatic radiotracer accumulation, unresponsive to medical treatment, were submitted to surgery. In 21 of these 24 patients, the histopathological results confirmed the PET findings. In focal forms, selective surgery was followed by clinical remission without carbohydrate intolerance. CONCLUSION: These data demonstrate that PET with [18F]fluoro-L-DOPA is an accurate non-invasive technique allowing differential diagnosis between focal and diffuse forms of HI.


Striatal dopamine synthesis in first-degree relatives of patients with schizophrenia.


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BACKGROUND: First degree relatives (FDR) of patients with schizophrenia have higher risk of developing schizophrenia than the general population. Previous positron emission tomography (PET) studies have shown that striatal presynaptic dopamine synthesis capacity is increased in schizophrenia. We investigated whether this same phenomenon is shared by individuals with increased genetic risk for schizophrenia. METHODS: We used 6-[18F]-fluorodopa (FDOPA) PET imaging to measure striatal dopamine synthesis capacity. We studied 17 nonpsychotic subjects with an FDR with schizophrenia. This group was compared to 17 healthy subjects with no FDRs with schizophrenia. RESULTS: A conventional region of interest (ROI)-analysis indicated that FDOPA uptake (Ki(i)) in the caudate-putamen was statistically significantly higher in the FDR group than in the control group. A voxel-level analysis confirmed these results. CONCLUSIONS: These results suggest that the changes of striatal presynaptic dopamine synthesis seen previously in neuroleptic-naïve schizophrenic patients is also present in FDRs of patients with schizophrenia. These findings have implications for the early detection of psychosis as well as for pharmacological interventions in individuals at risk for psychosis.


Elevated [18F]fluorodopamine turnover in brain of patients with schizophrenia: an [18F]fluorodopa/positron emission tomography study.


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Previous positron emission tomography (PET) studies with levodopa analogs have revealed a modestly increased capacity for dopamine synthesis in the striatum of patients with schizophrenia compared with healthy age-matched control subjects. We hypothesized that not just the synthesis but also the turnover of radionabeled dopamine is elevated in patients. To test the hypothesis, we reanalyzed 2-h-long [18F]fluorodopa (FDOPA)/PET recordings from eight unmedicated patients with schizophrenia and 15 healthy age-matched control subjects, using new methods for the quantification of [18F]fluorodopamine steady-state kinetics. The fractional rate constant for the catabolism and elimination of [18F]fluorodopamine was elevated nearly twofold in striatum, the largest biochemical difference in brain of schizophrenics yet reported. The magnitude of the intrinsic blood-brain FDOPA clearance with correction for this loss of [18F]fluorodopamine metabolites was increased by 20% in caudate and putamen and by 50% in amygdala and midbrain of the patients. However, the magnitude of the steady-state storage of FDOPA and its decarboxylated metabolites (V(d)) was reduced by one-third in the caudate nucleus and amygdala of the schizophrenic group. Thus, reduced steady-
state storage of [18F]fluorodopamine occurs in the midst of accelerated synthesis in brain of untreated patients. Positive scores of the positive and negative syndrome scale correlated inversely with the magnitude of V(d) in amygdala, suggesting an association between positive symptoms and impaired steady-state storage of FDOPA metabolites in that structure.


Striatal dopaminergic activity (FDOPA-PET) associated with cognitive items of a depression scale (MADRS) in Parkinson's disease.

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Motor symptoms form the hallmark of Parkinson's disease (PD), although other features such as depression are often present. Currently-used depression rating scales measure affective and somatic symptoms. These somatic symptoms of depression can also be core PD symptoms, suggesting an overlap of symptoms between depression and PD. Using in vivo radiotracer methods, striatal dopaminergic dysfunction is found in both PD and depression. This study investigates to what extent the overlapping symptoms of depression and PD are associated with the striatal dopaminergic dysfunction typical of PD. Symptoms of depression were assessed in 23 PD patients who did not have major depression according to the Montgomery-Asberg depression rating scale (MADRS; cut-off < 18) and according to a trained psychologist who interviewed all patients. The striatal dopaminergic activity of patients was assessed with FDOPA-PET. Dopaminergic activity of the putamen and caudate nucleus was associated with MADRS total score and specifically with the symptom 'Concentration difficulties'. These results suggest that the typical striatal dopaminergic dysfunction of PD can cause symptoms that can also be categorized as symptoms of depression. In particular, cognitive symptoms measured with a depression rating scale may be based on the dopaminergic dysfunction of the striatum in PD patients.


Role of 18F-dopa PET/CT imaging in the management of patients with 111In-pentetreotide negative GEP tumours.


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PURPOSE: To assess whether 18F-dopa PET/CT is able to provide information relevant in changing the clinical management of patients with gastro-enteropancreatic (GEP) tumours where there is negative or inconclusive conventional radiological imaging (ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI)) and 111In-pentetreotide scintigraphy.

MATERIALS AND METHODS: From January 2005 to October 2006, 84 patients with clinical and biochemical suspicion of GEP tumours were investigated by US and CT scans, MRI and 111In-pentetreotide scintigraphy. In 13/84 (15.4%) both conventional radiological imaging and 111In-pentetreotide scintigraphy provided negative or inconclusive findings, and patients were referred for 18F-dopa PET/CT imaging. Each patient received 5.3 MBq x kg(-1) 18F-dopa intravenously, and imaged 60 min later using a hybrid PET/CT scanner. RESULTS: 18F-dopa PET/CT detected the primary tumour in all 13 patients (size range, 7-26 mm, mean, 18 mm; SUVmax range, 2.3-16.3, mean, 5.7) and further 12 unsuspected lesions (size range, 12-23 mm, mean 17; SUVmax range 2.8-12.7, mean 4.6). Confirmation of the PET/CT findings was obtained in all patients from histopathological analysis of tissue obtained after surgery and/or biopsy. All the 18F-dopa-positive primary lesions were confirmed as being the primary tumour at histology, whereas of the other 12 unsuspected 18F-dopa-positive lesions, 11 were found to be metastatic deposits and one due to unspecific inflammation (one false positive result). Notably, the results of 18F-dopa PET/CT imaging changed the clinical management in 11/13 patients (84%). CONCLUSIONS: Our preliminary results suggest that 18F-dopa PET/CT has a promising role in GEP patients with negative or inconclusive findings at conventional radiological imaging and 111In-pentetreotide scintigraphy. The findings were helpful in biopsy guidance and played a major role in changing the management of those patients.


Diagnostic impact of PET with 18F-FDG, 18F-DOPA and 3-O-methyl-6-[18F]fluoro-DOPA in recurrent or metastatic medullary thyroid carcinoma.

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PURPOSE: In patients with medullary thyroid carcinoma (MTC), rising levels of the tumour markers calcitonin and CEA after primary surgery indicate tumour recurrence or metastases. The only chance of cure is the resection of localised tumour tissue. For positron emission tomography (PET) with (18)F-fluorodeoxyglucose ((18)F-FDG) and (18)F-dihydroxyphenylalanine ((18)F-
DOPA), sensitivities of 78% and 63% have been reported, but in a considerable percentage of MTC patients the source of tumour marker elevation is not detected. The aim of this retrospective data evaluation was to compare the value of PET with (18)F-FDG, (18)F-DOPA and the amino acid tracer 3-O-methyl-6-[(18)F]fluoro-DOPA ((18)F-OMFD) in the detection of MTC recurrence.

METHODS: Fifteen patients with elevated calcitonin were investigated with PET as part of their individual clinical work-up. All patients underwent (18)F-FDG PET and (18)F-DOPA PET, and ten patients underwent (18)F-OMFD PET. RESULTS: With (18)F-FDG, seven patients showed foci in the neck, mediastinum, upper abdomen or bone. In seven patients, (18)F-DOPA revealed suspicious foci; five of these seven patients showed partially corresponding uptake of (18)F-FDG in the neck and mediastinum. Two of these patients underwent surgical surgery and metastases were verified. With (18)F-OMFD, a small focus in the liver was suspected in one patient without a correlate on (18)F-FDG PET, (18)F-DOPA PET or conventional imaging. CONCLUSION: (18)F-FDG and (18)F-DOPA showed foci that were highly suspicious for local recurrence or metastasis of MTC, although histological verification in these patients with numerous previous surgical interventions was performed in only two patients. The amino acid tracer (18)F-OMFD had no diagnostic impact in these patients.


Diagnosis and localization of focal congenital hyperinsulinism by 18F-fluorodopa PET scan.

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OBJECTIVES: To assess the accuracy of 18F-fluoro-L-dihydroxyphenylalanine ([18F]-DOPA) PET scans to diagnose focal versus diffuse disease and to localize focal lesions in infants with congenital hyperinsulinism. STUDY DESIGN: Twenty-four infants with hyperinsulinism unresponsive to medical therapy were studied. Patients were injected intravenously with [18F]-DOPA, and PET scans were obtained for 1 hour. Images were coregistered with abdominal CT scans. RESULTS: The diagnosis of focal or diffuse hyperinsulinism was correct in 23 of the 24 cases (96%) and equivocal in 1 case. [18F]-DOPA PET identified focal areas of high uptake of radiopharmaceutical in 11 patients. Pathology results confirmed that all 11 had focal adenomatosis, and the locations of these lesions matched the areas of increased [18F]-DOPA uptake on the PET scans in all of the cases. CONCLUSIONS: [18F]-DOPA PET scans were 96% accurate in diagnosing focal or diffuse disease and 100% accurate in localizing the focal lesion. These results suggest that [18F]-DOPA PET imaging should be considered in all infants with congenital hyperinsulinism who need to have pancreatectomy.


PET scanning for infants with HHI: a small step for affected infants, a giant leap for the field.

Sperling MA.

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Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients.


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CONTEXT AND OBJECTIVE: Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography (PET) is a promising method in localizing neuroendocrine tumors. Recently, it has been shown to differentiate focal forms of congenital hyperinsulinism of infancy. The current study was set up to determine the potential of 18F-DOPA PET in identifying the insulin-secreting tumors or beta-cell hyperplasia of the pancreas in adults. PATIENTS AND METHODS: We prospectively studied 10 patients with confirmed hyperinsulinemic hypoglycemia and presumed insulin-secreting tumor using 18F-DOPA PET. Anatomical imaging was performed with computed tomography (CT) and magnetic resonance imaging (MRI). All patients were operated on, and histological verification was available in each case. Semiquantitative PET findings in the pancreas using standardized uptake values were compared to standardized uptake values of seven consecutive patients with nonpancreatic neuroendocrine tumors. RESULTS: By visual inspection of 18F-DOPA PET images, it was possible in nine of 10 patients to localize the pancreatic lesion, subsequently confirmed by histological analysis. 18F-DOPA uptake was enhanced in six of seven solid insulinomas and in the malignant insulinoma and its hepatic metastasis. Two patients with beta-cell hyperplasia showed increased focal uptake of 18F-DOPA in the affected areas. As compared to CT or MRI, 18F-DOPA PET was more sensitive in localizing diseased pancreatic tissue. CONCLUSION: 18F-DOPA PET was useful in most patients with insulinoma and negative CT, MRI, and ultrasound results. In agreement with previous findings in infants, preoperative 18F-DOPA imaging seems to be a method of choice for the detection of beta-cell hyperplasia in adults. It should be considered for the detection of insulinoma or beta-cell hyperplasia in patients with confirmed hyperinsulinemic hypoglycemia when other diagnostic work-up is negative.
Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007.

ICRP.

In this report, the Commission provides biokinetic and dosimetric models for 33 radiopharmaceuticals, as well as recommendations related to breast feeding for mothers who have undergone a nuclear medicine investigation. The report is based on Addenda 3-9 to Publication 53. Addenda 3-7 have been available on the ICRP website (www.icrp.org) as interim reports. The work has been carried out by a Joint Task Group of ICRP Committees 2 and 3. This publication provides biokinetic models, absorbed doses, and effective doses for the following radiopharmaceuticals: 11C-acetate; 11C-amino acids; 11C-brain receptor substances; 11C-methionine; 18F-amino acids; 18F-FET; 18F-FDG; 111In-monoclonal antibodies/fragments; 123I-fatty acids (BMIPP, IPPA); 123I-monoclonal antibodies/fragments; 131I-monoclonal antibodies/fragments; and 201Tl-ion. The publication also provides realistic maximum models for 11C- and 18F-substances, for which no specific models are available.

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A biologically adapted dose-escalation approach, demonstrated for 18F-FET-PET in brain tumors.

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PURPOSE: To demonstrate the feasibility of a biologically adapted dose-escalation approach to brain tumors. MATERIAL AND METHODS: Due to the specific accumulation of fluoroethyltyrosine (FET) in brain tumors, (18)F-FET-PET imaging is used to derive a voxel-by-voxel dose distribution. Although the kinetics of (18)F-FET are not completely understood, the authors regard regions with high tracer uptake as vital and aggressive tumor and use a linear dose-escalation function between SUV (standard uptake value) 3 and SUV 5. The resulting dose distribution is then planned using the inverse Monte Carlo treatment-planning system IKO. In a theoretical study, the dose range is clinically adapted from 1.8 Gy to 2.68 Gy per fraction (with a total of 30 fractions). In a second study, the maximum dose of the model is increased step by step from 2.5 Gy to 3.4 Gy to investigate whether a significant dose escalation to tracer-accumulating subvolumes is possible without affecting the shell-shaped organ at risk (OAR). For all dose-escalation levels the dose difference Delta D of each voxel inside the target volume is calculated and the mean dose difference Delta D and their standard deviation sigma Delta D are determined. The dose to the OAR is evaluated by the dose values D OAR 50% and D OAR 5%, which are the dose values not exceeded by 50% and 5% of the volume, respectively. RESULTS: The inhomogeneous dose prescription is achieved with high accuracy (Delta D < 0.03 +/- 0.3 Gy/fraction). The maximum dose can be increased remarkably, without increasing the dose to the OAR (standard deviation of D OAR 50% < 0.02 Gy/fraction and of D OAR 5% < 0.05 Gy/fraction). CONCLUSION: Assuming that regions with high tracer uptake can be interpreted as target for radiotherapy, (18)F-FET-PET-based dose painting by numbers applied to brain tumors is a feasible approach. The dose, and therefore potentially the chance of tumor control, can be enhanced. The proposed model can easily be transferred to other tracers and tumor entities.


Assessment of various strategies for 18F-FET PET-guided delineation of target volumes in high-grade glioma patients.


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PURPOSE: The purpose of the study is to assess the contribution of (18)F-fluoro-ethyl-tyrosine ((18)F-FET) positron emission tomography (PET) in the delineation of gross tumor volume (GTV) in patients with high-grade gliomas. Seven image segmentation techniques were used to delineate (18)F-FET PET GTVs, and the results were compared to the manual MRI-derived GTV (GTV(MRI)). PET image segmentation techniques included manual delineation of contours (GTV(man)), a 2.5 standardized uptake value (SUV) cutoff (GTV(2.5)), a fixed threshold of 40% and 50% of the maximum signal intensity (GTV(40%) and GTV(50%)), signal-to-background ratio (SBR)-based adaptive thresholding (GTV(SBR)), gradient find (GTV(GF)), and region growing (GTV(RG)). Overlap analysis was also conducted to assess geographic mismatch between the GTVs delineated using the different techniques. RESULTS: Contours defined using GTV(2.5) failed to provide successful delineation technically in three patients (18% of cases) as SUV(max) < 2.5 and clinically in 14 patients (78% of cases). Overall, the majority of GTVs defined on PET-based techniques were usually smaller than GTV(MRI) (67% of cases). Yet, PET detected frequently tumors that are not visible on MRI and added substantially tumor extension outside the GTV(MRI) in six patients (33% of cases). CONCLUSIONS: The selection of the most appropriate (18)F-FET PET-based segmentation algorithm is crucial, since it impacts both the volume and shape of the resulting GTV. The 2.5 SUV isocountour and GF segmentation techniques performed poorly and should not be used for GTV delineation. With adequate setting, the SBR-based PET technique may add considerably to conventional MRI-guided GTV delineation.
Molecular imaging probes used for positron emission tomography (PET) in oncology are reviewed. Although [18F] FDG is presently the most useful probe for imaging tumors, there is a need for complementary probes of FDG with some limitations on detection in the brain or inflammatory region. The review is mostly focused on 18F-labeled probes designed for amino acid transport and protein synthesis, DNA synthesis, membrane lipid, and hypoxia such as FET, FLT, FMAU, fluoroiodine, and FMISO, together with our original probes of FMT and FRP-170.


Prospective comparison of FDG and FET PET/CT in patients with head and neck squamous cell carcinoma.


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AIM: The clinical usefulness of 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography (FDG-PET) in head and neck squamous cell carcinoma (HNSCC) is now well-documented. However, its sensitivity is greater than its specificity due to false-positive results in inflammatory or infectious lesions, which are frequent in this area, in particular after treatment by surgery and/or radiotherapy. O-2-fluoro-(18F)-ethyl-L-tyrosine (FET) has been reported not to be taken up by such lesions, and a preliminary study indicated that this may be clinically useful in HNSCC. We performed a prospective study to compare the diagnostic performances of FDG and FET PET/CT in the different settings of HNSCC. MATERIALS AND METHODS: Twenty-seven patients (20 men and seven women, aged 48-76, among 30 patients included) and 69 suspected cancer sites are now evaluable on basis of postsurgical histology and/or follow-up greater than 6 months; 15 patients were referred for initial staging and 12 during posttherapy follow-up, a recurrence being suspected in eight of them. FDG and FET PET/CT were performed on two different days, the patient fasting for 6 h, 1 h after injection of 5 MBq/kg of body mass of each radiopharmaceutical. Both PET/CT examinations were blind read more than 6 months after the end of inclusions in a random order for each tracer and with a time interval greater than 1 month between FDG and FET PET/CT blind readings. RESULTS: Overall diagnostic performances, derived from blind reading: FDG PET/CT on a per patient basis: sensitivity 100%, specificity 93%; FDG PET/CT on a per site basis: sensitivity 95%, specificity 63%, accuracy 83%; FET PET/CT on a per patient basis: sensitivity 70%, specificity 100%, accuracy 78%; FET PET/CT on a per site basis: sensitivity 64%, specificity 100%, accuracy 78%. At site level, sensitivity was significantly greater with FDG (p<0.02) and specificity with FET (p<0.01). The statistical level of significance was not reached at patient level. CONCLUSION: Although its sensitivity was confirmed, FET did not appear to be suited as a first-line PET tracer in HNSCC imaging and cannot replace FDG for staging due to insufficient sensitivity. However, it was useful in a few selected cases to favor a wait and see attitude when a FDG+ FET- focus was discovered in patients referred for systematic FDG PET during follow-up. In contrast, second primary cancers should not be ruled out if FDG was clearly positive in the lungs or the digestive tract.


Metabolic imaging of cerebral gliomas: spatial correlation of changes in O-(2-18F-fluoroethyl)-L-tyrosine PET and proton magnetic resonance spectroscopic imaging.


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The aim of this study was to determine the spatial correlation of O-(2-(18)F-fluoroethyl)-L-tyrosine ((18)F-FET) uptake and the concentrations of choline (Cho), creatine (Cr), and total N-acetylaspartate (tNAA) determined with proton magnetic resonance spectroscopic imaging ((1)H MRSI) in cerebral gliomas for the multimodal evaluation of metabolic changes. METHODS: (18)F-FET PET and 2-dimensional (1)H MRSI were performed in 15 patients with cerebral gliomas of World Health Organization (WHO) grades II-IV. PET and (1)H MRSI datasets were coregistered by use of mutual information. On the basis of their levels of (18)F-FET uptake, 4 different areas in a tumor (maximum, strong, moderate, and low (18)F-FET uptake) were defined on PET slices as being congruent with the volume of interest in the (1)H MRSI experiment. (18)F-FET uptake in lesions was evaluated as tumor-to-brain ratios. Metabolite concentrations for Cho, Cr, and tNAA and Cho/tNAA ratios were computed for these 4 areas in the tumor and for the contralateral normal brain. RESULTS: In the area with maximum (18)F-FET uptake, the concentration of tNAA (R=0.588) and the Cho/tNAA ratio (R=0.945) correlated significantly with (18)F-FET uptake. In the areas with strong and moderate (18)F-FET uptake, only the Cho/tNAA ratios (R=0.811 and R=0.531, respectively) were significantly associated with amino acid transport. At low (18)F-FET uptake, analysis of the correlations of amino acid uptake and metabolite concentrations yielded a significant result only for the concentration of Cr (R=0.626). No correlation was found for metabolite concentrations determined with (1)H MRSI and...
(18)F-FET uptake in normal brain tissue. Maximum (18)F-FET uptake and the tNAA concentration were significantly different between gliomas of WHO grades II and IV, with P values of 0.032 and 0.016, respectively. CONCLUSION: High (18)F-FET uptake, which is indicative of tumor cell infiltration, associates with neuronal cell loss (tNAA) and changes in ratios between parameters representing membrane proliferation and those of neuronal loss (Cho/tNAA ratio), which can be measured by (1)H MRSI. The significant correlation coefficients detected for Cr in regions with low (18)F-FET uptake suggests an association between the mechanism governing amino acid transport and energy metabolism in areas that are infiltrated by tumor cells to a lesser extent. These findings motivate further research directed at investigating the potential of (1)H MRSI to define tumor boundaries in a manner analogous to that of amino acid PET.


Prognostic value of 18F-fluoroethyl-L-tyrosine PET and MRI in small nonspecific incidental brain lesions.

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Nonspecific incidental brain lesions (NILs) are being detected more frequently because of an increasing number of screening or research MRI scans of the brain, and their natural course is uncertain. METHODS: In a prospective cohort study starting in 1999, we determined the outcomes of patients with incidental, nonenhancing, supratentorial, lobar, and small-volume (<10 mL) lesions, depending on the findings of MRI and PET with the (18)F-labeled amino acid fluoroethyl-l-tyrosine ((18)F-FET). Patients with seizures, focal neurologic deficits, signs of local or systemic infection or inflammation, known brain disease, or any kind of previous cerebral treatment were excluded. Finally, 21 patients were eligible. MRI was performed in 19 of these patients because of nonspecific symptoms (such as headaches, dizziness, or sudden deafness), whereas 2 patients were healthy volunteers in MRI studies. Clinical follow-up and MRI scans were obtained at 4- to 6-mo intervals, and follow-up ranged from 3 to 8.5 y. Mean lesion-to-brain (L/B) ratios of >or=1.6 on (18)F-FET PET were rated as positive. RESULTS: Four different outcome groups were identified. In group A, 5 NILs regressed or vanished completely. All of these lesions were circumscribed on MRI, and (18)F-FET uptake was negative, with an L/B ratio of 1.2+/-0.2 (mean +/- SD). In group B, 10 NILs were stable, without growth. All of these lesions were circumscribed on MRI, and (18)F-FET uptake was negative (L/B ratio: 1.0+/-0.1). In group C, 2 NILs grew slowly over years, and an astrocytoma of World Health Organization (WHO) grade II was diagnosed after resection in each case. The lesions were circumscribed on MRI, and (18)F-FET uptake was negative (L/B ratios: 0.7 and 1.0). In group D, 4 NILs showed sudden and rapid growth, with clinical deterioration, and a high-grade glioma of WHO grade III or IV was diagnosed after resection in all cases. The lesions were diffuse on MRI, and (18)F-FET uptake was significantly increased (L/B ratio: 2.0+/-0.4) (P<0.01 for group D vs. group A or group B). CONCLUSION: For NILs, a circumscribed growth pattern on MRI and normal or low (18)F-FET uptake on PET are strong predictors for a benign course, with the eventual development of a low-grade glioma. In contrast, NILs with a diffuse growth pattern on MRI and increased (18)F-FET uptake indicate a high risk for the development of a high-grade glioma.


[Improved diagnostics of cerebral gliomas using FET PET]

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Positron emission tomography (PET) using radiolabeled amino acids has shown great potential for more accurate diagnostics of cerebral gliomas. O-(2-[18F]Fluoroethyl)-L-tyrosine (FET) is a new tracer for PET which can be produced with high efficiency and distributed on a wide clinical scale in Germany. In a biopsy-controlled study, a significant improvement of the detection of true tumor extent of cerebral gliomas could be demonstrated by the combined use of PET PET and MRT in comparison with MRT alone. Advantages of FET PET are an improved guidance of biopsies, an improved planning of surgery and radiation therapy, and the differentiation of tumor recurrence from unspecified post-therapeutic tissue changes. Furthermore, FET PET appears to be particularly valuable in the prognosis of low-grade gliomas.


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OBJECTIVE: To explore prospectively the positive predictive value of O-(2-[(18)F]fluoroethyl)-L-tyrosine (FET)-PET in selected patients with a magnetic resonance imaging (MRI)-based suspicion of a glioma recurrence or progression. Methods Patients with a supratentorial glioma (initial World Health Organization (WHO) grade II, III or IV) were considered eligible if they had both an MRI-(new/progressive contrast-enhancing lesion) and FET-PET-based diagnosis of a recurrence/progression after various forms and combinations of irradiation and chemotherapy. Criterion for tumour recurrence/progression in FET-PET was a standardized uptake value (SUVmax)/Background (BG) ratio of ≥2.0 in the late uptake phase. All patients underwent multimodal (MRI, FET-PET) imaging-guided stereotactic biopsy. The positive predictive value was defined as the proportion of MRI and FET-PET findings indicating glioma recurrence/progression that also tested positive for tumour recurrence/progression after stereotactic biopsy. RESULTS: Thirty-one patients with initially WHO grade II (17), WHO grade III (6), and grade IV glioma (8) were included. In 26 patients FET-PET results indicating tumour recurrence/progression were concordant with the biopsy results. In five patients histopathologic evaluation failed to reveal a "vital" tumour. FET-PET findings were also discordant with the radiographic and clinical follow-up in these five patients. The positive predictive value of FET-PET was 84%. CONCLUSION: The positive predictive value of FET-PET using the standard ratio method is high, but not high enough to replace stereotactic biopsy in this highly selected study cohort. Whether the calculation of FET uptake in the early phase and/or the evaluation of uptake kinetics will improve the positive predictive value of PET-PET deserves prospective evaluation.

Differential uptake of O-(2-18F-fluoroethyl)-L-tyrosine, L-3H-methionine, and 3H-deoxyglucose in brain abscesses.


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The amino acid O-(2-[(18)F]fluoroethyl)-L-tyrosine ([18]F-FET) has been shown to be a useful tracer for brain tumor imaging. Experimental studies demonstrated no uptake of [18]F-FET in inflammatory cells but increased uptake has been reported in single cases of human brain abscesses. To explore this inconsistency, we investigated the uptake of [18]F-FET in comparison with that of L-[methyl-(3)H]methionine ([3]H-MET) and D-[3H]deoxyglucose ([3]H-DG) in brain and calf abscesses in rats. METHODS: Abscesses were induced in the brain (n = 9) and calf (n = 5) of Fisher CDF rats after inoculation of Staphylococcus aureus. Five days later, [18]F-FET and [3]H-MET (n = 10) or [18]F-FET and [3]H-DG (n = 4) were injected intravenously. One hour after injection the rats were sacrificed, and the brain or calf muscle was investigated using dual-tracer autoradiography. Lesion-to-background ratios (L/B) and standardized uptake values (SUVs) were calculated. The autoradiograms were compared with histology and immunostaining for glial fibrillary acidic protein (GFAP), CD68 for macrophages, and CD11b for microglia. RESULTS: [18]F-FET uptake in the area of macrophage infiltration and activated microglia at the rim of the brain abscesses was low (L/B: 1.5 +/- 0.4). In contrast, high uptake was observed for [3]H-MET as well as for [3]H-DG (L/B: 4.1 +/- 1.1 for [3]H-MET vs. 3.1 +/- 1.5 for [3]H-DG; P < 0.01 vs. [18]F-FET). Results for calf abscesses were similar. In the vicinity of the brain abscesses, slightly increased uptake was noted for [18]F-FET (L/B: 1.8 +/- 0.3) and [3]H-MET (L/B: 1.8 +/- 0.4), whereas [3]H-DG distribution was normal (L/B: 1.2 +/- 0.2). Anti-GFAP immunofluorescence showed a diffuse astrocytosis in those areas. CONCLUSION: Our results demonstrate that there is no accumulation of [18]F-FET in macrophages and activated microglia in experimental brain abscesses, whereas [3]H-MET and [3]H-DG exhibit high uptake in these cells. Thus, the specificity of [18]F-FET for gliomas may be superior to that of [3]H-MET and [3]H-DG. Increased [18]F-FET uptake in human brain abscesses appears to be related to reactive astrocytosis.

Uptake of 18F-Fluorocholine, 18F-FET, and 18F-FDG in C6 gliomas and correlation with 131I-SIP(L19), a marker of angiogenesis.


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Targeting extracellular structures that are involved in angiogenic processes, such as the extra domain B of fibronectin, is a promising approach for the diagnosis of solid tumors. The aim of this study was to determine uptake of the [18]F-labeled PET tracers ([18]F)-fluorocholine (N,N-dimethyl-N-[(18)F]-fluoromethyl)-2-hydroxyethylammonium), ([18]F)-fluoro-ethyl-L-tyrosine (FET), and ([18]F)-FDG in C6 gliomas of the rat and to correlate it with uptake of the anti-extra domain B antibody ([131]I)-SIP(L19) as a marker of neoangiogenesis. METHODS: C6 gliomas were orthotopically induced in 17 rats. Uptake of all tracers was measured using quantitative autoradiography, and uptake of ([18]F)-fluorocholine, ([18]F)-FET, and ([18]F)-FDG was correlated with uptake of ([131]I)-SIP(L19) on a pixelwise basis. RESULTS: The mean ([131]I)-SIP(L19), ([18]F)-fluorocholine, ([18]F)-FET, and ([18]F)-FDG standardized uptake values in the tumor and the contralateral normal cortex (in parentheses) were 0.31 +/- 0.22 (not detectable), 2.00 +/- 0.53 (0.49 +/- 0.07), 3.67 +/- 0.36 (1.42 +/- 0.22), and 7.23 +/- 1.22 (3.64 +/- 0.51), respectively. The ([131]I)-SIP(L19) uptake pattern correlated best with ([18]F)-fluorocholine uptake (z = 0.80, averaged z-transformed Pearson correlation coefficient) and ([18]F)-FET uptake (z = 0.79) and least with ([18]F)-FDG (z = 0.37). CONCLUSION: One day after intravenous injection, ([131]I)-SIP(L19)
displayed a very high tumor-to-cortex ratio, which may be used in the diagnostic work-up of brain tumor patients. Of the 3 investigated (18)F tracers, (18)F-fluorocholine and (18)F-FET correlated better with the pattern of (131)I-SIP(L19) uptake than did (18)F-FDG. Whether this means that (18)F-fluorocholine and (18)F-FET are better suited than (18)F-FDG to monitor antiangiogenic therapy should be investigated in future studies.


Prognostic value of O-(2-18F-fluoroethyl)-L-tyrosine PET and MRI in low-grade glioma.


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In glioma of World Health Organization (WHO) grade II (low-grade glioma), the natural course of a particular patient is not predictable and the treatment strategy is controversial. We determined prognostic factors in adult patients with untreated, nonenhancing, supratentorial low-grade glioma with special regard to PET using the amino acid O-(2-(18)F-fluoroethyl)-L-tyrosine ((18)F-FET) and MRI. METHODS: In a prospective study, baseline (18)F-FET PET and MRI analyses were performed on 33 consecutive patients with histologically confirmed low-grade glioma. None of the patients had radiation or chemotherapy. Clinical, histologic, therapeutic (initial cytoreduction vs. biopsy), (18)F-FET uptake, and MRI morphologic parameters were analyzed for their prognostic significance. Statistical endpoints were clinical or radiologic tumor progression, malignant transformation to glioma of WHO grade III or IV (high-grade glioma), and death. RESULTS: Baseline (18)F-FET uptake and a diffuse versus circumscribed tumor pattern on MRI were highly significant predictors of prognosis (P < 0.01). By the combination of these prognostically significant variables, 3 major prognostic subgroups of low-grade glioma patients could be identified. The first of these subgroups was patients with circumscribed low-grade glioma on MRI without (18)F-FET uptake (n = 11 patients, progression in 18%, no malignant transformation and no death). The second subgroup was patients with circumscribed low-grade glioma with (18)F-FET uptake (n = 13 patients, progression in 46%, malignant transformation to a high-grade glioma in 15%, and death in 8%). The third subgroup was patients with diffuse low-grade glioma with (18)F-FET uptake (n = 9 patients, progression in 100%, malignant transformation to a high-grade glioma in 78%, and death in 56%). CONCLUSION: We conclude that baseline amino acid uptake on (18)F-FET PET and a diffuse versus circumscribed tumor pattern on MRI are strong predictors for the outcome of patients with low-grade glioma.

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Preferred transport of O-(2-[18F]fluoroethyl)-D-tyrosine (D-FET) into the porcine brain.


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Amino acids are valuable tracers for brain tumor imaging with positron emission tomography (PET). In this study the transport of O-(2-[18F]fluoroethyl)-D-tyrosine (D-FET) across the blood-brain barrier (BBB) was studied with PET in anesthetized piglets and patients after subtotal resection of brain tumors and compared with O-(2-[18F]fluoroethyl)-L-tyrosine (L-FET) and 3-O-methyl-6-[18F]fluoro-L-DOPA (L-OMFD). In piglets, compartmental modeling of PET data was used to calculate the rate constants for the blood-brain (K(1)) and the brain-blood (k(2)) transfer of D-FET, L-FET and L-OMFD. In patients standardized uptake values (SUVs) were calculated in brain cortex and lesions. Additionally, affinity determinations on various amino acid transporters (LAT1, LAT2, PAT1, XPCT) were performed in vitro using unlabeled D-FET, L-FET and L-OMFD. The initial brain uptake of D-FET in piglets was more than two-fold higher than that of L-FET, whereas the initial brain uptake of D-FET in patients was similar to that of L-FET. Calculation of K(1) and k(2) from the brain uptake curves and the plasma input data in piglets revealed about 4- and 2-fold higher values for D-FET compared to L-FET and L-OMFD, respectively. The distribution volume of D-FET in the piglet brain was slightly higher than that of L-FET as it was also found for most other organs. In brain tumor patients, initial D-FET uptake in the brain was similar to that of L-FET but showed faster tracer washout. L-FET uptake remained rather constant and provided a better delineation of residual tumor than D-FET. In conclusion, our data indicate considerable differences of stereoselective amino acid transport at the BBB in different species. Therefore, the results from animal experiments concerning BBB amino acid transport may not be transferable to humans.


O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) uptake in mouse thymoma cells, and its biodistribution in mice and human volunteers.

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Amino acids such as [(11)C-methyl]l-methionine are particularly useful in brain tumor diagnosis, but unspecific uptake (e.g., in cerebral ischemia) has been reported. O-(2-[18F]fluoroethyl)-l-tyrosine ([18F]FET) shows a clinical potential similar to that of l-methionine (MET) in brain tumor diagnosis but is applicable on a wider clinical scale. The aim of this study was to evaluate the cerebral ischemia) has been reported. O-(2-[18F]fluoroethyl)-l-tyrosine ([18F]FET) shows a clinical potential similar to that of l-methionine (MET) in brain tumor diagnosis but is applicable on a wider clinical scale. The aim of this study was to evaluate the uptake of [(18)F]FET in reactive astrocytes versus the preferential uptake of [(3)H]MET in macrophages. CONCLUSIONS: [(18)F]FET, like [(3)H]MET, may exhibit significant uptake in the periphery of cortical infarctions, which has to be considered in the differential diagnosis of unknown brain lesions. There are discrepancies between [(18)F]FET and [(3)H]MET uptake in the area of infarctions that appear to be caused by the preferential uptake of [(18)F]FET in reactive astrocytes versus the preferential uptake of [(3)H]MET in macrophages.

Differential uptake of [18F]FET and [3H]-methionine in focal cortical ischemia.


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PET and malignant cerebral tumors


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Normal biodistribution of FDG includes intense physiologic uptake in the brain, which consumes glucose. The high background therefore makes it difficult to detect the foci taking up glucose, which correspond to malignant lesions. FDG PET is nevertheless clinically useful for detecting high-grade gliomas, cerebral lymphomas and, in some cases, unexpected brain metastases in whole-body PET examinations. As an adjunct to CT and MRI, FDG-PET can make stereotactic radiosurgery more precise in targeting primary or secondary brain cancers and can differentiate necrotic fibrosis from viable cancer tissue during follow-up in cases of abnormal or equivocal MRI results. When available, methionine-(11C) PET delineates low grade gliomas accurately. Several fluorine (18F)-labeled radiopharmaceuticals have been proposed in this setting, with PET and FDOPA apparently the most effective. Four original clinical cases illustrating performances of PET and FDOPA PET in this setting are presented.
The ability to monitor tumor responses during prodrug activation gene therapy and other anticancer gene therapies is critical for their translation into clinical practice. Previously, we demonstrated the feasibility of noninvasive in vivo imaging with 131I-5-iodo-2'-fluoro-1-beta-D-arabinofuranosyluracil (131I-FIAU) for monitoring herpes simplex virus type 1 thymidine kinase (HSV1-tk) cancer gene expression in an experimental animal model. Here we tested the efficacy of SPECT with 123I-FIAU and PET with 5-18F-fluoro-2'-deoxyuridine (18F-FUdR), 2-18F-fluoroethyl-L-tyrosine (18F-FET), and 18F-FDG for monitoring tumor responses during prodrug activation gene therapy with HSV1-tk and ganciclovir (GCV).

METHODS: In the flanks of FVB/N female mice, 4 tumors per animal were established by subcutaneous injection of 1 x 10^5 cells of NG4TL4 sarcoma cells, HSV1-tk-transduced NG4TL4-STK cells, or a mixture of these cells in different proportions to model different efficacies of transfection and HSV1-tk gene expression levels in tumors. Ten days later, the animals were treated with GCV (10 mg/kg/d intraperitoneally) for 7 d. Gamma-Imaging with 123I-FIAU and PET with 18F-FUdR, 18F-FET, and 18F-FDG were performed before and after initiation of therapy with GCV in the same animal. RESULTS: Before GCV treatment, no significant difference in weight and size was found in tumors that expressed different HSV1-tk levels, suggesting similar in vivo proliferation rates for NG4TL4 and NG4TL4-STK sarcomas. The accumulation of 123I-FIAU at 24 h after injection was directly proportional to the percentage of NG4TL4-STK cells in the tumors. The 123I-FIAU accumulation at 4 and 7 d of GCV therapy decreased significantly compared with pretreatment levels and was proportional to the percentage of HSV1-tk-positive tumor cells. Tumor uptake of 18F-FUdR in all HSV1-tk-expressing tumors also decreased significantly compared with pretreatment levels and was proportional to the percentage of HSV1-tk-positive tumor cells. The accumulation of 18F-FET decreased minimally (about 1.5-fold) and 18F-FDG decreased only 2-fold after 7 d of GCV therapy, and the degree of reduction was proportional to the percentage of HSV1-tk-positive tumor cells. CONCLUSION: We have shown that gamma-camera imaging with 123I-FIAU was the most reliable method for prediction of tumor response to GCV therapy, which was proportional to the magnitude of HSV1-tk expression in tumor tissue. 123I-FIAU imaging can be used to verify the efficacy of elimination of HSV1-tk-expressing cells by therapy with GCV. PET with 18F-FUdR reliably visualizes proliferating tumor tissue and is most suitable for the assessment of responses in tumors undergoing HSV1-tk plus GCV prodrug activation gene therapy. PET with 18F-FDG or 18F-FET can be used as additional "surrogate" biomarkers of the treatment response, although these radiotracers are less sensitive than 18F-FUdR for monitoring tumor responses to prodrug activation gene therapy with HSV1-tk and GCV in this sarcoma model.

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18F-FET PET for planning of thermo therapy using magnetic nanoparticles in recurrent glioblastoma.


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PURPOSE: Thermotherapy using magnetic nanoparticles (nano cancer therapy) is a new concept of local tumor therapy, which is based on controlled heating of intra-tumoural injected magnetic nanoparticles. The aim of this study was to evaluate the usefulness of PET with a recently introduced amino acid tracer O-2-[18F]fluoroethyl)-L-tyrosine (FET) for targeting the nanoparticles implantation. MATERIALS AND METHODS: Eleven patients with glioblastoma recurrences underwent MR and FET-PET imaging for planning of the nano cancer therapy. Thereafter, the gross tumour volumes (GTV) were defined, taking into consideration the results of both imaging tools. RESULTS: The MRI-based mean GTV was 24.3 cm³ (range 2.5-59.7) and the PET-based mean GTV 31.9 cm³ (range 5.2-77.9). On the average the MRI identified an additional 8.9 +/- 4.7 cm³ and the PET-PET scan-an additional 16.5 +/- 15.2 cm³ outside of the common GTV (15.4 +/- 11.0 cm³). The mean final GTV accounted to 33.8 cm³ (range, 5.2-77.9). The additional information of FET-PET led to an increase in GTV by 22-286% in eight patients and to a decrease of 23% and 26%, respectively, in two patients. In one patient, the final GTV was defined on the basis of MRI data only. CONCLUSIONS: FET-PET adds important information on the actual tumour volume in recurrent glioblastomas and is highly valuable for defining the target volume for the nano cancer therapy.
Evaluation of D-isomers of O-18F-fluoromethyl, O-18F-fluoroethyl and O-18F-fluoropropyl tyrosine as tumour imaging agents in mice.

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The aim of this study was to evaluate the properties of the D-amino acid isomers O-(18)F-fluoromethyl tyrosine ((18)F-FMT), O-(18)F-fluoroethyl tyrosine ((18)F-FET) and O-(18)F-fluoropropyl tyrosine ((18)F-FPT) as tumour-detecting agents with PET in comparison with the corresponding L-isomers. L- or D-(18)F-FMT, (18)F-FET or (18)F-FPT, prepared by (18)F-fluoromethylation, (18)F-fluoroethylation or (18)F-fluoropropylation of L- and D-tyrosine, was intravenously injected into BALB/cA Jcl-nu mice bearing HeLa tumour cells. At 5, 15, 30 and 60 min post intravenous administration, the uptake of each compound in normal abdominal organs and xenotransplanted HeLa cells was determined using the tissue dissection method. Metabolic stability analyses of these compounds in the plasma were performed with the thin-layer chromatography method. In the plasma fraction, although L- and D-isomers of (18)F-FMT, (18)F-FET and (18)F-FPT provided comparable metabolic stability, D-isomers of these labelled compounds revealed a faster elimination rate than their L-isomers, with a higher peak uptake in the blood and kidney 5 min post administration. Compared with natural amino acid ligands, such as L-(11)C-methionine, the uptake of L-isomers of these labelled compounds was relatively low and stable in the abdominal organs, while D-isomers revealed much lower and faster clearance rates compared with the corresponding L-isomers. Among the abdominal organs, the pancreas showed relatively high uptake of all the labelled compounds used here, and the uptake of D-isomers was much lower than that of the L-isomers. Although tumour uptake levels of D-isomers of (18)F-FMT, (18)F-FET and (18)F-FPT were almost 95%, 43% and 39% of the uptake levels of each of the L-isomers 60 min post administration, the tumour-to-blood ratios of these D-isomers were 181%, 137% and 101% of the ratios of the corresponding L-isomers. D-isomers of (18)F-FMT and (18)F-FET indicated improved tumour-to-liver ratios compared with the corresponding L-isomers, and D-(18)F-FET showed the highest tumour-to-pancreas ratio among all the other compounds assayed here. These results suggest that D-isomers of (18)F-fluoroalkyl tyrosine analogues are potential tracers for tumour imaging with PET.


18F-FET PET differentiation of ring-enhancing brain lesions.


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The aim of this study was to explore the differential diagnostic value of PET using the amino acid O-(2-(18)F-fluoroethyl)-L-tyrosine ((18)F-FET) in patients with newly diagnosed solitary intracerebral lesions showing ring enhancement on contrast-enhanced MRI. METHODS: (18)F-FET PET analyses were performed on 14 consecutive patients with intracerebral ring-enhancing lesions. Eleven of the patients were additionally studied with (18)F-FDG PET. In all patients, the main differential diagnosis after MRI was a malignant lesion, in particular glioblastoma multiforme, versus a benign lesion, in particular brain abscess. A malignant tumor was suspected for lesions showing increased (18)F-FET uptake on PET images with a mean lesion-to-brain ratio of at least 1.6 ((18)F-FET PET positive). A nonneoplastic lesion was suspected in cases of minimal or absent (18)F-FET uptake, with a mean lesion-to-brain ratio of less than 1.6 ((18)F-FET PET negative). Histologic diagnosis was obtained by serial biopsies in 13 of the 14 patients. One patient refused the biopsy, but follow-up indicated an abscess because his lesion regressed under antibiotic therapy. RESULTS: Histology and clinical follow-up showed high-grade malignant gliomas in 5 patients and nonneoplastic lesions in 9 patients. The findings of (18)F-FET PET were positive in all 5 glioma patients and in 3 of 9 patients with nonneoplastic lesions, including 2 patients with brain abscesses and 1 patient with a demyelinating lesion. The findings of (18)F-FDG PET were positive (mean lesion-to-gray matter ratio > or = 0.7) in 4 of 4 glioma patients and 3 of 7 patients with nonneoplastic lesions. CONCLUSION: Although (18)F-FET PET has been shown to be valuable for the diagnostic evaluation of brain tumors, our data indicate that, like (18)F-FDG PET, (18)F-FET PET has limited specificity in distinguishing between neoplastic and nonneoplastic ring-enhancing intracerebral lesions. Thus, histologic investigation of biopsy specimens remains mandatory to make this important differential diagnosis.


O-(2-[18F]fluoroethyl)-L-tyrosine: uptake mechanisms and clinical applications.


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O-(2-[18F]fluoroethyl)-L-tyrosine (FET) is a promising tracer for PET that has demonstrated convincing results especially in the diagnostics of brain tumors. In contrast to other radiolabeled amino acids, it can be produced with high efficiency and distributed in a satellite concept like the widely used 2-[18F]fluoro-2-deoxy-D-glucose. Although FET is not incorporated into proteins, it shows high uptake in cerebral gliomas and in extracranial squamous cell carcinomas owing to increased transport. The tracer exhibits high in vivo stability, low uptake in inflammatory tissue and suitable uptake kinetics for clinical imaging, which indicates that it may become a new standard tracer for PET. In this article, the present knowledge on the uptake mechanisms and the clinical applications of FET are reviewed and the clinical perspectives are discussed.

Comparative evaluation of FET and FDG for differentiating lung carcinoma from inflammation in mice.

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BACKGROUND: Clinical FDG/PET (2-deoxy-2-18F-fluoro-D-glucose/positron emission tomography) studies encounter difficulties in detecting early stage lung cancers. The aim of this study was to evaluate the ability of O-2-18F-fluoroethyl-L-tyrosine (FET) and FDG to differentiate between inflammation and lung carcinoma in mice. MATERIALS AND METHODS: Sixty-four C57BL/6 mice were inoculated with 2x10^6 LLC1 lung carcinoma cells in the right hind flank on day 0 and were then injected with 0.1 mL turpentine in the left thigh muscle on day 3. The progress of inflammation and tumor in mice was longitudinally monitored by FDG/microPET. The biodistribution study, pharmacokinetic evaluation and whole-body autoradiography of FET and FDG were performed on day 8 after tumor inoculation. RESULTS: The FDG uptakes in tumor and inflammatory lesions were 4.42-fold and 3.53-fold (n = 4) higher, respectively, than that in muscle at 90 min post-injection and the tumor-to-inflammation ratio was 1.25. For FET/microPET, the tumor uptake was 2.07-fold and 2.07-fold (n = 4) higher than those in muscle and inflammatory lesions at 90 min post-injection, respectively. The distribution half-life (t1/2, alpha) and the elimination half-life (t1/2, beta) of FET were 39 min and 205 min, respectively. CONCLUSION: FDG delineated both tumor and inflammation, while FET accumulated in tumor to a significantly higher extent. Our results demonstrated the potential of FET to distinguish epidermoid lung carcinoma from inflammatory lesions in mice.

Differentiation of tumour and inflammation: characterisation of [methyl-3H]methionine (MET) and O-(2-[18F]fluoroethyl)-L-tyrosine (FET) uptake in human tumour and inflammatory cells.

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PURPOSE: Previous studies suggest that radiolabelled amino acids could be superior to FDG in differentiating tumour and inflammation. Therefore the aim of this study was to investigate the uptake of FET and MET in human tumour and inflammatory cells and to investigate their uptake kinetics. METHODS: For uptake studies, cells were incubated with 370 kBq FET or 3.7 kBq MET for 15 min. Kinetic studies were performed at variable concentrations of FET and MET. Competitive inhibition studies were done with BCH, MeAIB and L- -serine. RESULTS: All inflammatory cells incorporated more MET than the tumour cells. The uptake of FET, in contrast, was significantly lower in all inflammatory cells than in the tumour cells. In tumour cells the uptake of MET was about five times the uptake of FET. The competitive inhibitors reduced uptake of both tracers to 20-40% in tumour cells and to 70% in inflammatory cells. Kinetic studies showed that MET and FET transport was saturable in all cells except macrophages and followed a Michaelis-Menten kinetic. Highest capacity (V (max)) and affinity (K (m)) for the uptake of MET was observed in granulocytes. Capacity and affinity for FET uptake were highest in the DHL-4 cells. CONCLUSION: In contrast to MET, FET accumulated to a significantly greater extent in tumour cells than in inflammatory cells. The marked differences between tumour and inflammatory cells concerning FET and MET uptake suggest that FET and MET are substrates of different subtypes of the L system.

Uptake of 18F-fluorocholine, 18F-fluoro-ethyl-L- -tyrosine and 18F-fluoro-2-deoxyglucose in F98 gliomas in the rat.


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INTRODUCTION: The positron emission tomography (PET) tracers (18)F-fluoro-ethyl-L- -tyrosine (FET), (18)F-fluorocholine (N,N-dimethyl-N-[18F]fluoromethyl-2-hydroxyethylammonium (FCH)) and (18)F-fluoro-2-deoxyglucose (FDG) are used in the...
diagnosis of brain tumours. The aim of this study was threefold: (a) to assess the uptake of the different tracers in the F98 rat glioma, (b) to evaluate the impact of blood-brain barrier (BBB) disruption and microvessel density (MVD) on tracer uptake and (c) to compare the uptake in the tumours to that in the radiation injuries (induced by proton irradiation of healthy rats) of our previous study. METHODS: F98 gliomas were induced in 26 rats. The uptake of FET, FCH and FDG was measured using autoradiography and correlated with histology, disruption of the BBB and MVD. RESULTS: The mean FET, FCH and FDG standardised uptake values (SUVs) in the tumour and the contralateral normal cortex (in parentheses) were 4.19+/−0.86 (1.32+/−0.26), 2.98+/−0.58 (0.51+/−0.11) and 11.02+/−3.84 (4.76+/−1.77) respectively. MVD was significantly correlated only with FCH uptake. There was a trend towards a negative correlation between the degree of BBB disruption and FCH uptake and a trend towards a positive correlation with FET uptake. The ratio of the uptake in tumours to that in the radiation injuries was 1.97 (FCH), 2.71 (FET) and 2.37 (FDG). CONCLUSION: MVD displayed a significant effect only on FCH uptake. The degree of BBB disruption seems to affect the accumulation of FET and FCH, but not FDG. Mean tumour uptake for all tracers was significantly higher than the accumulation in radiation injuries.


Analysis of 18F-FET PET for grading of recurrent gliomas: is evaluation of uptake kinetics superior to standard methods?


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The aim of the present study was to evaluate whether extended analyses of O-(2-18F-fluoroethyl)-L-tyrosine (FET) uptake kinetics provide results superior to those of standard tumor-to-background ratios in predicting tumor grade in patients with pretreated gliomas. METHODS: Dynamic 18F-FET PET studies (0-40 min after injection of 180 MBq of 18F-FET) were performed on 45 glioma patients with suspected tumor recurrence after multimodal treatment. For the standard method, tumoral maximal standardized uptake value (SUVmax) and the ratio to the background were derived from a summed image 20-40 min after injection. Dynamic data evaluation comprised several approaches: first, SUV within a 90% isocountour threshold (SUV90) and the respective ratio to the background calculated for each time frame between 5 and 40 min after injection; second, the time to peak analysis; and third, various parameters accounting for the individual time course of 18F-FET uptake. Results were correlated with the histopathologic findings of MRI/PET-guided stereotactic biopsies and were evaluated with respect to their discriminatory power to separate low- from high-grade tumors using receiver-operating characteristic (ROC) analyses. RESULTS: The parameters taking into account the individual time course of 18F-FET uptake were able to differentiate low-grade from high-grade recurrent astrocytomas with high diagnostic accuracy, reaching the best differentiation with a sensitivity and specificity of 92% and an area under the ROC curve (AUC) of 0.94. For the other parameters, the respective values were considerably lower (time to peak: 85% sensitivity and 88% specificity; SUV90-to-background ratio for single-frame evaluation of the early-uptake phase: 100% sensitivity, 62% specificity, and 0.81 AUC). The lowest performance was provided by the standard method (SUVmax: 73% sensitivity, 54% specificity, and 0.60 AUC. SUVmax-to-background ratio: 62% sensitivity, 62% specificity, and 0.59 AUC), Time-activity curves (5-40 min after injection) slightly and steadily increased in tumor-free patients and in low-grade tumors, whereas high-grade tumors showed an early peak around 10-15 min after injection followed by a decrease. CONCLUSION: This study has shown differences in the dynamics of 18F-FET uptake between recurrent low- and high-grade gliomas. Therefore, parameters addressing the different kinetic behaviors allow discrimination with high diagnostic power between these 2 prognostically different groups. Thus, the techniques introduced here are clearly superior to the yet most widely used standard method.


18F-FET PET compared with 18F-FDG PET and CT in patients with head and neck cancer.


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Recent studies suggest a somewhat selective uptake of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) in cerebral gliomas and in squamous cell carcinoma (SCC) and a good distinction between tumor and inflammation. The aim of this study was to investigate the diagnostic potential of 18F-FET PET in patients with SCC of the head and neck region by comparing that tracer with 18F-FDG PET and CT. METHODS: Twenty-one patients with suspected head and neck tumors underwent 18F-FET PET, 18F-FDG PET, and CT within 1 wk before operation. After coregistration, the images were evaluated by 3 independent observers and an ROC analysis was performed, with the histopathologic result used as a reference. Furthermore, the maximum standardized uptake values (SUVs) in the lesions were determined. RESULTS: In 18 of 21 patients, histologic examination revealed SCC, and in 2 of these patients, a second SCC tumor was found at a different anatomic site. In 3 of 21 patients, inflammatory tissue and no tumor were identified. Eighteen of 20 SCC tumors were positive for both 18F-FDG uptake and 18F-FET uptake, one 0.3-cm SCC tumor was detected neither with 18F-FDG PET nor with 18F-FET PET, and one 0.7-cm SCC tumor in a 4.3-cm ulcer was overestimated as a 4-cm tumor on 18F-FDG PET and missed on 18F-FET PET. Inflammatory tissue was positive for 18F-FDG uptake (SUV, 3.7-4.7) but negative for 18F-FET uptake (SUV, 1.3-1.6). The SUVs of 18F-FDG in SCC were significantly higher (13.0 +/- 9.3) than those of 18F-FET (4.4 +/- 2.2). The ROC analysis showed significantly superior detection of SCC with (18F)-FET PET or 18F-FDG PET than with CT. No
resultant difference (P = 0.71) was found between 18F-FDG PET and 18F-FET PET. The sensitivity of 18F-FDG PET was 93%, specificity was 79%, and accuracy was 83%. 18F-FET PET yielded a lower sensitivity of 75% but a substantially higher specificity of 95% (accuracy, 90%). CONCLUSION: 18F-FET may not replace 18F-FDG in the PET diagnostics of head and neck cancer but may be a helpful additional tool in selected patients, because 18F-FET PET might better differentiate tumor tissue from inflammatory tissue. The sensitivity of 18F-FET PET in SCC, however, was inferior to that of 18F-FDG PET because of lower SUVs.

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Positron emission tomography with O-(2-[18F]fluoroethyl)-l-tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas.

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OBJECTIVE: New treatment modalities are available for patients with glioma, which may lead to unspecific changes in posttherapeutic magnetic resonance imaging (MRI) findings. Differentiation between tumor- and therapy-associated contrast enhancement on MRI scans after treatment may be difficult. The aim of this study was to analyze the diagnostic value of O-(2-[18F]fluoroethyl)-l-tyrosine (FET)-positron emission tomography (PET) and MRI in the detection of tumor recurrence in patients with glioma after radiotherapy, radiosurgery, or multimodal treatment. METHODS: The study included 36 patients with gliomas and neuroradiological diagnosis of tumor recurrence and 9 patients who had undergone radioimmunotherapy. Patients were consecutively treated between September 2001 and May 2003. A contemporary FET-PET investigation was performed in all patients. A tissue diagnosis was made for comparative analysis in all patients with progressive neuroradiological or clinical findings (32 of 45 patients). In patients with transient neuroradiological or clinical deterioration (13 of 45 patients), clinical follow-up was used to support or contradict the imaging-based diagnosis. RESULTS: Tumor recurrence was documented in 31 of 45 patients, and 14 of 45 patients were tumor free. FET-PET and MRI revealed a correct diagnosis in 44 and 36 patients, respectively. The accuracy of FET-PET was 92.9%, and sensitivity was 100% (in patients suspected of having recurrent tumor as revealed by MRI). Sensitivity of MRI was 93.5%, and specificity was 50% (P < 0.05). CONCLUSION: For patients with gliomas undergoing multimodal treatment or various forms of irradiation, conventional follow-up with MRI is insufficient to distinguish between benign side effects of therapy and tumor recurrence. FET-PET is a powerful tool to improve the differential diagnosis in these patients.


Evaluation of F-18-labeled amino acid derivatives and [18F]FDG as PET probes in a brain tumor-bearing animal model.

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2-Deoxy-2-[18F]fluoro-d-glucose ([18F]FDG) has been extensively used as positron emission tomography (PET) tracer in clinical tumor imaging. This study compared the pharmacokinetics of two [18F]-labeled amino acid derivatives, O-2-[18F]fluoroethyl-l-tyrosine ([18F]FET) and 4-borono-2-[18F]fluoro-l-phenylalanine-fructose ([18F]FBPA-Fr), to that of [18F]FDG in an animal brain tumor model. METHODS: A self-modified automated PET tracer synthesizer was used to produce no-carrier-added (nca) l-[18F]FET. The cellular uptake, biodistribution, autoradiography and microPET imaging of l-[18F]FET, l-[18F]FBPA-Fr and [18F]FDG were performed with F98 glioma cell culture and F98 glioma-bearing Fischer344 rats. RESULTS: The radiochemical purity of l-[18F]FET was >98% and the radiochemical yield was 50% in average of 16 runs. The uptake of l-[18F]FET and l-[18F]FBPA-Fr in the F98 glioma cells increased rapidly for the first 5 min and reached a steady-state level after 10 min of incubation, whereas the cellular uptake of [18F]FDG kept increasing during the study period. The biodistribution of l-[18F]FET, l-[18F]FBPA-Fr and [18F]FDG in the brain tumors was 1.26+/-0.22, 0.86+/-0.08 and 2.77+/-0.44 %ID/g at 60 min postinjection, respectively, while the tumor-to-normal brain ratios of l-[18F]FET (3.15) and l-[18F]FBPA-Fr (3.44) were higher than that of [18F]FDG (1.44). Both microPET images and autoradiograms of l-[18F]FET and l-[18F]FBPA-Fr exhibited remarkable uptake with high contrast in the brain tumor, whereas [18F]FDG showed high uptake in the normal brain and gave blurred brain tumor images. CONCLUSION: Both l-[18F]FET and l-[18F]FBPA-Fr are superior to [18F]FDG for the brain tumor imaging as shown in this study with microPET.
O-(2-[18F]fluoroethyl)-L-tyrosine PET for monitoring the effects of convection-enhanced delivery of paclitaxel in patients with recurrent glioblastoma.


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PURPOSE: Convection-enhanced delivery (CED) of paclitaxel is a new locoregional approach for patients with recurrent glioblastoma. The aim of this study was to evaluate O-(2-[18F]fluoroethyl)-L-tyrosine (FET) positron emission tomography (PET) in monitoring the effects of this type of direct drug delivery. METHODS: Eight patients with recurrent glioblastoma underwent CED of paclitaxel, which was infused over stereotactically placed catheters into the tumour. FET PET and MRI were performed before and 4 weeks after therapy and then at 3-month intervals to document follow-up. For quantitative evaluation, SUV(max)(tumour)/SUV(mean)(background) ratios were calculated. RESULTS: At baseline all tumours showed gadolinium enhancement and high FET uptake (SUV(max)/BG 3.2±0.8). Four weeks after CED, a statistically significant decrease in FET uptake was seen (SUV(max)/BG-17%; p<0.01). During follow-up, no recurrence was observed within the CED area. Two out of eight patients with extended tumours died 4 and 5 months after treatment, most probably from local complications. Temporarily stable disease with stable FET uptake was observed in six of eight patients; this was followed by progression and increasing FET uptake ratios (+46%) distant from the CED area in five of the six patients 3-13 months after CED. One patient still presents stable FET uptake 10 months after CED. MRI showed unchanged/increasing contrast enhancement and oedema without ability to reliably assess disease progression. CONCLUSION: FET PET is a valuable tool in monitoring the effects of CED of paclitaxel. In long-term follow-up, stable or decreasing FET uptake, even in contrast-enhancing lesions, is suggestive of reactive changes, whereas increasing ratios appear always to be indicative of recurrence. Therefore, FET PET is more reliable than MRI in differentiating stable disease from tumour regrowth.


PET with O-(2-[18F]fluoroethyl)-L-tyrosine in peripheral tumors: first clinical results.


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O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) PET has shown promising results in brain tumor diagnosis. The aim of this prospective study was to evaluate 18F-FET PET in comparison with 18F-FDG PET in patients with peripheral tumors. METHODS: Forty-four consecutive patients with suspected malignant tumors underwent 18F-FET PET and 18F-FDG PET within 7 d. Whole-body PET studies were performed 1 h after intravenous injection of 370 MBq of 18F-FET or 18F-FDG. Six patients were excluded from the analysis because a malignant tumor could not be verified. In 38 patients (7 with colorectal cancer, 6 with pancreatic cancer, 9 with head-neck cancer, 4 with lymphomas, 3 with lung cancer, 3 with ovarian cancer, 4 with breast cancer, and 2 with prostatic cancer), 18F-FET PET and 18F-FDG PET were compared. RESULTS: 18F-FET was positive in only 13 of 38 patients (8 with head-neck cancer, 3 with breast cancer, and 2 with lung cancer), whereas 18F-FDG exhibited increased uptake in 37 of 38 patients. All squamous cell carcinomas were found to be 18F-FET-positive tumors (8 head-neck cancer and 2 lung cancer), whereas most adenocarcinomas were found to be 18F-FET-negative tumors. In patients with colorectal cancer, pancreatic cancer, ovarian cancer, prostatic cancer, and lymphomas, no increased 18F-FET uptake could be identified. All lesions that exhibited increased 18F-FET uptake also showed increased 18F-FDG uptake. No additional lesion was identified by 18F-FET PET but not by 18F-FDG PET. A subgroup analysis of patients with head-neck carcinomas allowed a better distinction between malignant and inflammatory tissues with 18F-FET than with 18F-FDG. CONCLUSION: 18F-FET is inferior to 18F-FDG as a PET tracer for general tumor diagnosis. Our preliminary results suggest rather selective uptake of 18F-FET in squamous cell carcinomas. Compared with 18F-FDG PET, 18F-FET PET may allow a better distinction between tumors and inflammatory tissues in patients with squamous cell carcinomas.


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OBJECT: The purpose of this study was to determine the predictive value of [18F]fluoroethyl-L-tyrosine (FET)-positron emission tomography (PET) and magnetic resonance (MR) spectroscopy for tumor diagnosis in patients with suspected gliomas. METHODS: Both FET-PET and MR spectroscopy analyses were performed in 50 consecutive patients with newly diagnosed intracerebral lesions supposed to be diffuse gliomas on contrast-enhanced MR imaging. Lesion/brain ratios of FET uptake greater than 1.6 were considered positive, that is, indicative of tumor. Results of MR spectroscopy were considered positive when N-acetylaspartate (NAA) was decreased in conjunction with an absolute increase of choline (Cho) and an NAA/Cho ratio of 0.7 or less. An FET lesion/brain ratio, an NAA/Cho ratio, and signal abnormalities on MR images were compared with histological findings in
neuronavigated biopsy specimens. The FET lesion/brain ratio and the NAA/Cho ratio were identified as significant independent predictors for the histological identification of tumor tissue. The accuracy in distinguishing neoplastic from nonneoplastic tissue could be increased from 68% with the use of MR imaging alone to 97% with MR imaging in conjunction with FET-PET and MR spectroscopy. Sensitivity and specificity for tumor detection were 100 and 81% for MR spectroscopy and 88 and 88% for FET-PET, respectively. Results of histological studies did not reveal tumor tissue in any of the lesions that were negative on FET-PET and MR spectroscopy. In contrast, a tumor diagnosis was made in 97% of the lesions that were positive with both methods. CONCLUSIONS: In patients with intracerebral lesions supposed to be diffuse gliomas on MR imaging, FET-PET and MR spectroscopy analyses markedly improved the diagnostic efficacy of targeted biopsies.


O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas.


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MRI is commonly used to determine the location and extent of cerebral gliomas. We investigated whether the diagnostic accuracy of MRI could be improved by the additional use of PET with the amino acid O-(2-[18F]fluoroethyl)-L-tyrosine (FET). In a prospective study, PET with FET and MRI was performed in 31 patients with suspected cerebral gliomas. PET and MRIs were co-registered and 52 neuronavigated tissue biopsies were taken from lesions with both abnormal MRI signal and increased FET uptake (match), as well as from areas with abnormal MR signal but normal FET uptake or vice versa (mismatch). Biopsy sites were labelled by intracerebral titanium pellets. The diagnostic performance for the identification of cellular tumour tissue was analysed for either MRI alone or MRI combined with FET PET using alternative free response receiver operating characteristic curves (ROCs). Histologically, 26 biopsy samples corresponded to cellular glioma tissue and 26 to peritumoral brain tissue. The diagnostic performance, as determined by the area under the ROC curve (Az), was Az = 0.80 for MRI alone and Az = 0.98 for the combined MRI and FET PET approach (P < 0.001). MRI yielded a sensitivity of 96% for the detection of tumour tissue but a specificity of only 53%, and combined use of MRI and FET PET yielded a sensitivity of 93% and a specificity of 94%. Combined use of MRI and FET PET in patients with cerebral gliomas significantly improves the identification of cellular glioma tissue and allows definite histological tumour diagnosis. Thus, our findings may have considerable impact on target selection for diagnostic biopsies as well as therapy planning.


O-(2-[18F]fluoroethyl)-L-tyrosine PET in the clinical evaluation of primary brain tumours.


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PURPOSE: The aim of this study was to evaluate the differential uptake of O-(2-[18F]fluorethyl)-L-tyrosine (FET) in suspected primary brain tumours. METHODS: Positron emission tomography (PET) was performed in 44 patients referred for the evaluation of a suspected brain tumour. Acquisition consisted of four 10-min frames starting upon i.v. injection of FET. Tumour uptake was calculated as the ratio of maximal tumour intensity to mean activity within a reference region (FETmax). RESULTS: FET uptake above the cortical level was observed in 35/44 lesions. All histologically confirmed gliomas and many other lesions showed FET uptake to a variable extent. No uptake was observed in nine lesions (one inflammatory lesion, one dysmature lesion, one mature teratoma, six lesions without histological confirmation). An analysis of uptake dynamics was done in the patients with increased FET uptake (22 gliomas, three lymphomas, three non-neoplastic lesions, three lesions with unknown histology and four other primaries). Upon classification of tumours into low (i.e. WHO I and II) and high grade (i.e. WHO III and IV), a significant difference in FETmax between the two categories was observed only in the first image frame (0-10 min p.i.), with FETmax=2.0 in low-grade and 3.2 in high-grade tumours (p<0.05); no significant differences were found in frame 4 (30-40 min p.i.), with FETmax=2.4 vs 2.7. Similar results were obtained when the analysis was applied only to astrocytic tumours (2.0 vs 3.1 in the first frame; 2.4 vs 2.6 in the fourth frame). CONCLUSION: These initial results indicate that FET PET is a useful method to identify malignant brain lesions. It appears that high- and low-grade brain tumours exhibit a different uptake kinetics of FET. A kinetic analysis of FET PET may provide additional information in the differentiation of suspected brain lesions.
Uptake of 18F-fluorocholine, 18F-fluoroethyl-L-tyrosine, and 18F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumor recurrence.


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Differentiation between posttherapy radiation necrosis and recurrent tumor in humans with brain tumor is still a difficult diagnostic task. The new PET tracers (18)F-fluoro-ethyl-L-tyrosine (FET) and (18)F-fluorocholine (N,N-dimethyl-N-(18)F-fluoromethyl-2-hydroxyethylammonium [FCH]) have shown promise for improving diagnostic accuracy. This study assessed uptake of these tracers in experimental radiation injury. METHODS: In a first model, circumscribed lesions were induced in the cortex of 35 rats using proton irradiation of 150 or 250 Gy. After radiation injury developed, uptake of (18)F-FET, (18)F-FCH, and (18)F-FDG was measured using autoradiography and correlated with histology and disruption of the blood-brain barrier as determined with Evans blue. In a second model, uptake of the tracers was assessed in acute cryolesions, which are characterized by the absence of inflammatory cells. RESULTS: Mean (18)F-FET, (18)F-FCH, and (18)F-FDG standardized uptake values in the most active part of the radiation lesion and the contralateral normal cortex (in parentheses) were 2.27 +/- 0.46 (1.42 +/- 0.23), 2.52 +/- 0.42 (0.61 +/- 0.12), and 6.21 +/- 1.19 (4.35 +/- 0.47). The degree of uptake of (18)F-FCH and (18)F-FDG correlated with the density of macrophages. In cryolesions, (18)F-FET uptake was similar to that in radiation lesions, and (18)F-FCH uptake was significantly reduced. CONCLUSION: Comparison of tracer accumulation in cryolesions and radiation injuries demonstrates that (18)F-FET uptake is most likely due to a disruption of the blood-brain barrier alone, whereas (18)F-FCH is additionally trapped by macrophages. Uptake of both tracers in the radiation injuries is generally lower than the published uptake in tumors, suggesting that (18)F-FET and (18)F-FCH are promising tracers for separating radiation necrosis from tumor recurrence. However, the comparability of our data with the literature is limited by factors such as different species and acquisition protocols and modalities. Thus, more studies are needed to settle this issue. Nevertheless, (18)F-FCH and (18)F-FET seem superior to (18)F-FDG for this purpose.


Value of O-(2-18F-fluoroethyl)-L-tyrosine PET for the diagnosis of recurrent glioma.

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PURPOSE: The prognosis of patients with recurrent gliomas depends on reliable and early diagnosis of tumour recurrence after initial therapy. In this context, magnetic resonance imaging (MRI) and computed tomography (CT) often fail to differentiate between radiation- and tumour-induced contrast enhancement. Furthermore, absence of contrast enhancement, or even of 18F-fluorodeoxyglucose uptake in PET, does not exclude recurrence. The aim of this study was to establish the diagnostic value of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET in recurrent gliomas. METHODS: Fifty-three patients with glioma (primary grading: 27=WHO grade IV, 16=grade III, 9=grade II, 1=grade I) and clinically suspected recurrence underwent FET PET scans 4-180 months after different treatment modalities. For semiquantitative evaluation, maximal SUV (SUVmax) and mean SUV within 80% and 70% isocountour thresholds (SUV80/SUV70) were evaluated and the respective ratios to the background (BG) were calculated. PET results were correlated with MRI/CT, clinical follow-up or biopsy findings. RESULTS: All patients presented with FET uptake, of varying intensity, in the area of the primary tumour after initial therapy. In the 42 patients with confirmed recurrence, there was additional distinct focal FET uptake with significantly higher values compared with those in the 11 patients without clinical signs of recurrence and showing only low and homogeneous FET uptake at the margins of the resection cavity. With respect to tumour grading, there was a slight but non-significant increase from WHO II (SUVmax/BG: 2.53 +/- 0.28) to WHO III (SUVmax/BG: 2.84 +/- 0.49) and WHO IV (SUVmax/BG: 3.55 +/- 1.07) recurrence. CONCLUSION: FET PET reliably distinguishes between post-therapeutic benign lesions and tumour recurrence after initial treatment of low- and high-grade gliomas.


Comparison of O-(2-18F-fluoroethyl)-L-tyrosine PET and 3-123I-iodo-alpha-methyl-L-tyrosine SPECT in brain tumors.

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The aim of this study was to compare PET with O-(2-(18)F-fluoroethyl)-L-tyrosine ((18)F-FET) and SPECT with 3-((123)I-iodo-alpha-methyl-L-tyrosine ((123)I-IMT) in patients with brain tumors. METHODS: Twenty patients with a suspected brain tumor were investigated by (18)F-FET PET, (123)I-IMT SPECT, and MRI within 3 wk. Region-of-interest analyses were performed on coregistered PET/SPECT/MRI images and the tumor-to-brain ratio (TBR), muscle-to-brain ratio (MBR), cerebellum-to-brain ratio (CerBR), and sin-to-brain ratio (SBR) were calculated. In addition, the presence of tumor and the discrimination of anatomic structures on (18)F-FET PET and (123)I-IMT SPECT images were visually determined by 3 observers who were unaware of clinical data. RESULTS: The TBR of (18)F-FET and (123)I-IMT uptake in cerebral tumors showed a highly significant correlation (r = 0.96; P < 0.001). In the visual analysis for the presence or absence of tumors, no differences for (123)I-IMT SPECT and (18)F-FET PET were found in 19 of 20 patients; in one patient a low-grade glioma was only identified on (18)F-FET PET images but not on (123)I-IMT SPECT images. The contrast between tumor and normal brain was significantly higher in (18)F-FET PET (TBR, 2.0 +/- 0.9) than in (123)I-IMT SPECT (TBR, 1.5 +/- 0.5). The discrimination of anatomic structures yielded a significantly better score on (18)F-FET PET images (rating score, 2.6 +/- 0.9) compared with (123)I-IMT SPECT images (rating score, 1.7 +/- 0.9). The uptake of (18)F-FET in the muscles was significantly higher compared with (123)I-IMT (MBR (18)F-FET, 1.4 +/- 0.3; MBR (123)I-IMT, 0.6 +/- 0.2; P < 0.001) and (18)F-FET demonstrated a significantly higher blood-pool radioactivity than (123)I-IMT (SBR (18)F-FET, 1.3 +/- 0.2; SBR (123)I-IMT, 0.8 +/- 0.2; P < 0.001). CONCLUSION: The significant correlation of the TBRs of (18)F-FET and (123)I-IMT indicates that clinical experiences of brain tumor diagnostics with (123)I-IMT SPECT might be valid for (18)F-FET PET although substantial differences of the physiologic behavior were identified in extracerebral tissue. As (18)F-FET PET allows improved discrimination of anatomic structures and the tumor-to-brain contrast was significantly superior compared with (123)I-IMT SPECT scans, the results are encouraging for further evaluation of (18)F-FET for imaging brain tumors.


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The whole-body distribution of O-(2-([18]F)[fluoroethyl])-L-tyrosine (FET) was studied in seven patients with brain tumours by positron emission tomography (PET). Based on the IMEDOSE and MIRDOSO procedures, radiation absorbed doses were estimated from whole-body PET scans acquired approximately 70 and 200 min after i.v. injection of 400 MBq FET. After injection of FET, the peak of radioactivity in the blood was observed after 1.5 min, and a plateau of nearly constant radioactivity was reached at 20 min. The whole-body distribution of FET showed the highest activities in the urinary tract. All other organs exhibited only moderate FET uptake (SUV </=1.6) which remained constant between early and late PET scans. No increased uptake was seen in the bone, the biliary tract or the pancreas. Twenty-two percent of the injected activity was excreted 5 h p.i. (approx. 5.3% ID/h). The highest absorbed dose was found for the urinary bladder wall. The effective dose according to ICRP 60 was 16.5 micro Sv/MBq for adults, which would lead to an effective dose of 6.1 mSv in a PET study using 370 MBq FET.


Pharmacokinetics and radiation dosimetry estimation of O-(2-[18F]fluoroethyl)-L-tyrosine as oncologic PET tracer.


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An easy-to-automate synthetic procedure and the kinetics and radiation dosimetry of O-(2-[18F]fluoroethyl)-L-tyrosine (FET), a recently developed amino acid tracer with potential applications in tumor imaging with PET, are described. FET was prepared in high radiochemical yield, 20-25% with no decay correction, and radiochemical purity of more than 95% in less than 60min synthesis time by a modified two-step procedure and manual operation. The kinetics and radiation dosimetry of FET were evaluated by using mice biodistribution data and the medical internal radiation dosimetry (MIRD) method. The bone (total) was the organ receiving the highest dose, 4.78x10(-3)mGy/MBq, and the brain and the whole body received the lowest dose, 1.6x10(-3)mGy/MBq, respectively. The effective dose was 9.0x10(-3)mSv/MBq. The data show that a 370-MBq (10mCi) injection of FET leads to an estimated effective dose of 3.3mSv and an estimated dose to the whole body of 0.6mGy. The potential radiation risks associated with this study are well within accepted limits.


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O-(2-[18F]Fluoroethyl)-L-tyrosine (FET) is a recently described amino acid analogue that has shown high accumulation in animal tumours. The aim of this study was to compare the uptake of FET with that of L-[methyl-11C]methionine (MET) in patients with suspected primary or recurrent intracerebral tumours. Sixteen consecutive patients with intracerebral lesions were studied on the same day by positron emission tomography (PET) using MET and FET. Uptake of FET and MET was quantified by standardized uptake values. Tracer kinetics for normal brain and intracerebral lesions were compared. On the basis of the MET-PET studies, viable tumour tissue was found in 13 patients. All tumours showed rapid uptake of FET and were visualized with high contrast. Mean uptake of FET for normal grey matter, white matter and tumour tissue was 1.1±0.2, 0.8±0.2 and 2.7±0.8 SUV, respectively. In all three tissues, uptake of MET was slightly higher (1.4±0.2, 0.9±0.1 and 3.3±1.0 SUV; P<0.01). However, contrast between tumour and normal tissues was not significantly different between MET and FET. Uptake of FET in non-neoplastic lesions (1.0±0.1 SUV) was significantly lower than in tumour tissue (P=0.007). For all lesions there was a close correlation (r=0.98) between MET and FET uptake. In conclusion, PET studies of human brain tumours, the uptake and image contrast of FET appear to be very similar to those of MET. The specificity of FET for tumour tissue is promising but has to be addressed in a larger series of patients with non-neoplastic lesions.


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The aim of the study was to investigate the transport mechanism and uptake kinetics of the new 18F-labeled amino acid O-(2-[18F]fluoroethyl)-L-tyrosine (L-[18F]FET) and D-[18F]FET in human SW 707 colon carcinoma cells and the in vivo biodistribution of this tracer in SW 707 tumor-bearing mice. METHODS: SW 707 cells were incubated with L- and D-[18F]FET under physiologic amino acid concentrations with and without the competitive transport inhibitors 2-amino-2 norbornane-carboxylic acid and a-(methylamino)isobutyric acid plus serine. For the investigation of the transport capacity, unlabeled L-FET was added to the samples. In addition, xenotransplanted mice were injected intravenously with L-[18F]FET; killed 10, 30, 60 and 120 min after injection; and the radioactivity concentration in different organs was measured in a gamma counter. RESULTS: The in vitro kinetic experiments showed a fast initial uptake of L-[18F]FET into the cells up to 6 min, followed by a nearly constant tracer concentration. The accumulation factor, calculated as the ratio between intracellular and extracellular tracer concentration, ranged from 3.0 to 5.0. In comparison, D-[18F]FET did not accumulate in the cells. Washing the cells in medium at 37 degrees C, after a 30-min incubation with L-[F-18]FET, led to a rapid decrease of radioactivity, which demonstrates the bidirectional transport. In addition, experiments with increasing concentrations of unlabeled L-FET indicated a linear correlation between L-FET uptake rate and the extracellular concentration. Results of transport inhibition experiments with the specific competitive inhibitors demonstrated that the uptake of L-FET into SW 707 cells was caused mainly (>80%) by the transport system L. In the in vivo studies, the half-life (t1/2 beta) of L-[18F]FET in the plasma was determined to be 94 min and the uptake into the brain increased to 120 min with a brain-to-blood ratio of 0.86. The xenotransplanted tumor showed higher uptake of L-[18F]FET (>6 %ID/g) at 30 and 60 min than all other organs, except the pancreas. The tumor-to-blood ratio reached about 2 between 30 and 120 min. CONCLUSION: L-[18F]FET, which is transported by the specific amino acid transport system L, seems to be a potential amino acid tracer for tumour imaging and therapy monitoring with PET.


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The aim of the study was to develop a simple 18F-labeled amino acid as a PET tracer for cerebral and peripheral tumors. O-(2-[18F]fluoroethyl)-L-tyrosine (L-[18F]FET) was synthesized and biologically evaluated. Results of the first human PET study are reported. METHODS: No carrier added (n.c.a.) and D-[18F]FET were prepared by 18F-fluoroethylation of L- and D-tyrosine in a two-step procedure. Biodistribution studies were performed in mice. The metabolic fate of L-[18F]FET was investigated in plasma, brain, tumor and pancreatic tissue samples using chromatographic procedures. Tumor uptake studies were performed in mammary carcinoma-bearing mice and in mice with the colon carcinoma SW 707. In a human PET study, a 59-y-old man with a recurrent astrocytoma was imaged using n.c.a. L-[18F]FET. RESULTS: Synthesis of [18F]FET was accomplished in about 50 min with an overall radiochemical yield of 40%. The uptake of L-[18F]FET in the brain of mice reached a level >2% ID/g between 30 and 60 min postinjection. The brain uptake of the D-isomer was negligible, indicating blood-brain barrier penetration by a specific amino acid transport system. L-[18F]FET is not incorporated into proteins. High-performance liquid chromatography (HPLC) analysis of brain, pancreas and tumor homogenates as well as plasma samples of mice at 10, 40 or 60 min postinjection showed only unchanged L-[18F]FET. Activity uptake in the bone did not exceed 2% ID/g at 40 min postinjection. The brain uptake of L-[18F]FET in mice bearing mammary carcinomas and colon carcinomas reached 7.1%±4.2% ID/g and 6.4%±1.7% ID/g 1h postinjection, respectively. In the first human study, L-[18F]FET-PET allowed a clear delineation of a recurrent astrocytoma. Thirty-five minutes postinjection, the tumor-to-cortex ratio was >2.7. A tumor-to-blood ratio >1.5 was reached at 30 min postinjection and continued to increase. No significant activity accumulation was observed in peripheral organs after approximately 40 min postinjection.
CONCLUSION: The high in vivo stability of L-[18F]FET, its fast brain and tumor uptake kinetics, its low accumulation in nontumor tissue and its ease of synthesis strongly support further evaluation of L-[18F]FET as an amino acid tracer for cerebral and peripheral tumors.
Fluorocholine


**Three-phase 18F-fluorocholine PET/CT in the evaluation of prostate cancer recurrence.**


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**AIM:** Contribution of 3-phase 18F-fluorocholine PET/CT in suspected prostate cancer recurrence at early rise of PSA. **PATIENTS,** METHODS: Retrospective analysis was performed in 47 patients after initial treatment with radiotherapy (n=30) or surgery (n=17). Following CT, 10 minutes list-mode PET acquisition was done over the prostate bed after injection of 300 MBq of 18F-fluorocholine. Three timeframes of 3 minutes each were reconstructed for analysis. All patients underwent subsequent whole body PET/CT. Delayed pelvic PET/CT was obtained in 36 patients. PET/CT was interpreted visually by two observers and SUVmax determined for suspicious lesions. Biopsies were obtained from 13 patients. RESULTS: Biopsies confirmed the presence of cancer in 11 of 13 patients with positive PET for a total of 15 local recurrences in which average SUVmax increased during 14 minutes post injection and marginally decreased in delayed scanning. Conversely inguinal lymph nodes with mild to moderate metabolic activity on PET showed a clearly different pattern with decreasing SUVmax on dynamic images. Three-phase PET/CT contributed to the diagnostic assessment of 10 of 47 patients with biological evidence of recurrence of cancer. It notably allowed the discrimination of confounding blood pool or urinary activity from suspicious hyperactivities. PET/CT was positive in all patients with PSA>or=2 ng/ml and in 4/13 patients presenting PSA values<2 ng/ml. CONCLUSION: 18F-fluorocholine 3-phase PET/CT showed a progressively increasing SUVmax in biopsy confirmed cancer lesions up to 14 minutes post injection while decreasing in inguinal lymph nodes interpreted as benign. Furthermore, it was very useful in differentiating local recurrences from confounding blood pool and urinary activity.

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**Imaging of organ-confined prostate cancer: functional ultrasound, MRI and PET/computed tomography.**

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**PURPOSE OF REVIEW:** To review the current status of advanced imaging techniques in identification of organ-confined prostate cancer with a focus on their impact on patient management. **RECENT FINDINGS:** Transrectal ultrasound suffers from poor accuracy despite significant technical improvements. Generally used to distinguish cancers with extraprostatic spread, MRI is now focusing on intraprostatic prostate cancer identification. At 1.5T, the most recent high-resolution pelvic phased-array coils provide excellent imaging of the whole gland, including this challenging anterior part. Improvements in accuracy for cancer detection and volume estimation result from dynamic contrast-enhanced and diffusion-weighted imaging sequences. Histological correlations showed high sensitivity/specitivity for significant volume cancers. 3T MRI scanners will improve these results. Most of the recent PET/computed tomography imaging studies use choline derivatives ((11)C-choline and (18)F-fluorocholine). Their results are promising but insufficient to be currently recommended in routine practice. **SUMMARY:** Considerable advances have been made in the identification of organ-confined prostate cancer with multiparametric MRI. Only prebiopsy MRI can provide best quality of cancer assessment and allows for targeting biopsies. It is hoped that advances in 3T MRI as well as in radiotracers for PET/computed tomography will further improve diagnosis, treatment selection, planning and outcomes.


[Development of molecular imaging probes in oncology]

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Molecular imaging probes used for positron emission tomography(PET)in oncology are reviewed. Although [18F] FDG is presently the most useful probe for imaging tumors, there is a need for complementary probes of FDG with some limitations on detection in the brain or inflammatory region. The review is mostly focused on 18F-labeled probes designed for amino acid transport and protein synthesis, DNA synthesis, membrane lipid, and hypoxia such as PET, FLT, FMAU, fluorocholine, and FMISO, together with our original probes of FMT and FRP-170.
BACKGROUND AND PURPOSE: In the experimental field of animal models, co-registration between positron emission tomography (PET) and magnetic resonance imaging (MRI) data still relies on non-automated post-processing using sophisticated algorithms and software developments. We assessed the value of an empirical method using alginate moulding for PET-MR co-registration in a tumor rat model. METHODS: Male WAG/RijHsd rats bearing grafting syngenic rhabdomyosarcoma were examined under general anesthesia by MRI using a clinical whole-body 3-T system equipped with a sensitivity-encoding four-channel wrist coil and by a small animal PET system using labelled [(18)F]-fluorocholine as tracer. An alginate mould including a system of external fiducials was manufactured for each animal, allowing strict immobilization and similar positioning for both modalities. Fourteen rats (27 tumors) had only one MR/PET imaging session. Five rats (9 tumors) had a similar MR/PET session before and 3 days after external radiation therapy (13 Gy in one fraction) using the same mould. Co-registration was performed using the Pmod software release 2.75 software (PMOD Technologies, Ltd., Adliswil, Switzerland) with mutual information algorithm. RESULTS: The manufacture of the alginate moulds was easy and innocuous. Imaging sessions were well tolerated. PET-MR co-registration based on mutual information was perfect at visual examination, which was confirmed by the superimposition of external fiducials on fused images. Reuse of the same mould for the post-therapeutic session was feasible 3 days after the pre-therapeutic one in spite of tumor growth. CONCLUSION: The empirical method using alginate moulding with external fiducials for PET-MR co-registration in a rodent tumor model was feasible and accurate.
Recent developments in urologic oncology: positron emission tomography molecular imaging.

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PURPOSE OF REVIEW: Traditional morphologically based imaging modalities in uro-oncology are now being complemented by the functional and molecular imaging technique positron emission tomography (PET). This review highlights the most important recent developments. RECENT FINDINGS: Prostate cancer: PET imaging with the new radiotracers 11C-choline, 18F-fluorocholine, and 11C-acetate show promising results. The role of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid remains to be elucidated further. 18F-fluoride PET is useful for the detection of bone metastases. Bladder cancer: 18F-fluorodeoxyglucose (FDG) PET/CT with delayed images after a diuretic and oral hydration may improve detection of locally recurrent or residual bladder tumours. Both 18F-FDG PET and 11C-choline PET may be useful for staging of bladder cancer. Renal cancer: 18F-FDG PET has a role in staging and restaging of the disease. Recently, 124I-cG250 PET has shown promising results in the detection of clear-cell renal carcinoma. Testicular cancer: 18F-FDG PET is useful in staging and follow-up after treatment. There are no important recent developments with new radiopharmaceuticals in testicular cancer. SUMMARY: The utility of PET molecular imaging in uro-oncology expanded due to the new metabolic PET tracers with more favourable properties.


Use of step-section histopathology to evaluate 18F-fluorocholine PET sextant localization of prostate cancer.

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To assess positron emission tomography (PET) with fluoride-18 fluorocholine for sextant localization of malignant prostate tumors. Histopathologic analysis was performed on step-sectioned whole-mounted prostate specimens from 15 patients who underwent PET with fluorocholine prior to radical prostatectomy. The maximum standardized uptake value (SUVmax) corresponding to prostate sextants on PET was measured by region of interest analysis and compared with histopathologic results. Histopathology demonstrated malignant involvement in 61 of 90 prostate sextants. The mean total tumor volume per specimen was 4.9 mL (range 0.01-28.7 mL). Mean SUVmax was 6.0+/2.0 in malignant sextants and 3.8+/1.4 in benign sextants (p<.0001). The area under the receiver operating characteristic curve was 0.82 for sextant detection of malignancy based on SUVmax measurement. Tumor diameter directly correlated with sextant SUVmax in malignant sextants (r=.54, p<.05). In 13 subjects, the largest tumor in the specimen corresponded to the sextant with the highest SUVmax. Fluorocholine PET can serve to localize dominant areas of malignancy in patients with prostate cancer. However, PET with fluorocholine may fail to identify sextants with smaller volumes of malignancy.


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PURPOSE: [(18)F]Fluorocholine ([(18)F]FCH) was developed as an analog of [(11)C]choline for tumor imaging; however, its metabolic handling remains ill defined. In this study, the metabolism of [(18)F]FCH is evaluated in cultured 9L glioma cells and Fisher 344 rats bearing 9L glioma tumors. METHODS: 9L glioma cells were incubated with [(18)F]FCH and [(14)C]choline under normoxic and hypoxic (1% O(2)) conditions and analyzed for metabolic fate. [(18)F]FCH and [(14)C]choline kinetics and metabolism were studied in Fisher 344 rats bearing subcutaneous 9L tumors. RESULTS: [(18)F]FCH and [(14)C]choline were similarly metabolized in 9L cells in both normoxic and hypoxic conditions over a 2-h incubation period. In normoxia, radioactivity was predominantly phosphorylated form for both tracers after 5-min incubation. In hypoxia, the tracers remained mainly in nonmetabolized form at early timepoints (<20 min). Slow dephosphorylation of intracellular [(18)F]phosphofluorocholine (0.043-0.060 min(-1)) and [(14)C]phosphocholine (0.072-0.088 min(-1)) was evidenced via efflux measurements. In rat, both [(18)F]FCH and [(14)C]choline showed high renal and hepatic uptake. Blood clearance of both tracers was rapid with oxidative metabolites, [(18)F]fluorobetaine and [(14)C]betaine, representing the majority of radiolabel in plasma after 5 min postinjection. Oxidation (in liver) and lipid incorporation (in lung) were somewhat slower for [(18)F]FCH relative to [(14)C]choline. The majority of radiolabel in hypoxic subcutaneous tumor, as in hypoxic cultured 9L cells, was found as nonmetabolized [(18)F]FCH and [(14)C]choline. CONCLUSIONS: [(18)F]FCH mimics choline uptake and metabolism by 9L glioma cells and tumors. However, subtle changes in
biodistribution, oxidative metabolism, dephosphorylation, lipid incorporation, and renal excretion show moderate effects of the presence of the radiofluorine atom in [(18)F]FCH. The decrease in phosphorylation of exogenous choline by cancer cells should be considered in interpretation of positron emission tomography images in characteristically hypoxic tumors.

**Fluorocholine**


The value of 18F-choline PET/CT in patients with elevated PSA-level and negative prostate needle biopsy for localisation of prostate cancer.

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PURPOSE: Patients with persistent elevated PSA and repeated negative prostate biopsy, that means having the prostate biopsied at multiple times, were investigated with 18F-choline PET/CT to delineate prostate cancer and guide renewed prostate biopsy. METHODS: Twenty patients with elevated PSA and negative prostate biopsies underwent 18F-choline PET/CT. We performed an early examination of the pelvic region 3-5 min after application. After 30 minutes a whole body PET/CT examination was performed. Image analysis was performed visually and by semi-quantitative analysis calculating the maximum standardised uptake value (SUVmax). 18F-choline uptake was defined as focal, multifocal or inhomogeneous. After the 18F-choline PET/CT, all patients underwent a repeated prostate biopsy, and in the cases where a focal or multifocal uptake was found, the biopsy was guided by the result of the examination. RESULTS: Qualitative image analysis revealed focal 18F-choline uptake in 13 out of 20 patients. In five patients, prostate cancer was revealed by repeated aspiration biopsy. None of the patients with a multifocal or inhomogeneous 18F-choline uptake had a malignant neoplasm in the prostate. Semiquantitative analysis performed with SUVmax was not helpful in the result of the examination. CONCLUSION: The use of 18F-choline cannot be generally recommended for localising prostate cancer; however, in highly selected patients, we found useful additional information. In 25% of patients, 18F-choline PET/CT allowed the identification of neoplastic prostatic zones.


Feasibility of 18F-fluoromethylcholine PET/CT for imaging of vessel wall alterations in humans--first results.


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PURPOSE: Recently published data indicated (18)F-fluorocholine to be feasible for imaging vulnerable atherosclerotic plaques in an animal model. METHODS: Five patients undergoing whole-body (18)F-fluoromethylcholine-(18)F-FMCH-) PET/CT for imaging of prostate cancer disease were retrospectively evaluated. Whole-body PET scans were started immediately after i.v. injection of (18)F-FMCH. About 5-15 min after tracer injection, acquisition of scans of the pelvis and abdomen was performed. PET, CT, and PET/CT slices were generated for review and visual analyses of the abdominal aorta and the common iliac arteries were performed. Vascular findings in examined arteries and surrounding structures due to artifacts were excluded from further analysis. The lower threshold of (18)F-FMCH uptake was set above the background activity within the examined vessels. Morphological classification of vessel wall alterations (WA) included structural wall alterations without additional calcification (SWA), structural wall alterations associated with calcifications (SWC), and solely calcified lesions (CL). They were correlated with (18)F-FMCH uptake qualified as present and vice versa. RESULTS: A total of 31 WA were identified. Positive (18)F-FMCH uptake was found in 14 lesions (SWA: n = 5; SWC: n = 9). Sixteen of 17 (18)F-FMCH negative lesions were identified as CL without additional structural vessel wall alteration. One SWA did not show any (18)F-FMCH accumulation. None of the CLs as well as unaltered parts of the vessel wall showed (18)F-FMCH uptake. CONCLUSIONS: Our initial data in five patients with a total of 31 vessel wall alterations show promising results indicating for the first time the feasibility of (18)F-FMCH for in vivo imaging of structural WA in humans.


In vitro and in vivo studies with [(18)F]fluorocholine on digestive tumoral cell lines and in an animal model of metastasized endocrine tumor.

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PURPOSE: The aim of this study was to investigate (a) in vitro the relationship between [(18)F]fluorocholine [(18)F]FCH) uptake and cell growth in endocrine cell lines and (b) in vivo the uptake of [(18)F]FCH by tumoral sites in an animal model of metastasized endocrine tumor. METHODS: In vitro studies were conducted on three endocrine and two nonendocrine digestive tumoral cell lines. The proliferative ratio was estimated using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. The
uptake of [(18)F]FCH and that of [(18)F]fluorodeoxyglucose ([(18)F]FDG) were measured before and after cytotoxic therapy. [(18)F]FCH biodistribution was studied in nude mice and in an endocrine xenografted mice model. RESULTS: The [(18)F]FCH uptake in tumoral cell lines was related to their proliferative capacities as measured by the MTT assay in basal conditions. After cytotoxic therapy, the IC(50) values calculated with the [(18)F]FCH incorporation test were very close to those determined with the MTT assay. Biodistribution studies showed that [(18)F]FCH was predominantly concentrated in the liver and kidney of nude mice. In the STC-1 xenografted animal model, the uptake of [(18)F]FCH in the primary tumor was only 1.1%. On autoradiography and micro-positron emission tomography, there was no uptake of [(18)F]FCH in liver metastases but there was a significant uptake of [(18)F]FDG. CONCLUSIONS: In vitro studies suggested that the incorporation of [(18)F]FCH in endocrine tumor cell lines was related to their growth capacities; however, in vivo studies conducted in an endocrine xenografted animal model showed an uptake of [(18)F]FCH in hepatic metastases lower than that in normal liver cells. An influence of the microenvironment or a competition phenomenon for [(18)F]FCH uptake between normal liver and endocrine tumor cells cannot be excluded.


Positron emission tomography and positron emission tomography/computerized tomography of urological malignancies: an update review.

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PURPOSE: Appropriate imaging in uro-oncology is a crucial component at primary diagnosis, followup and recurrence to achieve an accurate assessment of the disease and determine the most effective treatment. We summarize recent developments in positron emission tomography and positron emission tomography/computerized tomography for prostate, bladder and renal cancer.

MATERIALS AND METHODS: The recent published literature on positron emission tomography and positron emission tomography/computerized tomography in uro-oncology was searched and reviewed. RESULTS: For prostate cancer 18F-fluorodeoxyglucose is not highly effective for primary diagnosis but it has a limited role in staging and recurrence detection. Promising results have been shown by 11C-choline, 18F-fluorocholine, 11C-acetate and 18F-fluoride. The role of 11C-methionine, 18F-fluoro-5-alpha-dihydrotestosterone and anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid remains to be elucidated. For bladder cancer 18F-fluorodeoxyglucose positron emission tomography is useful for identifying distant metastases but not for detecting primary tumors due to the urinary excretion of 18F-fluorodeoxyglucose. The role of 11C-choline and 11C-methionine remains to be evaluated further in clinical studies. For renal cancer 18F-fluorodeoxyglucose is of limited use for primary diagnosis but it has a role in staging and restaging of the disease. More clinical data are needed to investigate the roles of 18F-fluoromisonidazole and 18F-fluoroethylmide. CONCLUSIONS: Several advances in positron emission tomography and positron emission tomography/computerized tomography for urological cancer have been made in recent years. However, larger clinical trials are needed to establish the role of this imaging method for urological malignancy. In the near future the new radiotracers and further advancement in this imaging technique are expected to improve the performance of positron emission tomography/computerized tomography in uro-oncology.


Cancer imaging with fluorine-18-labeled choline derivatives.

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The choline transporter and choline kinase enzyme frequently are overexpressed in malignancy. Therefore, positron-emitter-labeled compounds derived from choline have the potential to serve as oncologic probes for positron emission tomography. The fluorine-18 ((18)F)-labeled choline derivative fluorocholine (FCH) in particular has demonstrated potential utility for imaging of a variety of neoplasms, including those of the breast, prostate, liver, and brain. The pharmacokinetics of FCH and other choline tracers allow for whole-body imaging within minutes of injection while still achieving high tumor-to-background contrast in most organs, including the brain. These features, along with the possibility of imaging malignancies that have proved elusive with the use of (18)F-fluorodeoxyglucose positron emission tomography support further clinical investigations of (18)F-labeled choline tracers.


(18)F-labeled positron emission tomographic radiopharmaceuticals in oncology: an overview of radiochemistry and mechanisms of tumor localization.

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Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in a living system. At present, positron emission tomography/computed tomography (PET/CT) is one of the most rapidly growing areas of medical imaging, with many applications in the clinical management of patients with cancer. Although [(18)F]fluorodeoxyglucose (FDG)-PET/CT imaging provides high specificity and sensitivity in several kinds of cancer and has many applications, it is important to recognize that FDG is not a "specific" radiotracer for imaging malignant disease. Highly "tumor-specific" and "tumor cell signal-specific" PET radiopharmaceuticals are essential to meet the growing demand of radioisotope-based molecular imaging technology. In the last 15 years, many alternative PET tracers have been proposed and evaluated in preclinical and clinical studies to characterize the tumor biology more appropriately. The potential clinical utility of several (18)F-labeled radiotracers (eg, fluoride, FDOPA, FLT, FMISO, FES, and FCH) is being reviewed by several investigators in this issue. An overview of design and development of (18)F-labeled PET radiopharmaceuticals, radiochemistry, and mechanism(s) of tumor cell uptake and localization of radiotracers are presented here. The approval of clinical indications for FDG-PET in the year 2000 by the Food and Drug Administration, based on a review of literature, was a major breakthrough to the rapid incorporation of PET into nuclear medicine practice, particularly in oncology. Approval of a radiopharmaceutical typically involves submission of a "New Drug Application" by a manufacturer or a company clearly documenting 2 major aspects of the drug: (1) manufacturing of PET drug using current good manufacturing practices and (2) the safety and effectiveness of a drug with specific indications. The potential routine clinical utility of (18)F-labeled PET radiopharmaceuticals depends also on regulatory compliance in addition to documentation of potential safety and efficacy by various investigators.


**Solitary brain lesions enhancing at MR imaging: evaluation with fluorine 18 fluorocholine PET.**

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PURPOSE: To prospectively determine whether differences between benign and malignant brain lesions can be depicted with fluorine 18 [(18)F] fluorocholine positron emission tomography (PET). MATERIALS AND METHODS: Thirty consecutive patients (14 women, 16 men; age range, 26-79 years) with solitary brain lesions that were enhanced at magnetic resonance (MR) imaging underwent whole-brain (18)F-fluorocholine PET after giving informed consent in this institutional review board-approved, HIPAA-compliant study. Histopathologic diagnoses were made in 24 cases (13 high-grade gliomas, eight metastases to the brain, and three benign lesions). In six cases, benign lesions were diagnosed on the basis of longitudinal follow-up MR findings. The maximum standardized uptake value (SUV(max)) for lesion and peritumoral regions was measured on PET images, and a lesion-to-normal tissue uptake ratio (LNR) was calculated. Differences were assessed with one-way analysis of variance, Fisher exact, and Student t tests. RESULTS: Differences in SUV(max) between high-grade gliomas (1.89 +/- 0.78 [mean +/- standard deviation]), metastases (4.11 +/- 1.68), and benign lesions (0.59 +/- 0.31) were significant (P < .0001). LNRs also differed significantly (5.15 +/- 2.51, 10.91 +/- 2.14, and 1.28 +/- 0.32, respectively; P < .0001). These differences were also significant at pairwise analysis. The peritumoral LNR exceeded 2.0 in seven high-grade gliomas and no metastases (P = .02). In 14 radiation-treated patients, the lesions classified as benign demonstrated significantly less uptake compared with the recurrent tumors (SUV(max): 0.72 +/- 0.38 vs 2.27 +/- 1.24; P < .01; LNR: 1.36 +/- 0.43 vs 5.88 +/- 3.66; P < .01). CONCLUSION: High-grade gliomas, metastases, and benign lesions can be distinguished on the basis of measured fluorocholine uptake. Increased peritumoral fluorocholine uptake is a distinguishing characteristic of high-grade gliomas.


**[18F]fluorocholine PET/CT in the assessment of bone metastases in prostate cancer.**

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**Uptake of 18F-Fluorocholine, 18F-FET, and 18F-FDG in C6 gliomas and correlation with 131I-SIP(L19), a marker of angiogenesis.**


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Targeting extracellular structures that are involved in angiogenic processes, such as the extra domain B of fibronectin, is a promising approach for the diagnosis of solid tumors. The aim of this study was to determine uptake of the (18)F-labeled PET tracers (18)F-fluorocholine (N,N-dimethyl-N-(18)F-fluoromethyl-2-hydroxyethylammonium), (18)F-fluoro-ethyl-l-tyrosine (FET), and (18)F-FDG in C6 gliomas of the rat and to correlate it with uptake of the anti-extra domain B antibody (131I-SIP(L19)) as a marker of neoangiogenesis. METHODS: C6 gliomas were orthotopically induced in 17 rats. Uptake of all tracers was measured using
fluorocholine and uptake of (18)F-fluorocholine, (18)F-FET, and (18)F-FDG was correlated with uptake of (131)I-
SIP(L19) on a pixelwise basis. RESULTS: The mean (131)I-SIP(L19), (18)F-fluorocholine, (18)F-FET, and (18)F-FDG standardized uptake values in the tumor and the contralateral normal cortex (in parentheses) were 0.31 +/- 0.22 (not detectable), 2.00 +/- 0.53 (0.49 +/- 0.07), 3.67 +/- 0.36 (1.42 +/- 0.22), and 7.23 +/- 1.22 (3.64 +/- 0.51), respectively. The (131)I-SIP(L19) uptake pattern correlated best with (18)F-fluorocholine uptake (z = 0.80, averaged z-transformed Pearson correlation coefficient) and (18)F-FET uptake (z = 0.79) and least with (18)F-FDG (z = 0.37). CONCLUSION: One day after intravenous injection, (131)I-SIP(L19) displayed a very high tumor-to-cortex ratio, which may be used in the diagnostic work-up of brain tumor patients. Of the 3 investigated (18)F tracers, (18)F-fluorocholine and (18)F-FET correlated better with the pattern of (131)I-SIP(L19) uptake than did (18)F-FDG. Whether this means that (18)F-fluorocholine and (18)F-FET are better suited than (18)F-FDG to monitor antiangiogenic therapy should be investigated in future studies.


Asymmetric F-18 fluorocholine uptake of submaxillary glands revealing intraglandular lithiasis.

Clarençon F, Kerrou K, Gutman F, Chevallier D, Montravers F, Talbot JN.


18F-choline PET/CT for initial staging of advanced prostate cancer.

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PURPOSE: Accurate detection of lymph node metastases in prostate cancer has important implications for prognosis and approach to treatment. We investigated whether preoperative [18F]fluorocholine combined in-line positron emission tomography-computerized tomography and intraoperative laparoscopic radioisotope guided sentinel pelvic lymph node dissection can detect pelvic lymph node metastases in patients with clinically localized prostate cancer as reliably as extended pelvic lymph node dissection. MATERIALS AND METHODS: A total of 20 patients (mean age 63.9 +/- 6.7 years, range 52 to 75) with clinically localized prostate cancer, prostate specific antigen greater than 10 ng/ml, and/or a Gleason score sum of 7 or greater and negative bone scan were enrolled in the study. [18F]fluorocholine combined in-line positron emission tomography-computerized tomography was performed before surgery. Sentinel pelvic lymph node dissection preceded extended pelvic lymph node dissection including the area of the obturator fossa, external iliac artery/vein and internal iliac artery/vein up to the bifurcation of the common iliac artery. Laparoscopic radical prostatectomy was performed afterward. RESULTS: In 10 of the 20 patients (50%) lymph node metastases were detected, and were exclusively found outside the obturator fossa in 62%. These metastases would not have been identified with standard lymph node dissection of the obturator fossa only. [18F]fluorocholine combined in-line positron emission tomography-computerized tomography was true positive in 1, false-positive in 2, false-negative in 9 and true negative in 8 patients. The largest lymph node metastasis not seen with [18F]fluorocholine combined in-line positron emission tomography-computerized tomography was 8 mm. Laparoscopic sentinel guided lymph node dissection revealed lymph node metastases in 8 of 10 patients. In the other 2 patients sentinel lymph node dissection was not conclusive. In 1 patient normal nodal tissue was completely replaced by cancer and, therefore, there was no tracer uptake in the involved pelvic sidewall/node, and the other patient had no tracer activity at all in the involved pelvic sidewall. Extended pelvic lymph node dissection missed 1 lymph node metastasis (2 mm diameter near pudendal artery) which was detected by sentinel pelvic lymph node dissection only. CONCLUSIONS: Extended pelvic lymph node dissection reveals a higher number of lymph node metastases as described for obturator fossa dissection only. [18F]fluorocholine combined in-line positron emission tomography-computerized tomography is not useful in searching for occult lymph node metastases in clinically localized prostate cancer. Sentinel guided pelvic lymph node dissection allows the detection of even small lymph node metastases. The accuracy of sentinel pelvic lymph node dissection is comparable to that of extended pelvic lymph node dissection when the limitations of the method are taken into consideration.
correlation with FET uptake. The ratio of the uptake in tumours to that in radiation injuries was 1.97 (FCH), 2.71 (FET) and 2.37 (0.51±0.11) and 11.02±3.84 (4.76±1.77) respectively. MVD was significantly correlated only with FCH uptake. There was a trend towards a negative correlation between the degree of BBB disruption and FCH uptake and a trend towards a positive correlation with FET uptake. The ratio of the uptake in tumours to that in the radiation injuries was 1.97 (FCH), 2.71 (FET) and 2.37

Uptake of 18F-fluorocholine, 18F-fluoro-ethyl-L-tyrosine and 18F-fluoro-2-deoxyglucose in F98 gliomas in the rat. 

INTRODUCTION: The positron emission tomography (PET) tracers (18)F-fluoro-ethyl-L-tyrosine (FET), (18)F-fluorocholine (FCH) and (18)F-fluorodeoxyglucose (FDG) are used in the diagnosis of brain tumours. The aim of this study was threefold: (a) to assess the uptake of the different tracers in the F98 rat glioma, (b) to evaluate the impact of blood-brain barrier (BBB) disruption and microvessel density (MVD) on tracer uptake and (c) to compare the uptake in the tumours to that in the radiation injuries (induced by proton irradiation of healthy rats) of our previous study. METHODS: One hundred consecutive prostate cancer patients with a persistent increase in serum PSA (>0.1 ng/ml) after radical prostatectomy (58 cases), radiotherapy (21 cases) or hormonal therapy alone (21 cases) were investigated. After injection of 3.7-4.07 MBq/kg of FET, both early (at <15 min) and delayed (at >60 min) PET/CT scans were performed in 43 patients, delayed PET/CT scans in 53 patients and early PET/CT scans in four patients. RESULTS: Of the 100 patients, 54 (PSA 0.22-5.11.79 ng/ml) showed positive FCH PET/CT scans. Thirty-two patients had bone and/or abdominal lymph node uptake, while 17 showed pelvic activity. Malignant disease was confirmed in all but one. Delayed SUV(max) of bone metastases was significantly higher (p<0.0001 by paired t test) than that measured at <15 min, whereas no differences were observed between early and delayed SUVs of malignant lymph nodes or pelvic disease. Forty-six patients (PSA 0.12-14.3 ng/ml) showed negative FCH PET/CT scans. Of the negative PET/CT scans, 89% were obtained in patients with serum PSA <4 ng/ml and 87% in patients with a Gleason score <8. In none of these cases could recurrent tumour be proven clinically during a follow-up of 6 months. CONCLUSION: FCH PET/CT is not likely to have a significant impact on the care of prostate cancer patients with biochemical recurrence until PSA increases to above 4 ng/ml. However, in selected patients, FCH PET/CT helps to exclude distant metastases when salvage local treatment is intended.

PET/CT in patients with hepatocellular carcinoma using [(18)F]fluorocholine: preliminary comparison with [(18)F]FDG PET/CT. 

PURPOSE: The diagnostic accuracy of [(18)F]fluorodeoxyglucose (FDG) PET is insufficient to characterise hepatocellular carcinoma (HCC) in liver masses and to diagnose all cases of recurrent HCC. HCC has been reported to take up [(11)C]acetate, but routine use of this tracer is difficult. Choline is another tracer of lipid metabolism, present in large amounts in HCC. In a proof-of-concept study, we evaluated [(18)F]fluoromethylcholine (FCH) uptake by HCC and compared FCH PET/CT with FDG PET/CT. 

METHODS: Twelve patients with newly diagnosed (n=8) or recurrent HCC (n=4) were prospectively enrolled. HCC was assessed by histology in eight cases and by American Association for the Study of Liver Diseases (AASLD) criteria in four cases. All patients underwent whole-body PET/CT 10 min after injection of 4 MBq/kg FCH. Within 1 week, 9 of the 12 patients also underwent whole-body FDG PET/CT 1 h after injection of 5 MBq/kg FDG. RESULTS: The per-patient analysis showed a detection rate of 12/12 using FCH PET/CT for both newly diagnosed and recurrent HCC. The median signal to noise ratio was 1.5+/0.38. There was a trend towards a higher FCH SUV(max) in well-differentiated HCC (15.6+/7.79 vs 11.9+/0.9, NS). Of the nine patients who underwent FCH and FDG PET/CT, all nine were positive with FCH whereas only five were positive with FDG. CONCLUSION: FCH PET/CT provides a high detection rate for HCC, making it potentially useful in the initial evaluation of HCC or in the detection of recurrent disease. The favourable result of this proof-of-concept study opens the way to a phase III prospective study.

Uptake of 18F-fluorochrome, 18F-fluoro-ethyl-L-tyrosine and 18F-fluoro-2-deoxyglucose at the F98 glioma in the rat. 

INTRODUCTION: The positron emission tomography (PET) tracers (18)F-fluoro-ethyl-L-tyrosine (FET) and (18)F-fluorocholine (FCH) and (18)F-fluorodeoxyglucose (FDG) are used in the diagnosis of brain tumours. The aim of this study was threefold: (a) to assess the uptake of the different tracers in the F98 rat glioma, (b) to evaluate the impact of blood-brain barrier (BBB) disruption and microvessel density (MVD) on tracer uptake and (c) to compare the uptake in the tumours to that in the radiation injuries (induced by proton irradiation of healthy rats) of our previous study. METHODS: Four weeks after injection of 4 MBq/kg FCH, both early (at <15 min) and delayed (at >60 min) PET/CT scans were performed in 43 patients, delayed PET/CT scans in 53 patients and early PET/CT scans in four patients. RESULTS: Of the 100 patients, 54 (PSA 0.22-511.79 ng/ml) showed positive FCH PET/CT scans. Thirty-two patients had bone and/or abdominal lymph node uptake, while 17 showed pelvic activity. Malignant disease was confirmed in all but one. Delayed SUV(max) of bone metastases was significantly higher (p<0.0001 by paired t test) than that measured at <15 min, whereas no differences were observed between early and delayed SUVs of malignant lymph nodes or pelvic disease. Forty-six patients (PSA 0.12-14.3 ng/ml) showed negative FCH PET/CT scans. Of the negative PET/CT scans, 89% were obtained in patients with serum PSA <4 ng/ml and 87% in patients with a Gleason score <8. In none of these cases could recurrent tumour be proven clinically during a follow-up of 6 months. CONCLUSION: FCH PET/CT is not likely to have a significant impact on the care of prostate cancer patients with biochemical recurrence until PSA increases to above 4 ng/ml. However, in selected patients, FCH PET/CT helps to exclude distant metastases when salvage local treatment is intended.

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Localization of primary prostate cancer with dual-phase 18F-fluorocholine PET.

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This study compared 18F-fluorocholine uptake in malignant and benign areas of the prostate at 2 time points to determine the suitability of delayed or dual-phase 18F-fluorocholine PET for localizing malignancy in the prostate gland. METHODS: Twenty-six men (15 newly diagnosed with prostate cancer, 2 with recurrent prostate cancer, 6 with no evidence of prostate cancer recurrence after treatment, and 3 with no history of prostate cancer) underwent dual-phase PET consisting of initial whole-body PET starting 7 min after injection of 3.3–4 MBq/kg of 18F-fluorocholine followed by 1-h delayed PET of the pelvis. Tracer uptake in the prostate on the initial and delayed images was measured on a sextant basis. Prostate biopsy or whole-prostate histologic examination after radical prostatectomy was used to classify a prostate sextant as a dominant malignant region or probable benign region. For each sextant, a retention index based on the measured maximum standardized uptake value (SUVmax) was calculated on the initial and delayed images. In 15 prostates with both benign and malignant sextants on histologic examination, a malignant-to-benign ratio of SUVmax was also calculated for each time point. RESULTS: A dominant malignant region was found in 17 subjects, and a probable benign region was found in 24 subjects. The mean SUVmax for dominant malignant regions increased significantly between initial and delayed scans, from 7.6 to 8.6 (mean retention index, +14%; 95% confidence interval, 6%–22%; P = 0.002). The mean SUVmax for probable benign regions decreased significantly between initial and delayed scans, from 4.8 to 3.9 (mean retention index, -17%; 95% confidence interval, -10% to -23%, P < 0.001). The mean malignant-to-benign ratio increased significantly, from 1.4 on the initial scan to 1.8 on the delayed scan (P = 0.003). The areas under the receiver operating characteristic curves for distinguishing dominant malignant regions from probable benign regions based on initial SUVmax, delayed SUVmax, and retention index were 0.81, 0.92, and 0.93, respectively. CONCLUSION: On dual-phase PET of the prostate, areas of malignancy consistently demonstrated stable or increasing 18F-fluorocholine uptake, whereas most areas containing benign tissue demonstrated decreasing uptake. Delayed or dual-phase imaging after injection of 18F-fluorocholine may improve the performance of 18F-fluorocholine PET for localizing malignant areas of the prostate.


18F-choline images murine atherosclerotic plaques ex vivo.


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OBJECTIVE: Current imaging modalities of atherosclerosis mainly visualize plaque morphology. Valuable insight into plaque biology was achieved by visualizing enhanced metabolism in plaque-derived macrophages using 18F-fluoro(2-deoxy)glucose (18F-FDG). Similarly, enhanced uptake of 18F-fluorocholine (18F-FCH) was associated with macrophages surrounding an abscess. As macrophages are important determinants of plaque vulnerability, we tested 18F-FCH for plaque imaging. METHODS AND RESULTS: We injected 18F-FCH (n=5) or 18F-FDG (n=5) intravenously into atherosclerotic apolipoprotein E-deficient mice. En face measurements of aortae isolated 20 minutes after 18F-FCH injections demonstrated an excellent correlation between fat stainings and autoradiographies (r=0.842, P<0.0001), achieving a sensitivity of 84% to detect plaques by 18F-FCH. In contrast, radiotracer uptake 20 minutes after 18F-FDG injections correlated less with en face fat stainings (r=0.261, P<0.05), reaching a sensitivity of 64%. Histological analyses of cross-sections 20 minutes after coinjections of 18F-FCH and 14C-FDG (n=3) showed that 18F-FCH uptake correlated better with fat staining (r=0.740, P<0.0001) and macrophage-positive areas (r=0.740, P<0.0001) than 14C-FDG (fat: r=0.236, P=0.29 and CD68 staining: r=0.352, P=0.11), respectively. CONCLUSIONS: 18F-FCH identifies murine plaques better than 18F-FDG using ex vivo imaging. Enhanced 18F-FCH uptake into macrophages may render this tracer a promising candidate for imaging plaques in patients.
Fluorocholine


Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA < 5 ng/ml?


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According to reports, re-staging of patients suffering from prostate cancer by positron emission tomography (PET) using C-11-choline has failed to produce positive findings at a PSA level of < 5 ng/ml. Hence, the purpose of our study has been to determine whether this is true also for PET/CT using F-18-fluorocholine (FCH PET/CT) or whether it is possible to obtain true positive results by FCH PET/CT even at lower PSA levels. METHODS: In 34 patients with prostate cancer who had undergone initial therapy (radical prostatectomy n = 31, radiotherapy n = 3), a PET/CT scan was performed using F-18-fluorocholine (FCH) during follow-up in case of demonstrable or rising PSA levels. Current PSA levels were determined in all patients at the time of examination. RESULTS: Median PSA in FCH positive patients was 6.1 ng/ml (mean PSA 17.1 ng/ml), median PSA in FCH negative patients was 2.3 ng/ml (mean PSA 3.4 ng/ml), respectively (p < 0.05). In eight of 17 examinations (47%) with PSA < 5 ng/ml, at least one FCH-positive focus was detected. So far the findings could be confirmed by correlating imaging methods (CT and/or MR), biopsy/histology and the course of the disease, respectively, in seven of the eight FCH-positive cases with PSA < 5 ng/ml, so that a true positive FCH PET/CT finding was obtained in all in seven of 17 (41%) examinations with PSA < 5 ng/ml. In four of these seven FCH PET-positive patients with PSA < 5 ng/ml, adjuvant hormonal therapy was administered at the time of the examination or prior to the examination. CONCLUSION: In re-staging patients with prostate cancer, FCH PET/CT is able to yield true positive findings even at PSA < 5 ng/ml. Therefore, FCH PET/CT should not be restricted to patients with PSA > 5 ng/ml.


Fluorocholine PET/CT in patients with prostate cancer: initial experience.


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Institutional review board approval and written informed consent were obtained. Patients with newly diagnosed prostate cancer and patients suspected of having recurrent cancer were prospectively evaluated with fluorine 18 fluorocholine (FCH) combined in-line positron emission tomography (PET) and computed tomography (CT). In 19 patients (mean age, 67 years +/- 8; range, 57-85 years), standardized uptake values of FCH in 17 different tissues were determined by using volumes of interest. In nine patients evaluated at initial staging, histologic findings of the resected prostate were compared to FCH uptake. Only small variations of physiologic tracer accumulation were measured in all organs but the kidneys. Differentiation of benign hyperplasia from cancerous lesions was not possible with FCH PET/CT. However, in patients with recurrent prostate cancer, FCH PET/CT is a promising imaging modality for detecting local recurrence and lymph node metastases.


Prostate cancer localization with 18fluorine fluorocholine positron emission tomography.

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PURPOSE: We evaluated positron emission tomography (PET) with fluorine fluorocholine (F FCH) for the pretreatment localization of prostate cancer. MATERIALS AND METHODS: A total of 17 patients with prostate cancer who had not yet received treatment for the disease underwent whole body PET following intravenous administration of 3.3 to 4 MBq/kg F FCH. PET findings were compared with the results of prostate sextant biopsy and other imaging studies, and the clinical course. Tracer uptake in prostate sextants was measured as a maximum standardized uptake value (SUVmax) and evaluated as a predictor of the prostate sextant biopsy result by ROC analysis. RESULTS: Prostate sextants positive for malignancy on biopsy demonstrated significantly higher SUVmax than biopsy negative sextants (mean 5.5 vs 3.3, p <0.001). In all 6 cases in which biopsy identified malignancy on only 1 side of the prostate it was possible to identify correctly the affected side based on higher SUVmax. Area under the ROC curve for SUVmax as a discriminator of biopsy positive sextants was 0.86. In 2 patients PET demonstrated areas of abnormal uptake in the retroperitoneum. Computed tomography confirmed the presence of retroperitoneal lymphadenopathy in these areas. In the 2 patients these lesions regressed following hormonal treatment for prostate cancer. CONCLUSIONS: Malignant tumors in the prostate gland can be localized based on a standardized regional measurement of F FCH uptake. PET with F FCH is potentially useful for staging and localizing prostate cancer.
Uptake of 18F-fluorocholine, 18F-fluoroethyl-L-tyrosine, and 18F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumor recurrence.


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Differentiation between posttherapy radiation necrosis and recurrent tumor in humans with brain tumor is still a difficult diagnostic task. The new PET tracers (18)F-fluoro-ethyl-L-tyrosine (FET) and (18)F-fluorocholine (N,N-dimethyl-N-[18F]-fluoromethyl-2-hydroxyethylammonium [FCH]) have shown promise for improving diagnostic accuracy. This study assessed uptake of these tracers in experimental radiation injury. METHODS: In a first model, circumscribed lesions were induced in the cortex of 35 rats using proton irradiation of 150 or 250 Gy. After radiation injury developed, uptake of (18)F-FET, (18)F-FCH, and (18)F-FDG was measured using autoradiography and correlated with histology and disruption of the blood-brain barrier as determined with Evans blue. In a second model, uptake of the tracers was assessed in acute cryolesions, which are characterized by the absence of inflammatory cells. RESULTS: Mean (18)F-FET, (18)F-FCH, and (18)F-FDG standardized uptake values in the most active part of the radiation lesion and the contralateral normal cortex (in parentheses) were 2.27 +/- 0.46 (1.42 +/- 0.23), 2.52 +/- 0.42 (0.61 +/- 0.12), and 6.21 +/- 1.19 (4.35 +/- 0.47). The degree of uptake of (18)F-FCH and (18)F-FDG correlated with the density of macrophages. In cryolesions, (18)F-FET uptake was similar to that in radiation lesions, and (18)F-FET uptake was significantly reduced. CONCLUSION: Comparison of tracer accumulation in cryolesions and radiation injuries demonstrates that (18)F-FET uptake is most likely due to a disruption of the blood-brain barrier alone, whereas (18)F-FCH is additionally trapped by macropages. Uptake of both tracers in the radiation injuries is generally lower than the published uptake in tumors, suggesting that (18)F-FET and (18)F-FCH are promising tracers for separating radiation necrosis from tumor recurrence. However, the comparability of our data with the literature is limited by factors such as different species and acquisition protocols and modalities. Thus, more studies are needed to settle this issue. Nevertheless, (18)F-FCH and (18)F-FET seem superior to (18)F-FDG for this purpose.

Synthesis and preclinical evaluation of the choline transport tracer deshydroxy-[18F]fluorocholine ([18F]dOC).

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11C-labeled choline ([11C]CHO) and 18F-fluorinated choline analogues have been demonstrated to be valuable tracers for in vivo imaging of neoplasms by means of positron emission tomography (PET). The objective of the present study was to evaluate whether deshydroxy-[18F]fluorocholine, ([18F]dOC), a non-metabolizable [18F]fluorinated choline analogue, can serve as a surrogate for cholines that are able to be phosphorylated and thus allow PET-imaging solely by addressing the choline transport system. The specificity of uptake of [18F]dOC was compared with that of [11C]choline ([11C]CHO) in cultured rat pancreatic carcinoma and PC-3 human prostate cancer cells in vitro. In addition, biodistribution of [18F]dOC and [11C]CHO was compared in AR42J- and PC-3 tumor bearing mice. The in vitro studies revealed that membrane transport of both compounds can be inhibited in a concentration dependent manner by similar concentrations of cold choline (IC50 [18F]dOC= 11 microM; IC50 [11C]CHO=13 microM. In vitro studies with PC-3 and AR42J cells revealed that the internalized fraction of [18F]dOC after 5 min incubation time is comparable to that of [11C]CHO, whereas the uptake of [11C]CHO was superior after 20 min incubation time. As for [11C]CHO, kidney and liver were also the primary sites of uptake for [18F]dOC in vivo. Biodistribution data after simultaneous injection of both tracers into AR42J tumor bearing mice revealed slightly higher tumor uptake for [18F]dOC at 10 min post-injection, whereas [11C]CHO uptake was higher at later time points. In conclusion, [18F]dOC is taken up into AR42J rat pancreatic carcinoma and PC-3 human prostate cancer cells by a choline specific transport system. Similar transport rates of [18F]dOC and [11C]CHO result in comparable cellular uptake levels at early time points. In contrast to [18F]dOC, which is transported but not intracellularly trapped, the choline kinase substrate [11C]CHO is transported into tumor cells and retained. Thus, the signal obtained by imaging early after injection is mainly reflecting transport, whereas a valid quantification of choline kinase activity needs imaging at later time points. Further studies have to clarify whether quantification of the transport capacity or the choline kinase activity result in a better pathophysiological correlate and thus the more useful process for tumor characterization.

Combined use of F-18 fluorocholine positron emission tomography and magnetic resonance spectroscopy for brain tumor evaluation.

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BACKGROUND: Choline metabolism is often abnormal in malignant brain tumors. METHODS: Brain positron emission tomography (PET) imaging with 18F-fluorocholine (FCH) was performed on 2 patients with intracranial lesions suspected to be high-grade malignant gliomas on the basis of magnetic resonance (MR) imaging and multivoxel 1H-MR spectroscopic imaging (MRSI) findings. Standardized uptake value (SUV) measurements on PET were compared with measurements of choline/creatine metabolite ratio on MRSI in corresponding regions. Brain biopsy revealed glioblastoma multiforme (GBM) in one case and demyelinating disease in the other. RESULTS: In the case of GBM, the tumor demonstrated increased FCH uptake on PET. The mean and maximum SUV in areas of the tumor correlated with regional choline/creatine ratio measurements ($r = 0.76$, $P < .001$; $r = 0.83$, $P < .001$, respectively). In the case of tumefactive demyelinating lesions, the lesion demonstrated low FCH uptake, which did not correlate with choline/creatine ratio measurements. CONCLUSIONS: Assessments of choline metabolism may aid in evaluating intracranial mass lesions.

**Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer.**

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PURPOSE: Positron emission tomography (PET) imaging is used for the metabolic evaluation of cancer. [18F]fluorodeoxyglucose (FDG) is commonly used as a radiotracer but its low cellular uptake rate in prostate cancer limits its usefulness. We evaluated the novel choline analog [18F]fluorocholine (FCH) for detecting androgen dependent and androgen independent prostate cancer, and its metastases. MATERIALS AND METHODS: The cellular uptake of FCH and FDG was compared in cultured prostate cancer cells (LNCaP and PC-3). FCH and FDG were injected into nude mice xenografts (CWR-22 and PC-3) and radiotracer uptake in various organs were evaluated. Patients with androgen dependent (9) and independent (9) prostate cancer were studied by FCH and FDG PET. RESULTS: FCH uptake was 849% and 60% greater than FDG uptake in androgen dependent (LNCaP) and independent (PC-3) cells, respectively. The addition of hemicholinium-3 (5 mM.) 30 minutes before radiotracer administration inhibited FCH uptake by 79% and 70% in LNCaP and PC-3 cells, respectively, whereas FDG uptake was not significantly affected. Although nude mice xenografts showed that FDG uptake was equal to or greater than FCH uptake, clinical imaging in patients demonstrated 2 to 4-fold higher uptake of FCH in those with androgen and androgen independent prostate carcinoma (p <0.001). More lesions were detected by FCH than by FDG in primary tumors, osseous metastases and soft tissue metastases. CONCLUSIONS: In vitro data demonstrated greater FCH than FDG uptake in androgen dependent (LNCaP) and androgen independent (PC-3) prostate cancer cells. Although the murine xenograft data showed greater accumulation of FDG than FCH in PC-3 tumors, PET in humans showed that FCH was better than FDG for detecting primary and metastatic prostate cancer. Overall the data from this study suggest that FCH is preferable to FDG for PET of prostate carcinoma and support the need for future validation studies in a larger number of subjects.

**Pharmacokinetics and radiation dosimetry of 18F-fluorocholine.**

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18F-Fluorocholine (fluoromethyl-dimethyl-2-hydroxyethylammonium [FCH]) has been developed as an oncologic probe for PET. This study evaluates the kinetics and radiation dosimetry of 18F-FCH using murine and human biodistribution data. METHODS: The biodistribution of 18F-FCH was obtained at time points up to 10 h after administration in control and tumor-bearing anesthetized nude mice. Human biodistribution data within the first hour after injection were obtained from attenuation-corrected whole-body PET scans of male (n = 7) and female (n = 5) cancer patients. Radiation dosimetry estimates were calculated using the murine and human biodistribution data assuming no redistribution of tracer after 1 h. RESULTS: Rapid pharmacokinetics were observed for 18F-FCH in mice and humans. The biodistribution is nearly static after 10 min. The dose-critical organ is the kidney, which receives 0.17 +/- 0.05 and 0.16 +/- 0.07 mSv/MBq (0.64 +/- 0.18 and 0.55 +/- 0.32 rad/mCi) for females and males, respectively. The effective dose equivalent (whole body) from administration of 4.07 MBq/kg (0.110 mCi/kg) is approximately 0.01 Sv for females and males. CONCLUSION: 18F-FCH is rapidly cleared from the circulation and its biodistribution changes very slowly at >10 min after administration. The kidney is the dose-critical organ and limits administration levels of 18F-FCH to 4.07 MBq/kg (0.110 mCi/kg) in human research studies.
Fluorocholine

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Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers.


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Elevated levels of choline (trimethyl-2-hydroxyethylammonium) and choline kinase (CK) activity in neoplasms have motivated the development of positron-labeled choline analogs for noninvasive detection of cancer using PET. The aim of this study was to further evaluate [(18)F]fluorocholine (fluoromethyl-dimethyl-2-hydroxyethylammonium [FCH]) as an oncologic probe in comparison with several other closely related molecules. METHODS: FCH, [(18)F]fluoromethyl-methylethyl-2-hydroxyethylammonium (FMEC), [(18)F]fluoroethyl-dimethyl-2-hydroxyethylammonium (FEC), and [(18)F]fluoropropyl-dimethyl-2-hydroxyethylammonium (FPC) were synthesized through [(18)F]fluoroalkylation reactions. In vitro phosphorylation rates of the (18)F-labeled choline analogs and [methyl-(14)C]choline (CH) were studied using yeast CK. Several choline radiotracers were also evaluated in cultured PC-3 human prostate cancer cells. Data on chemical stability, radiation dosimetry, and toxicity of FCH were obtained. PET studies with FCH were performed on a patient with prostate cancer and a patient with a brain tumor. RESULTS: FCH and FMEC revealed in vitro phosphorylation by CK that was similar to that of choline, whereas rates of phosphorylation of FEC and FPC were 30% (P < 0.01) and 60% (P < 0.01) lower, respectively. Accumulations of FCH, CH, and FPC in cultured PC-3 cancer cells were comparable, whereas uptake of FEC was approximately one fifth that of FCH. Dosimetry estimates using FCH biodistribution data in mice indicated that the kidneys are radiation-dose-critical organs for FCH. PET images of a patient with recurrent prostate cancer showed uptake of FCH in the prostatic bed and in metastases to lymph nodes. FCH PET showed uptake in malignancies in a patient with metastatic breast cancer. PET revealed FCH uptake in biopsy-proven recurrent brain tumor with little confounding uptake by normal brain tissues. CONCLUSION: The fluoromethyl choline analog FCH may serve as a probe of choline uptake and phosphorylation in cancer cells, whereas fluoroethyl (FEC) and fluoropropyl (FPC) analogs appear to have relatively poorer biologic compatibility.

Preliminary PET studies on patients with prostate cancer and with breast cancer and brain tumor support further studies to evaluate the usefulness of FCH as an oncologic probe.


9:30-9:45. Preliminary Evaluation of F-18 Fluorocholine (FCH) as a PET Tumor Imaging Agent.


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The purpose of this study was to develop and evaluate an F-18 labeled choline tumor imaging agent. FCH was synthesized through the intermediate F-18 fluorobromomethane that was used to alkylate dimethylethanolamine. The isolated FCH was evaluated in PC-3 human prostate cancer cells, PC-3 human prostate cancer xenograft studies, and human prostate and brain tumor patients. FCH was accumulated at a slightly lower rate than FDG in the cultures of PC-3 cells. Inhibition of choline transport and phosphorylation by hemicholinium-3 resulted in a 90% decrease in FCH uptake without altering FDG uptake. FCH had a similar biodistribution as C-14 choline in mice, with the liver and kidneys being the primary sites of uptake. Tumor uptake of FCH and FDG were comparable at 45-60 mins after injections. The tumor:blood ratio was higher for FCH (5.3 +/- 2.4) than for FDG (3.2 +/- 0.3). Brain uptake of FCH was 10% that of FDG. FCH-PET studies were compared to FDG-PET studies. In the prostate cancer patients, more lesions have been seen on the FCH studies than on the FDG studies, and the standardized uptake values (SUV) have been higher with the FCH. Decreases in FCH-PET SUV have been noted in patients treated by androgen deprivation. Patients with suspected recurrent brain tumors have had more clearly defined abnormal accumulation on the FCH-PET scans than on the FDG-PET scans. The FCH is not accumulated by normal cortex. FCH is a promising imaging agent for the evaluation of metastatic prostate cancer and recurrent brain tumor.
Fluoride


Novel Strategy for a Cocktail 18F-Fluoride and 18F-FDG PET/CT Scan for Evaluation of Malignancy: Results of the Pilot-Phase Study.

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(18)F-FDG PET/CT is used for detecting cancer and monitoring cancer response to therapy. However, because of the variable rates of glucose metabolism, not all cancers are identified reliably. Sodium (18)F was previously used for bone imaging and can be used as a PET/CT skeletal tracer. The combined administration of (18)F and (18)F-FDG in a single PET/CT study for cancer detection has not been reported to date. METHODS: This is a prospective pilot study (November 2007-November 2008) of 14 patients with proven malignancy (6 sarcoma, 3 prostate cancer, 2 breast cancer, 1 colon cancer, 1 lung cancer, and 1 malignant paraganglioma) who underwent separate (18)F PET/CT and (18)F-FDG PET/CT and combined (18)F/(18)F-FDG PET/CT scans for the evaluation of malignancy (a total of 3 scans each). There were 11 men and 3 women (age range, 19-75 y; average, 50.4 y). RESULTS: Interpretation of the combined (18)F/(18)F-FDG PET/CT scans compared favorably with that of the (18)F-FDG PET/CT (no lesions missed) and the (18)F PET/CT scans (only 1 skull lesion seen on an (18)F PET/CT scan was missed on the corresponding combined scan). Through image processing, the combined (18)F/(18)F-FDG scan yielded results for bone radiotracer uptake comparable to those of the (18)F PET/CT scan performed separately. CONCLUSION: Our pilot-phase prospective trial demonstrates that the combined (18)F/(18)F-FDG administration followed by a single PET/CT scan is feasible for cancer detection. This combined method opens the possibility for improved patient care and reduction in health care costs.


Detection of bone metastases in patients with prostate cancer by 18F fluorocholine and 18F fluoride PET-CT: a comparative study.


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PURPOSE: The aim of this prospective study was to compare the potential value of (18)F fluorocholine (FCH) and (18)F fluoride positron emission tomography (PET)-CT scanning for the detection of bony metastases from prostate cancer. METHODS: Thirty-eight men (mean age, 69+/-8 years) with biopsy-proven prostate cancer underwent both imaging modalities within a maximum interval of 2 weeks. Seventeen patients were evaluated preoperatively, and 21 patients were referred for post-operative evaluation of suspected recurrence or progression based on clinical algorithms. The number, sites and morphological patterns of bone lesions on (18)F-PET/CT and (18)F-FDG PET/CT scans were compared. RESULTS: Concordant lesions between the two modalities with corresponding changes on CT were considered to be positive for malignancy; discordant lesions were verified by follow-up examinations. The mean follow-up interval was 9.1 months. RESULTS: Overall, 321 lesions were evaluated in this study. In a lesion-based analysis, a relatively close agreement was found between these two imaging modalities for detection of malignant bone lesions (kappa=0.57), as well as in a patient-based analysis (kappa=0.76). Sixteen malignant sclerotic lesions with a high density were negative in both (18)F FCH and (18)F fluoride PET-CT [mean Hounsfield unit (HU), 1,148+/-364]. There was also a significant correlation between tracer intensity by SUV and density of sclerotic lesions by HU both in (18)F FCH PET-CT (r=-0.28, p < 0.006) and (18)F fluoride PET-CT (r=-0.20, p<0.05). The sensitivity, specificity and accuracy of PET-CT in the detection of bone metastases in prostate cancer was 81%, 93% and 86% for (18)F fluoride, and 74% (p=0.12), 99% (p=0.01) and 85% for FCH, respectively. (18)F FCH PET-CT led to a change in the management in two out of 38 patients due to the early detection of bone marrow metastases. CONCLUSION: FCH PET-CT may be superior for the early detection (i.e. bone marrow involvement) of metastatic bone disease. In patients with FCH-negative suspicious sclerotic lesions, a second bone-seeking agent (e.g. (18)F fluoride) is recommended. (18)F fluoride PET-CT identified more lesions in some patients when compared with (18)F FCH PET-CT but did not change patient management. Furthermore, (18)F fluoride PET could be also negative in highly dense sclerotic lesions, which presumably reflects the effect of treatment. It will be important to clarify in future studies whether these lesions are clinically relevant when compared with metabolically active bone metastases.
Fluoride


**Fluorine-18 NaF PET imaging of child abuse.**

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We describe the use of 18F-NaF positron emission tomography (PET) whole-body imaging for the evaluation of skeletal trauma in a case of suspected child abuse. To our knowledge, 18F NaF PET has not been used in the past for the evaluation of child abuse. In our patient, this technique detected all sites of trauma shown by initial and follow-up skeletal surveys, including bilateral metaphyseal fractures of the proximal humeri. Fluorine-18 NaF PET has potential advantage over Tc-99m-labeled methylene diphosphonate (MDP) based upon superior image contrast and spatial resolution.

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**Skeletal PET with 18F-fluoride: applying new technology to an old tracer.**

**Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST.**

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Although (18)F-labeled NaF was the first widely used agent for skeletal scintigraphy, it quickly fell into disuse after the introduction of (99m)Tc-labeled bone-imaging agents. Recent comparative studies have demonstrated that (18)F-fluoride PET is more accurate than (99m)Tc-diphosphonate SPECT for identifying both malignant and benign lesions of the skeleton. Combining (18)F-fluoride PET with other imaging, such as CT, can improve the specificity and overall accuracy of skeletal (18)F-fluoride PET and probably will become the routine clinical practice for (18)F-fluoride PET. Although (18)F-labeled NaF and (99m)Tc-diphosphonate have a similar patient dosimetry, (18)F-fluoride PET offers shorter study times (typically less than 1 h), resulting in a more efficient workflow, improved patient convenience, and faster turnarounds of reports to the referring physicians. With the widespread availability of PET scanners and the improved logistics for the delivery of (18)F radiopharmaceuticals, prior limitations to the routine use of (18)F-fluoride bone imaging have largely been overcome. The favorable imaging performance and the clinical utility of (18)F-fluoride PET, compared with (99m)Tc-diphosphonate scintigraphy, support the reconsideration of (18)F-fluoride as a routine bone-imaging agent.

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**18F-Fluoride positron emission tomography and positron emission tomography/computed tomography.**

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(18)F-Fluoride is a positron-emitting bone-seeking agent, the uptake of which reflects blood flow and remodeling of bone. Assessment of (18)F-fluoride kinetics using quantitative positron emission tomography (PET) methods allows the regional characterization of lesions of metabolic bone diseases and the monitoring of their response to therapy. It also enables the assessment of bone viability and discrimination of uneventful and impaired healing processes of fractures, bone grafts and osteonecrosis. Taking advantage of the favorable pharmacokinetic properties of the tracer combined with the high performance of PET technology, static (18)F-fluoride PET is a highly sensitive imaging modality for detection of benign and malignant osseous abnormalities. Although (18)F-fluoride uptake mechanism corresponds to osteoblastic activity, it is also sensitive for detection of lytic and early marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal. The instant fusion of increased (18)F-fluoride uptake with morphological data of computed tomography (CT) using hybrid PET/CT systems improves the specificity of (18)F-fluoride PET in cancer patients by accurately differentiating between benign and malignant sites of uptake. The results of a few recent publications suggest that (18)F-fluoride PET/CT is a valuable modality in the diagnosis of pathological osseous conditions in patients also referred for nononcologic indications. (18)F-fluoride PET and PET/CT are, however, not widely used in clinical practice. The limited availability of (18)F-fluoride and of PET and PET/CT systems is a major factor. At present, there are not enough data on the cost-effectiveness of (18)F-fluoride PET/CT. However, it has been stated by some experts that (18)F-fluoride PET/CT is expected to replace (99m)Tc-MDP bone scintigraphy in the future.
Fluoride


Early experience with fluorine-18 sodium fluoride bone PET in young patients with back pain.

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PURPOSE: Skeletal positron emission tomography (PET) with fluorine-18 (18F) sodium fluoride (18F NaF) is an alternative to technetium-99m (99mTc)methylene diphosphonate (MDP) scintigraphy. Experience with pediatric PET is sparse, primarily in oncology. This study assesses the role of 18F NaF in evaluating young patients with back pain. METHODS: Ninety-four 18F NaF PET scans were performed in 94 patients (27 males, 67 females; mean age, 15 years; range, 4-26 years) with back pain. Three-dimensional PET acquisition was performed 30 minutes after administration of 18F NaF (2.1 MBq/kg; maximum, 148 MBq). Radiation doses are presented for 18F NaF and 99mTc MDP. RESULTS: 18F NaF PET revealed a possible cause of back pain in 55% (52/94). Fifteen patients had 2 or more potential sources of back pain. Diagnoses by PET were pars interarticularis/pedicle stress (34%), spinous process injury (16%), vertebral body ring apophyseal injury (14%), and sacroiliac joint inflammation/stress (3%). Comparing 18F NaF PET with 99mTc MDP scintigraphy, time between injection and scanning was shorter (0.5 hours vs 3 hours), radiation dosimetry was similar (3.5 mGy vs 2.8 mGy effective dose for a 55-kg patient for 18F NaF and 99mTc MDP, respectively), and cost of radiopharmaceutical was higher. CONCLUSIONS: 18F NaF bone PET can detect a variety of skeletal abnormalities in young patients with back pain. Relative to 99mTc MDP, images are of higher resolution. Total time from tracer administration to completion is shorter, and radiation dosimetry is similar. Higher cost for 18F NaF may be offset by enhanced patient throughput.


The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT.


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The aim of this study was to compare the detection of bone metastases by 99mTc-methylene diphosphonate (99mTc-MDP) planar bone scintigraphy (BS), SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT in patients with high-risk prostate cancer. METHODS: In a prospective study, BS and 18F-Fluoride PET/CT were performed on the same day in 44 patients with high-risk prostate cancer. In 20 of the latter patients planar BS was followed by single field-of-view (FOV) SPECT and in 24 patients by multi-FOV SPECT of the axial skeleton. Lesions were interpreted separately on each of the 4 modalities as normal, benign, equivocal, or malignant. RESULTS: In patient-based analysis, 23 patients had skeletal metastatic spread (52%) and 21 did not. Categorizing equivocal and malignant interpretation as suggestive for malignancy, the sensitivity, specificity, positive predictive value, and negative predictive value of planar BS were 70%, 57%, 64%, and 55%, respectively, of multi-FOV SPECT were 92%, 82%, 86%, and 90%, of (18)F-Fluoride PET were 100%, 62%, 74%, and 100%, and of 18F-Fluoride PET/CT were 100% for all parameters. Using the McNemar test, 18F-Fluoride PET/CT was statistically more sensitive and more specific than planar or SPECT BS (P < 0.05) and more specific than 18F-Fluoride PET (P < 0.001). SPECT was statistically more sensitive and more specific than planar BS (P < 0.05) but was less sensitive than 18F-Fluoride PET (P < 0.05). In lesion-based analysis, 156 lesions with increased uptake of 18F-Fluoride were assessed. Based on the corresponding appearance on CT, lesions were categorized by PET/CT as benign (n = 99), osteoblastic metastasis (n = 46), or equivocal when CT was normal (n = 11). Of the 156 18F-Fluoride lesions, 81 lesions (52%), including 34 metastases, were overlooked with normal appearance on planar BS. SPECT identified 62% of the lesions overlooked by planar BS. 18F-Fluoride PET/CT was more sensitive and more specific than BS (P < 0.001) and more specific than PET alone (P < 0.001). CONCLUSION: 18F-Fluoride PET/CT is a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer. It is more specific than 18F-Fluoride PET alone and more sensitive and specific than planar and SPECT BS. Detection of bone metastases is improved by SPECT compared with planar BS and by 18F-Fluoride PET compared with SPECT. This added value of 18F-Fluoride PET/CT may beneficially impact the clinical management of patients with high-risk prostate cancer.


Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET.


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Radionuclide bone scanning (RNB) is considered to be the most practical screening technique for assessing the entire skeleton for skeletal metastases. However, RNB has been shown to be of lower sensitivity than MRI and CT in detecting osteolytic metastases. A prospective study was designed to evaluate the accuracy of planar RNB versus tomographic bone imaging with 18F-labeled NaF and PET (18F PET) in detecting osteolytic and osteoblastic metastases and its dependency on their anatomic localization. METHODS: Forty-four patients with known prostate, lung or thyroid carcinoma were examined with both planar RNB and 18F PET. A panel of reference methods including MRI of the spine, 131I scintigraphy, conventional radiography and spiral CT was used as the gold standard. RNB and 18F PET were compared by a lesion-by-lesion analysis using a five-point score for receiver operating characteristic (ROC) curve analysis. RESULTS: 18F PET showed 96 metastases (67 of prostate carcinoma and 29 of lung or thyroid cancer), whereas RNB revealed 46 metastases (33 of prostate carcinoma and 13 of lung or thyroid cancer). All lesions found with RNB were also detected with 18F PET. Compared with 18F PET and the reference methods, RNB had a sensitivity of 82.8% in detecting malignant and benign osseous lesions in the skull, thorax and extremities and a sensitivity of 40% in the spine and pelvis. The area under the ROC curve was 0.99 for 18F PET and 0.64 for RNB. CONCLUSION: 18F PET is more sensitive than RNB in detecting osseous lesions. With RNB, sensitivity in detecting osseous metastases is highly dependent on anatomic localization of these lesions, whereas detection rates of osteoblastic and osteolytic metastases are similar. Higher detection rates and more accurate differentiation between benign and malignant lesions with 18F PET suggest the use of 18F PET when possible.


Assessment of malignant skeletal disease: initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET/CT.


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18F-fluoride PET/CT was performed on 44 oncologic patients to evaluate its diagnostic accuracy in assessing malignant osseous involvement and in differentiating malignant from benign bone lesions. METHODS: (18)F-fluoride PET and (18)F-fluoride PET/CT were interpreted separately. Lesions showing increased (18)F-fluoride uptake were categorized as malignant, benign, or inconclusive. The final diagnosis of lesions was based on histopathology, correlation with contemporaneous diagnostic CT or MRI, or clinical follow-up of at least 6 mo (mean, 10 +/- 3 mo). RESULTS: Increased (18)F-fluoride uptake was detected at 212 sites, including 111 malignant lesions, 89 benign lesions, and 12 lesions for which the final diagnosis could not be determined. In a lesion-based analysis, the sensitivity of PET alone in differentiating benign from malignant bone lesions was 72% when inconclusive lesions were considered false negative and 90% when inconclusive lesions were considered true positive. On PET/CT, 94 of 111 (85%) metastases presented as sites of increased uptake with corresponding lytic or sclerotic changes, and 16 of the 17 remaining metastases showed normal-appearing bone on CT, for an overall sensitivity of 99% for tumor detection. For only 1 metastasis was PET/CT misleading, suggesting the false diagnosis of a benign lesion. The specificity of PET/CT was significantly higher than that of PET alone (97% vs. 72%, P < 0.001). PET/CT identified benign abnormalities at the location exactly corresponding to the scintigraphic increased uptake for 85 of 89 (96%) benign lesions. In a patient-based analysis, the sensitivity of PET and PET/CT was 88% and 100%, respectively (P < 0.05) and the specificity was 56% and 88%, respectively (not statistically significant). Among the 12 patients referred for (18)F-fluoride assessment because of bone pain despite negative findings on (99m)Tc-methylene diphosphonate bone scintigraphy, (18)F-fluoride PET/CT suggested malignant bone involvement in all 4 patients with proven skeletal metastases, a potential benign cause in 4 of 7 patients who had no evidence of metastatic disease, and a soft-tissue tumor mass invading a sacral foramen in 1 patient. CONCLUSION: The results indicate that (18)F-fluoride PET/CT is both sensitive and specific for the detection of lytic and sclerotic malignant lesions. It accurately differentiated malignant from benign bone lesions and possibly assisted in identifying a potential cause for bone pain in oncologic patients. For most lesions, the anatomic data provided by the low-dose CT of the PET/CT study obviates the performance of full-dose diagnostic CT for correlation purposes.


[Positron-emission tomography of the skeletal system using 18FNa: the incidence, pattern of the findings and distribution of benign changes]

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PURPOSE: We evaluated the frequency, distribution and appearance of benign lesions in 18F-PET scans. METHODS: Between March 1996 and May 1997, 18F-PET scans were performed in 59 patients in addition to conventional planar bone scintigraphy. Eleven patients were subjected to additional SPECT imaging. The main indication was searching for bone metastases (58 pat.), The diagnosis was confirmed radiologically. RESULTS: With 18F-PET in 39 patients (66.1%) 152 benign lesions, mostly located in the spine were detected, 99mTc bone scans revealed 45 lesions in 10 patients. Osteoarthritis of the intervertebral articulations (69%) or of the acromioclavicular joint (15%) were the most common reasons for degenerative lesions detected with 18F-PET. Osteophytes appeared as hot lesions located at two adjacent vertebral endplates. Osteoarthritis of the intervertebral articulations showed an enhanced tracer uptake at these localizations, whereas endplate fractures of the vertebral bodies appeared very typical; solitary
Fractures of the ribs could not be differentiated from metastases. Rare benign lesions were not studied. CONCLUSION: Most of the degenerative lesions (84%) detected with 18F-PET had a very typical appearance and could be detected with the improved spatial resolution and advantages of a tomographic technique. 18F-PET had an increased accuracy in detecting degenerative bone lesions.
Flumazenil

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[18F]flumazenil binding to central benzodiazepine receptor studies by PET--quantitative analysis and comparisons with [11C]flumazenil.


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[(11)C]flumazenil is the reference radioligand for Positron Emission Tomography (PET) studies of central benzodiazepine (BZ) receptors. Fluorine is available in the flumazenil molecule and [(18)F]flumazenil has recently been prepared. The aim of the present PET-study in 8 male subjects was to examine the binding of [(18)F]flumazenil in the human brain by direct comparison with [(11)C]flumazenil. Each subject participated in two 93-minute PET-measurements with [(11)C]flumazenil and [(18)F]flumazenil, respectively. Data were analyzed using compartment models with metabolite-corrected arterial plasma input and reference tissue models using the pons as reference region. There was no evident difference between the kinetic behaviors of the two ligands. Overall, the noise in the time activity curves for [(18)F]flumazenil was lower at late time points, and the variance of the kinetic parameters was lower for [(11)C]flumazenil. In BZ receptor rich regions, such as the neocortex, the 3-compartment model was statistically favored, whereas the 2-compartment model was favored in the pons. Binding potential values obtained by the reference tissue models were in good agreement with those obtained by the kinetic analysis. There was no support for the presence of specific binding in the pons. In conclusion, the binding and the kinetic behavior of [(11)C]flumazenil and [(18)F]flumazenil were similar. The present analysis supports the use of pons as reference region in simplified protocols without arterial blood sampling. [(18)F]flumazenil should thus be an excellent choice for applied studies at centers not having a cyclotron.


Voxel- and ROI-based statistical analyses of PET parameters for guidance in the surgical treatment of intractable mesial temporal lobe epilepsy.


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OBJECTIVE: Positron emission tomography (PET) can be used to locate epileptic foci in patients with mesial temporal lobe epilepsy (MTLE) by measuring multiple parameters of the brain. We investigated a series of patients with MTLE using PET measurements of three parameters: the cerebral blood flow measured with [15 O] H2O, the uptake of [(18)F]fluorodeoxyglucose (FDG), an index of the cerebral metabolism rate of glucose, and the distribution volume (DV) of [11C] flumazenil (FMZ), an index of the binding potential of central benzodiazepine receptor. We compared predictive values obtained from two methods: a voxel-based statistical analysis using statistical parametric mapping (SPM) and an asymmetry index obtained by placing regions of interest (ROIs) on PET images.

METHODS: Preoperative PET data of 11 patients with surgically confirmed MTLE were retrospectively examined. In the voxel-based analysis, the PET data were analyzed using SPM99 by statistically comparing the voxel values of PET parameters between individual patients and the mean values of 12 normal volunteers. Voxel analyses were in good agreement with those obtained by the kinetic analysis. There was no support for the presence of specific binding in the pons. In conclusion, the binding and the kinetic behavior of [(11)C]flumazenil and [(18)F]flumazenil were similar. The present analysis supports the use of pons as reference region in simplified protocols without arterial blood sampling. [(18)F]flumazenil should thus be an excellent choice for applied studies at centers not having a cyclotron.


Radiosynthesis and biological evaluation of an 18F-labeled derivative of the novel pyrazolopyrimidine sedative-hypnotic agent indiplon.


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INTRODUCTION: Gamma amino butyric acid type A (GABA(A)) receptors are involved in a variety of neurological and psychiatric diseases, which have promoted the development and use of radiotracers for positron emission tomography imaging. Radiolabeled benzodiazepine antagonists such as flumazenil have most extensively been used for this purpose so far. Recently, the non-benzodiazepine pyrazolopyrimidine derivative indiplon with higher specificity for the alpha(1) subtype of the GABA(A) receptor has been introduced for treatment of insomnia. The aim of this study was the development and biological evaluation of an (18)F-labeled derivative of indiplon. METHODS: Both [(18)F]fluoro- indiplon and its labeling precursor were synthesized by two-step procedures starting from indiplon. The radiosynthesis of [(18)F]fluoro-indiplon was performed using the bromoacetyl precursor followed by multiple-stage purification using semipreparative HPLC and solid phase extraction. Stability, partition coefficients, binding affinities and regional brain binding were determined in vitro. Biodistribution and radiotracer metabolism were studied in...
Flumazenil

vivo. RESULTS: [(18)F]Fluoro-indiplon was readily accessible in good yields (38-43%), with high purity and high specific radioactivity (>150 GBq/micromol). It displays high in vitro stability and moderate lipophilicity. [(18)F]Fluoro-indiplon has an affinity to GABA(A) receptors comparable to indiplon (K(i)=8.0 nM vs. 3.4 nM). In vitro autoradiography indicates high [(18)F]fluoro-indiplon binding in regions with high densities of GABA(A) receptors. However, ex vivo autoradiography and organ distribution studies show no evidence of specific binding of [(18)F]fluoro-indiplon. Furthermore, the radiotracer is rapidly metabolized with high accumulation of labeled metabolites in the brain. CONCLUSIONS: Although [(18)F]fluoro-indiplon shows good in vitro features, it is not suitable for in vivo imaging studies because of its metabolism. Structural modifications are needed to develop derivatives with higher in vivo stability.


Biological properties of 2’-[18F]fluoroflumazenil for central benzodiazepine receptor imaging.

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A novel positron emitting agent, 2’-[18F]fluoroflumazenil (fluoroethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4H-benzo-[f]imidazo[1,5-a][1,4]diazepine-3-carboxylate, FFMZ), has been reported for benzodiazepine imaging. In the present study, biological properties of [18F]FFMZ were investigated. Stability tests of [18F]FFMZ in human and rat sera were performed. Biodistribution was investigated in mice and phosphorimages of brains were obtained from rats. A receptor binding assay was performed using rat brain (mixture of cortex and cerebellum) homogenate. A static positron emission tomography (PET) image was obtained from a normal human volunteer. Although [18F]FFMZ was stable in human serum, it was rapidly hydrolyzed in rat serum. The hydrolysis was 39%, 63% and 92% at 10, 30 and 60 min, respectively. According to the biodistribution study in mice, somewhat even distribution (between 2 approximately 3% ID/g) was observed in most organs. Intestinal uptake increased up to 6% ID/g at 1 h due to biliary excretion. Bone uptake slowly increased from 1.5% to 3.5% ID/g at 1 h. High uptakes in the cortex, thalamus and cerebellum, which could be completely blocked by coinjection of cold FMZ, were observed by phosphorimaging study using rats. Determination of Kd value and Bmax using rat brain tissue was performed by Scatchard plotting and found 1.45±0.26 nM and 1.08±0.03 pmol/mg protein, respectively. The PET image of the normal human volunteer showed high uptake in the following decreasing order: frontal cortex, temporal cortex, occipital cortex, cerebellum, parietal cortex and thalamus. In conclusion, the new FMZ derivative, [18F]FFMZ appears to be a promising PET agent for central benzodiazepine receptor imaging with a convenient labeling procedure and a specific binding property.


Assessment of regional GABA(A) receptor binding using 18F-fluoroflumazenil positron emission tomography in spastic type cerebral palsy.


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Periventricular leukomalacia (PVL) due to hypoxic-ischemic insult to the immature brain, chorioamnionitis and maternal infection are the major etiological factors of spastic type cerebral palsy (CP). Despite advances in preventing and treating certain causes of CP, the number of patients has remained essentially unchanged and the pathophysiological mechanisms related to motor dysfunction remain poorly understood. In this study, statistical parametric mapping (SPM) analysis of cerebral gamma-aminobutyric acid (GABA) receptor PET imaging using [18F]-fluoroflumazenil showed increased GABA(A) receptor binding in the bilateral motor and visual cortices in spastic diplegia (SD) type CP patients (n = 20) compared with normal controls (n = 10). As GABA(A) receptor signaling modulates biological perception and production of movement, complex motor skills and use-dependent plasticity in the motor cortex, increased GABA(A) receptor binding in the motor cortex might play a important role in poor motor control. Decreased GABA(A) receptor binding was seen in the brain stem in SD CP patients, which appears to be related to spastic symptom.


Preparation of highly specific radioactivity [18F]flumazenil and its evaluation in cynomolgus monkey by positron emission tomography.

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A straightforward method for the preparation of no-carrier-added (n.c.a.) [18F]flumazenil via standard nucleophilic radiofluorination of the corresponding nitro-analog Ro 15-2344 has been developed. The labeling was performed by employing the K18F/kryptofix complex in DMF at 160 degrees C for 30 min and equimolar ratio [K/K2.2.2]+18F-/precursor. Under these conditions, an 18F incorporation rate into flumazenil was in the range of 55-60%. The final product was isolated by HPLC purification within a total synthesis time of 75 min and a radiochemical yield of about 30% (EOB). Human post-mortem whole-hemisphere autoradiography of brain sections demonstrated selective uptake of the radioligand in the areas of high density of the central benzodiazepine receptors (BZR). PET studies in a cynomolgus monkey and metabolite studies by HPLC demonstrated similar results by [18F]flumazenil as for [11C]flumazenil. In blocking experiments, almost all radioactivity was inhibited by the addition of unlabeled flumazenil. [18F]Flumazenil is a suitable radioligand for PET assessment of the BZR.