IASON Literature Service
PET-Specialtracer

FDG-Neurology
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PET-[^{18}F] FDOPA
PET-[^{18}F] Flurocholine
PET-[^{18}F] FET
PET-[^{18}F]-NaF
PET-[^{18}F]-FLT
PET-[^{18}F]-FMISO
PET-[^{18}F]-FES
PET-[^{18}F]-Fallypride
PET-[^{18}F]-Mefway
PET-[^{68}Ga]^{68}Ga-PSMA-HBED
PET-[^{68}Ga]^{68}Ga-DOTA-Peptides

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Growing applications of FDG PET-CT imaging in non-oncologic conditions.

Zhuang H, Codreanu I.

Abstract
As the number of clinical applications of 2-[18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET-CT) grows, familiarity with the conditions that can be diagnosed by this modality and when relevant pieces of additional information can be obtained becomes increasingly important for both requesting physicians and nuclear medicine physicians or radiologists who interpret the findings.

Apart from its heavy use in clinical oncology, FDG PET-CT is widely used in a variety of non-oncologic conditions interconnecting to such disciplines as general internal medicine, infectious diseases, cardiology, neurology, surgery, traumatology, orthopedics, pediatrics, endocrinology, rheumatology, psychiatry, neuropsychology, and cognitive neuroscience.

The aim of this review was to summarize the current evidence of FDG PET-CT applications in evaluating non-oncologic pathologies and the relevant information it can add to achieve a final diagnosis.


Noninvasive quantification of cerebral metabolic rate for glucose in rats using 18F-FDG PET and standard input function.


Abstract
Measurement of arterial input function (AIF) for quantitative positron emission tomography (PET) studies is technically challenging. The present study aimed to develop a method based on a standard arterial input function (SIF) to estimate input function without blood sampling.

We performed 18F-fluorodeoxyglucose studies accompanied by continuous blood sampling for measurement of AIF in 11 rats. Standard arterial input function was calculated by averaging AIFs from eight anesthetized rats, after normalization with body mass (BM) and injected dose (ID). Then, the individual input function was estimated using two types of SIF: (1) SIF calibrated by the individual's BM and ID (estimated individual input function, EIFNS) and (2) SIF calibrated by a single blood sampling as proposed previously (EIF1S).

No significant differences in area under the curve (AUC) or cerebral metabolic rate for glucose (CMRGlc) were found across the AIF-, EIFNS-, and EIF1S-based methods using repeated measures analysis of variance. In the correlation analysis, AUC or CMRGlc derived from EIFNS was highly correlated with those derived from AIF and EIF1S. Preliminary comparison between AIF and EIFNS in three awake rats supported an idea that the method might be applicable to behaving animals.

The present study suggests that EIFNS method might serve as a noninvasive substitute for individual AIF measurement.

PREVALENCE AND PROGNOSIS OF PRODROMAL ALZHEIMER’S DISEASE AS ASSESSED BY MAGNETIC RESONANCE IMAGING AND 18F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY IN A COMMUNITY: REANALYSIS FROM THE OSAKI-TAJIRI PROJECT.

Meguro K, Akanuma K, Meguro M, Yamaguchi S, Ishii H, Tashiro M.

Abstract

Background: Dubois et al. proposed the criteria for prodromal Alzheimer's disease (AD) to detect dementia in its very early stage. Because detection requires magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography (PET), the prevalence and prognosis have not been fully investigated.

Methods: Our database included 346 healthy participants (Clinical Dementia Rating (CDR) 0), 119 with questionable dementia (CDR 0.5), and 32 dementia participants (CDR 1+) and was applied to investigate the prevalence of prodromal AD. Forty-four CDR 0.5 participants (37%) were randomly selected to undergo 18 F-fluorodeoxyglucose-PET. The same percentage was applied to select 128 CDR 0 and 12 CDR 1+ participants (total: n = 184) to calculate the prevalence. A neuroradiologist classified the PET images in a blinded manner based on the criteria of Silverman et al. Participants were considered to have prodromal AD if they exhibited 'parietal/temporal +/- frontal hypometabolism' (PET) with hippocampal atrophy (magnetic resonance imaging).

Results: Eighteen CDR 0.5 participants (40.9%) met the criteria for prodromal AD, which was a prevalence rate of 9.8% among older adults aged ≥65 years. Thirteen prodromal AD participants (72%) converted to AD during the 5-year follow-up period.

Discussion: The concept and criteria for prodromal AD are useful for predicting which subjects in a community will convert to AD.


Monitoring the Effect of Immunotherapy in Autoimmune Limbic Encephalitis Using 18F-FDG PET.

Trevino-Peinado C, Arbizu J, Irinia P, Riverol M, Martinez-Vila E.

Abstract

A 70-year-old woman with a history of autoimmune hepatitis and renal cell carcinoma presented with subacute cognitive impairment. A brain MRI revealed mild leukoaraiosis, whereas brain F-FDG PET/CT showed diffuse cerebral hypometabolism that resembled some of the patterns described in limbic encephalitis and neurodegenerative diseases.

With the suspicion of autoimmune encephalitis, the patient received immunotherapy with dramatic improvement of cognitive function and metabolic normalization at the 2-month follow-up on brain 18F-FDG PET/CT. Our results demonstrate that brain F-FDG PET/CT might be a useful tool in the assessment of patients with autoimmune encephalitis.

FDG-PET FINDINGS IN THREE CASES OF MILLS’ SYNDROME.

Van Laere K, Wilms G, Van Damme P.

Primary lateral sclerosis (PLS) is a rare subtype of motor neuron disease that exclusively affects upper motor neurons, usually beginning in the lower limbs and, less frequently in the bulbar region or the upper limbs. In contrast to amyotrophic lateral sclerosis (ALS), PLS typically has a symmetrical presentation and this characteristic was part of the initially proposed PLS criteria.

We report 18-fluorodeoxyglucose-positron-emission tomography (FDG-PET) findings in three cases with an asymmetrical subtype of PLS, more commonly known as Mills’ syndrome. There is no universally accepted definition of Mills’ syndrome, but it is mostly referred to as a slowly progressive motor syndrome with unilateral or asymmetrical pyramidal signs. In this syndrome, the disease process remains more or less restricted to the motor areas contralateral to the affected side, as suggested by a study visualising microglial activation using 11C-(R)-PK11195 PET.

Three female patients presented with an asymmetrical form of pure upper motor neuron dysfunction, starting in the right arm (patient 1 and 2) and the right leg (patient 3). The asymmetrical presentation correlated with clear regions of hypometabolism on FDG-PET in the contralateral Rolandic and peri-Rolandic areas, as can be seen in ALS or PLS6–8.

MRI of the brain was unrevealing in all three patients. Extensive investigations did not reveal other underlying pathologies. Mutations in C9orf72, SOD1, FUS and TARDBP were excluded in all three patients. There was a concordance in limb dominance and site of onset, as all three patients were right handed.

No clinical or electrodiagnostic signs of lower motor neuron involvement were noted up to 8 (patient 1), 4 (patient 2) and 2 years (patient 3) after disease onset. Over this period of time, the disease spread from the right arm to the right leg and, to a lesser degree, to the contralateral side (patient 1), remained restricted to the right arm (patient 2) and spread from the right leg to the right arm (patient 3). This suggests a disease propagation by contiguous spread, as opposed to a network-spreading pattern through the corpus callosum in typical PLS.


Imaging of autoimmune encephalitis - Relevance for clinical practice and hippocampal function.

Heine J, Prüss H, Bartsch T, Ploner CJ, Paul F, Finke C.

Abstract

The field of autoimmune encephalitides associated with antibodies targeting cell-surface antigens is rapidly expanding and new antibodies are discovered frequently. Typical clinical presentations include cognitive deficits, psychiatric symptoms, movement disorders and seizures and the majority of patients respond well to immunotherapy. Pathophysiological mechanisms and clinical features are increasingly recognized and indicate hippocampal dysfunction in most of these syndromes.

Here, we review the neuroimaging characteristics of autoimmune encephalitides, including N-methyl-d-aspartate (NMDA) receptor, leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) encephalitis as well as more recently discovered and less frequent forms such as dipeptidyl-peptidase-like protein 6 (DPPX) or glycine receptor encephalitis. We summarize findings of routine magnetic resonance imaging (MRI) investigations as well as 18F-fluoro-2-deoxy-d-glucose (FDG)-positron emission tomography (PET) and single photon emission tomography (SPECT) imaging and relate these observations to clinical features and disease outcome.
We furthermore review results of advanced imaging analyses such as diffusion tensor imaging, volumetric analyses and resting-state functional MRI. Finally, we discuss contributions of these neuroimaging observations to the understanding of the pathophysiology of autoimmune encephalitides.


[Recommendations for the use of PET imaging biomarkers in the diagnosis of neurodegenerative conditions associated with dementia: SEMNIM and SEN consensus].

[Article in Spanish]


Abstract
The new diagnostic criteria for Alzheimer's disease (AD) acknowledges the interest given to biomarkers to improve the specificity in subjects with dementia and to facilitate an early diagnosis of the pathophysiological process of AD in the prodromal or pre-dementia stage.

The current availability of PET imaging biomarkers of synaptic dysfunction (PET-FDG) and beta amyloid deposition using amyloid-PET provides clinicians with the opportunity to apply the new criteria and improve diagnostic accuracy in their clinical practice.

Therefore, it seems essential for the scientific societies involved to use the new clinical diagnostic support tools to establish clear, evidence-based and agreed set of recommendations for their appropriate use.

The present work includes a systematic review of the literature on the utility of FDG-PET and amyloid-PET for the diagnosis of AD and related neurodegenerative diseases that occur with dementia. Thus, we propose a series of recommendations agreed on by the Spanish Society of Nuclear Medicine and Spanish Society of Neurology as a consensus statement on the appropriate use of PET imaging biomarkers.


METABOLIC ACTIVITY OF RED NUCLEUS AND ITS CORRELATION WITH CEREBRAL CORTEX AND CEREBELLMUM - A STUDY USING A HIGH-RESOLUTION SEMICONDUCTOR PET SYSTEM.


Abstract
The red nucleus (RN) is a pair of small gray matter structures located in the midbrain and involved in muscle movement and cognitive functions. This retrospective study aimed to investigate the metabolism of human RN and its correlation to other brain regions.

Methods: We developed a high-resolution semiconductor PET system to image small brain structures. Twenty patients without neurological disorders underwent whole brain scanning after injection of 400 MBq F-18 fluorodeoxyglucose (FDG). The individual brain 18F-FDG-PET images were spatially normalized to generate a surface projection map using a 3-dimensional stereotactic surface projection (3D-SSP) technique. The correlation between the RN and each voxel on the cerebral and cerebellar cortices was estimated with Pearson's product-moment correlation analysis.
**Results:** Both right and left RNs were visualized with higher uptake than that in the background midbrain. The maximum standardized uptake value (SU.Vmax) values of RN were 7.64±1.92; these were higher than the values for the dentate nucleus but lower than those for the caudate nucleus, putamen, and thalamus. The voxel-by-voxel analysis demonstrated that the right RN was correlated more with ipsilateral association cortices than contralateral cortices, whereas the left RN was equally correlated with ipsilateral and contralateral cortices. The left RN showed a stronger correlation with the motor cortices and cerebellum than the right RN did.

**Conclusion:** Although non-specific background activity around RNs might have influenced the correlation patterns, these metabolic relationships suggested that RN cooperates with association cortices and limbic areas to conduct higher brain functions.


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**Classification of Parkinsonian syndromes from FDG-PET brain data using decision trees with SSM/PCA features.**

Mudali D, Teune LK, Renken RJ, Leenders KL, Roerdink JB.

**Abstract**

Medical imaging techniques like fluorodeoxyglucose positron emission tomography (FDG-PET) have been used to aid in the differential diagnosis of neurodegenerative brain diseases. In this study, the objective is to classify FDG-PET brain scans of subjects with Parkinsonian syndromes (Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy) compared to healthy controls.

The scaled subprofile model/principal component analysis (SSM/PCA) method was applied to FDG-PET brain image data to obtain covariance patterns and corresponding subject scores. The latter were used as features for supervised classification by the C4.5 decision tree method.

Leave-one-out cross validation was applied to determine classifier performance. We carried out a comparison with other types of classifiers. The big advantage of decision tree classification is that the results are easy to understand by humans.

A visual representation of decision trees strongly supports the interpretation process, which is very important in the context of medical diagnosis. Further improvements are suggested based on enlarging the number of the training data, enhancing the decision tree method by bagging, and adding additional features based on (f)MRI data.


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**Short-Term Practice Effects and Brain Hypometabolism: Preliminary Data from an FDG PET Study.**

Duff K, Horn KP, Foster NL, Hoffman JM.

**Abstract**

Practice effects are improvements in cognitive test scores due to repeated exposure to the same tests. Typically viewed as error, short-term practice effects have been shown to provide valuable clinical information about diagnosis, prognosis, and treatment outcomes in older patients with mild cognitive impairments.

This study examined short-term practice effects across one week and brain hypometabolism on fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) in 25 older adults (15 intact, 10 Mild Cognitive Impairment). Averaged cerebral brain metabolism on FDG PET was correlated with multiple cognitive scores at baseline in those with Mild Cognitive Impairment, and short-term practice effects accounted for additional variance in these same subjects.
The relationship between brain metabolism and cognition (either at baseline or practice effects) was minimal in the intact individuals. Although needing replication in larger samples, short-term practice effects on tests of executive functioning and memory may provide valuable information about biomarkers of Alzheimer's disease.


Amyloid and FDG-PET study of logopenic primary progressive aphasia: evidence for the existence of two subtypes.


Abstract
The logopenic variant of primary progressive aphasia (lvPPA) has been associated with Alzheimer disease, although this relationship is still subject to debate. The purpose of this study is to determine the frequency of amyloid biomarkers in patients with lvPPA, and record any potential clinical or topographic differences between patients with and without amyloid deposits.

We conducted cognitive examination and positron-emission tomography studies with fluorodeoxyglucose ((18)F) and florbetapir ((18)F) in a cohort of 16 patients diagnosed with lvPPA. We evaluated the prevalence of amyloid deposits as well as any clinical and metabolic differences between the groups with and without significant presence of amyloid deposits.

Eleven patients (69 %) were considered amyloid-positive. The amyloid-positive group displayed less metabolic activity in the left temporoparietal region than the control group, while the amyloid-negative group showed lower metabolism in the left temporoparietal region extending to the anterior temporal and basal frontal regions.

The percentage of change in patients with clinical and FDG-PET follow-up did not differ between the amyloid-positive and amyloid-negative subgroups. The frequency of amyloid-positive cases confirms that lvPPA is frequently associated with Alzheimer disease. Amyloid-negative patients show a different cerebral metabolic pattern. These findings show the relevance of using amyloid PET to study lvPPA, and also suggest that the logopenic variant may not be specific to Alzheimer disease in certain cases.


Clinical, FDG and amyloid PET imaging in posterior cortical atrophy.

Singh TD¹, Josephs KA, Machulda MM, Drubach DA, Apostolova LG, Lowe VJ, Whitwell JL.

Abstract
The purpose of this study was to identify the clinical, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) and amyloid-PET findings in a large cohort of posterior cortical atrophy (PCA) patients, to examine the neural correlates of the classic features of PCA, and to better understand the features associated with early PCA. We prospectively recruited 25 patients who presented to the Mayo Clinic between March 2013 and August 2014 and met diagnostic criteria for PCA. All patients underwent a standardized set of tests and amyloid imaging with [(11)C] Pittsburg compound B (PiB). Seventeen (68 %) underwent FDG-PET scanning.

We divided the cohort at the median disease duration of 4 years in order to assess clinical and FDG-PET correlates of early PCA (n = 13). The most common clinical features were simultanagnosia (92 %), dysgraphia (68 %), poly-mini-myoclonus (64 %) and oculomotor apraxia (56.5 %). On FDG-PET, hypometabolism was observed bilaterally in the lateral and medial parietal and occipital lobes.
Simultanagnosia was associated with hypometabolism in the right occipital lobe and posterior cingulum, optic ataxia with hypometabolism in left occipital lobe, and oculomotor apraxia with hypometabolism in the left parietal lobe and posterior cingulate gyrus.

All 25 PCA patients were amyloid positive. Simultanagnosia was the only feature present in 85% of early PCA patients. The syndrome of PCA is associated with posterior hemisphere hypometabolism and with amyloid deposition. Many of the classic features of PCA show associated focal, but not widespread, areas of involvement of these posterior hemispheric regions. Simultanagnosia appears to be the most common and hence sensitive feature of early PCA.


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**NEUROPSYCHOLOGICAL TESTING PREDICTS CEREBROSPINAL FLUID AMYLOID-B IN MILD COGNITIVE IMPAIRMENT.**

**Kandel BM, Avants BB, Gee JC, Arnold SE, Wolk DA.**

**Abstract**

**Background:** Psychometric tests predict conversion of mild cognitive impairment (MCI) to probable Alzheimer's disease (AD). Because the definition of clinical AD relies on those same psychometric tests, the ability of these tests to identify underlying AD pathology remains unclear.

**Objective:** To determine the degree to which psychometric testing predicts molecular evidence of AD amyloid pathology, as indicated by cerebrospinal fluid (CSF) amyloid-β (Aβ)1-42, in patients with MCI, as compared to neuroimaging biomarkers.

**Methods:** We identified 408 MCI subjects with CSF Aβ levels, psychometric test data, FDG-PET scans, and acceptable volumetric MR scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We used psychometric tests and imaging biomarkers in univariate and multivariate models to predict Aβ status.

**Results:** The 30-min delayed recall score of the Rey Auditory Verbal Learning Test was the best predictor of Aβ status among the psychometric tests, achieving an AUC of 0.67 ± 0.02 and odds ratio of 2.5 ± 0.4. FDG-PET was the best imaging-based biomarker (AUC 0.67 ± 0.03, OR 3.2 ± 1.2), followed by hippocampal volume (AUC 0.64 ± 0.02, OR 2.4 ± 0.3). A multivariate analysis based on the psychometric tests improved on the univariate predictors, achieving an AUC of 0.68 ± 0.03 (OR 3.38 ± 1.2). Adding imaging biomarkers to the multivariate analysis did not improve the AUC.

**Conclusion:** Psychometric tests perform as well as imaging biomarkers to predict presence of molecular markers of AD pathology in MCI patients and should be considered in the determination of the likelihood that MCI is due to AD.


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**Plaque Inflammation Imaging in Severe Carotid Stenosis and Recurrent Cerebral Ischemia.**

**Sharma VK, Paliwal PR, Sinha AK.**

**Abstract**

Strong relationship exists between the severity of carotid stenosis and early stroke-risk. Inflammation is believed to be an important event for atherosclerotic plaque destabilisation and subsequent thrombo-embolism. 18F-Fluoro-deoxyglucose Positron Emission Tomography (18F-FDG) can image...
Atherosclerotic inflammation, providing information about plaque biology, which may serve as a useful biomarker for the assessment of early stroke-risk.


J Alzheimers Dis. 2015 Apr 2. [Epub ahead of print]

EFFECTS OF AEROBIC TRAINING ON COGNITION AND BRAIN GLUCOSE METABOLISM IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT.


Abstract

Background: Aerobic training (AT) is a promising intervention for mild cognitive impairment (MCI).

Objective: To evaluate the effects of AT on cognition and regional brain glucose metabolism (rBGM) in MCI patients.

Methods: Subjects performed a twice-a-week, moderate intensity, AT program for 24 weeks. Assessment with ADAS-cog, a comprehensive neuropsychological battery, and evaluation of rBGM with positron emission tomography with 18F-fluorodeoxyglucose ([18F]FDG-PET) were performed before and after the intervention. Aerobic capacity was compared using the maximal oxygen consumption VO2max (mL/Kg/min). [18F]FDG-PET data were analyzed on a voxel-by-voxel basis with SPM8 software.

Results: Forty subjects were included, with a mean (M) age of 70.3 (5.4) years and an initial Mini-Mental State Exam score of 27.4 (1.7). Comparisons using paired t-tests revealed improvements in the ADAS-cog (M difference: -2.7 (3.7), p < 0.001) and VO2max scores (M difference: 1.8 (2.0) mL/kg/min, p < 0.001). Brain metabolic analysis revealed a bilateral decrease in the rBGM of the dorsal anterior cingulate cortex, pFWE = 0.04. This rBGM decrease was negatively correlated with improvement in a visuospatial function/attentional test (rho = -0.31, p = 0.04). Several other brain areas also showed increases or decreases in rBGM. Of note, there was an increase in the retrosplenial cortex, an important node of the default mode network, that was negatively correlated with the metabolic decrease in the dorsal anterior cingulate cortex (r = -0.51, p = 0.001).

Conclusion: AT improved cognition and changed rBGM in areas related to cognition in subjects with MCI.


Binding in working memory and frontal lobe in normal aging: is there any similarity with autism?


Abstract

Some studies highlight similarities between Autism Spectrum Disorder (ASD) and healthy aging. Indeed, the decline in older individuals’ ability to create a unified representation of the individual features of an event is thought to arise from a disruption of binding within the episodic buffer of working memory (WM) as the same way as observed in ASD. In both cases, this deficit may result from an abnormal engagement of a frontohippocampal network.

The objective of the present study is to identify both cognitive processes and neural substrates associated with the deficit of binding in WM in healthy aging. We studied the capacity of binding and the cognitive processes that might subvert its decline in 72 healthy participants aged 18-84 years.
We examined the behavioral data in relation to the changes in brain metabolism associated with the age-related decline in a subgroup of 34 healthy participants aged 20-77 years using the resting-state $^{18}$F fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET).

Forward stepwise regression analyses showed that the age-related decline in binding was partially explained by a decline in inhibition and processing speed. PET correlation analyses indicated that metabolism of the frontal regions, anterior and middle cingulate cortices is implicated in this phenomenon. These data suggest that executive functions and processing speed may play a crucial role in the capacity to integrate unified representations in memory in aging. Possible implications are discussed in ASD.


Functional neuroimaging findings in patients with lateral and mesio-lateral temporal lobe epilepsy; FDG-PET and ictal SPECT studies.

Joo EY, Seo DW, Hong SC, Hong SB.

Abstract
The differentiation of combined mesial and lateral temporal onset of seizures (mesio-lateral TLE, MLTLE) from lateral TLE (LTLE) is critical to achieve good surgical outcomes. However, the functional neuroimaging features in LTLE patients based on the ictal onset zone utilizing intracranial EEG (iEEG) in a large series have not been investigated.

We enrolled patients diagnosed with MLTLE (n = 35) and LTLE (n = 53) based on the site of ictal onset zone from iEEG monitoring. MLTLE is defined when ictal discharges originate from the mesial and lateral temporal cortices independently, whereas seizures of LTLE arise exclusively from the lateral temporal cortex. Compared to patients with LTLE, patients with MLTLE were more likely to have $^{18}$F- fluorodeoxyglucose positron emission tomography (FDG-PET) hypometabolism and hyperperfusion on ictal single-photon emission computed tomography (SPECT) restricted to the temporal areas. MLTLE patients had more frequent aura or secondarily generalized seizures than LTLE patients.

No significant differences were found in scalp EEG, MRI, and Wada asymmetry between groups. The overall seizure-free rate was good (73.8 %, mean follow-up = 9.7 years), which was not different (Engel class I, 74.3 % in MLTLE vs. 73.6 % in LTLE).

Post-surgical memory function was spared in LTLE patients, while visual memory was impaired in MLTLE patients when their mesial temporal structures were sufficiently resected. It suggests that functional neuroimaging (interictal PET and ictal and interictal SPECT) may play a crucial role to differentiate between MLTLE and LTLE.


COMPLETE REMISSION OF CRITICAL NEUROHISTIOCYTOSIS BY VEMURAFENIB.

Euskirchen P, Haroche J, Emile JF, Buchert R, Vandersee S, Meisel A.

Abstract
Objective: To describe a patient with life-threatening brainstem neurohistiocytosis who recovered completely upon targeted treatment with the V600E mutation-specific BRAF inhibitor vemurafenib.

Methods: We report clinical, histologic, genetic, and sequential imaging findings, including fluorodeoxyglucose (FDG)-PET, over a follow-up period of 11 months.
Results: The patient presented with central hyperventilation, skeletal and perirenal Erdheim-Chester disease, and cutaneous Langerhans cell histiocytosis. A BRAF V600E hotspot mutation was detected in all afflicted tissues. Therapy with vemurafenib led to complete and stable clinical remission of CNS lesions and systemic disease that could be demonstrated by brain MRI and whole-body FDG-PET.

Conclusions: Neurologic involvement in Erdheim-Chester disease usually confers a poor prognosis. In this patient, vemurafenib was well-tolerated and highly efficacious for severe brainstem involvement in Erdheim-Chester disease with overlapping Langerhans cell histiocytosis. This case illustrates the heterogeneous phenotypic spectrum of neurohistiocytosis and underscores the importance of genetic testing.


THE SEMANTIC VARIANT OF PRIMARY PROGRESSIVE APHASIA: CLINICAL AND NEUROIMAGING EVIDENCE IN SINGLE SUBJECTS.

Iaccarino L, Crespi C, Della Rosa PA, Catricalà E, Guidi L, Marcone A, Tagliavini F, Magnani G, Cappa SF, Perani D.

Abstract

Background/aim: We present a clinical-neuroimaging study in a series of patients with a clinical diagnosis of semantic variant of primary progressive aphasia (svPPA), with the aim to provide clinical-functional correlations of the cognitive and behavioral manifestations at the single-subject level.

Methods: We performed neuropsychological investigations, 18F-FDG-PET single-subject and group analysis, with an optimized SPM voxel-based approach, and correlation analyses. A measurement of white matter integrity by means of diffusion tensor imaging (DTI) was also available for a subgroup of patients.

Results: Cognitive assessment confirmed the presence of typical semantic memory deficits in all patients, with a relative sparing of executive, attentional, visuo-constructional, and episodic memory domains. 18F-FDG-PET showed a consistent pattern of cerebral hypometabolism across all patients, which correlated with performance in semantic memory tasks. In addition, a majority of patients also presented with behavioral disturbances associated with metabolic dysfunction in limbic structures. In a subgroup of cases the DTI analysis showed FA abnormalities in the inferior longitudinal and uncinate fasciculi.

Discussion: Each svPPA individual had functional derangement involving an extended, connected system within the left temporal lobe, a crucial part of the verbal semantic network, as well as an involvement of limbic structures. The latter was associated with behavioral manifestations and extended beyond the area of atrophy shown by CT scan.

Conclusion: Single-subject 18F-FDG-PET analysis can account for both cognitive and behavioral alterations in svPPA. This provides useful support to the clinical diagnosis.

PREDICTING AMYLOID STATUS IN CORTICOBASAL SYNDROME USING MODIFIED CLINICAL CRITERIA, MAGNETIC RESONANCE IMAGING AND FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY.


Abstract

Introduction: Group comparisons demonstrate greater visuospatial and memory deficits and temporoparietal-predominant degeneration on neuroimaging in patients with corticobasal syndrome (CBS) found to have Alzheimer's disease (AD) pathology versus those with underlying frontotemporal lobe degeneration (FTLD). The value of these features in predicting underlying AD pathology in individual patients is unknown. The goal of this study is to evaluate the utility of modified clinical criteria and visual interpretations of magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) for predicting amyloid deposition (as a surrogate of Alzheimer's disease neuropathology) in patients presenting with CBS.

Methods: In total, 25 patients meeting CBS core criteria underwent amyloid (Pittsburgh compound B; PIB) PET scans. Clinical records, MRI, and FDG scans were reviewed blinded to PIB results. Modified clinical criteria were used to classify CBS patients as temporoparietal variant CBS (tpvCBS) or frontal variant CBS (fvCBS). MRI and FDG-PET were classified based on the predominant atrophy/hypometabolism pattern (frontal or temporoparietal).

Results: A total of 9 out of 13 patients classified as tpvCBS were PIB+, compared to 2 out of 12 patients classified as fvCBS (P < 0.01, sensitivity 82%, specificity 71% for PIB+ status). Visual MRI reads had 73% sensitivity and 46% specificity for PIB+ status with moderate intra-rater reliability (Cohen's kappa = 0.42). Visual FDG reads had higher sensitivity (91%) for PIB+ status with perfect intra-rater reliability (kappa = 1.00), though specificity was low (50%). PIB results were confirmed in all 8 patients with available histopathology (3 PIB+ with confirmed AD, 5 PIB- with FTLD).

Conclusions: Splitting CBS patients into frontal or temporoparietal clinical variants can help predict the likelihood of underlying AD, but criteria require further refinement. Temporoparietal-predominant neuroimaging patterns are sensitive but not specific for AD.


The relationship between neuropsychological functioning and FDG-PET hypometabolism in intractable mesial temporal lobe epilepsy.


Abstract

We examined the relationship between baseline neuropsychological functioning and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in intractable mesial temporal lobe epilepsy (MTLE). We hypothesized relationships between dominant temporal lobe hypometabolism and verbal memory and between nondominant temporal lobe hypometabolism and nonverbal memory in line with the lateralized material-specific model of memory deficits in MTLE. We also hypothesized an association between performance on frontal lobe neuropsychological tests and prefrontal hypometabolism.

Thirty-two patients who had undergone temporal lobectomy for treatment of MTLE and who completed both presurgical FDG-PET and comprehensive neuropsychological investigations with widely used standardized measures were included. Age-adjusted composite measures were calculated for verbal memory, nonverbal memory, relative material-specific memory, IQ, executive function, attention/working memory, and psychomotor speed. Fluorodeoxyglucose positron emission
tomography was analyzed with statistical parametric mapping (SPM) to identify hypometabolism relative to healthy controls. Pearson's correlation was used to determine the relationship between regions of hypometabolism and neuropsychological functioning.

Dominant temporal lobe hypometabolism was associated with relatively inferior verbal memory, while nondominant temporal lobe hypometabolism was associated with inferior nonverbal memory. No relationship was found between performance on any frontal lobe measures and prefrontal hypometabolism. Statistical parametric mapping-quantified lateralized temporal lobe hypometabolism correlates with material-specific episodic memory impairment in MTLE. In contrast, prefrontal hypometabolism is not associated with performance on frontal lobe measures. We suggest that this is because frontal lobe neuropsychology tests may not be good measures of isolated frontal lobe functioning.


18F-FDG PET/CT QUALITATIVE AND QUANTITATIVE EVALUATION IN NEUROFIBROMATOSIS TYPE 1 PATIENTS FOR DETECTION OF MALIGNANT TRANSFORMATION: COMPARISON OF EARLY TO DELAYED IMAGING WITH AND WITHOUT LIVER ACTIVITY NORMALIZATION.

Chirindel A, Chaudhry M, Blakeley JO, Wahl R.

Abstract

18F-FDG PET/CT has shown increased accuracy, compared with morphologic imaging, in differentiating malignant peripheral nerve sheath tumors (MPNSTs) from benign neurofibromas (BNFs) in patients with neurofibromatosis type 1 (NF1). Delayed 18F-FDG PET imaging typically enhances malignant tumor to background. Our goal was to compare the effectiveness of early (1-h) and delayed (4-h) 18F-FDG PET/CT imaging in differentiating MPNSTs from BNFs in patients with NF1, with and without liver activity normalization.

Methods: NF1 patients presenting new symptoms or enlarging lesions were clinically evaluated with early and delayed 18F-FDG PET/CT imaging. SULmax (maximum standardized uptake value derived for lean body) and SULmax/liver (lesion uptake adjusted to mean liver activity) were obtained for all sites identified with abnormal metabolic activity. Qualitative and quantitative evaluations, including receiver-operating-characteristic (ROC) comparison of early and delayed imaging sessions, were performed. Histopathology and clinical follow-up (1-9 y) were considered as a gold standard.

RESULTS: Forty-one NF1 patients with early and delayed 18F-FDG PET/CT scans were identified, and 93 lesions were retrospectively analyzed, representing 24 MPNSTs (all histologically confirmed) and 69 BNFs (26 histologically confirmed). Qualitative evaluation on early imaging showed sensitivity, specificity, positive predictive value, and negative predictive value for separating MPNSTs from BNFs of 91%, 84%, 67%, and 96% versus 91%, 81%, 63%, and 96%, respectively, on 4-h delayed imaging. The mean SULmax was significantly higher for MPNSTs than BNFs on both early scans (6.5 vs. 2.0, P < 0.01) and delayed imaging (8.3 vs. 2.3, P < 0.02).

However, SULmax overlap between benign and malignant lesions persisted even after normalization to mean liver activity. ROC-derived best SULmax cutoffs were 3.2 on early (area under the curve, 0.973) and 4.1 on delayed scans (area under the curve, 0.978). ROC analysis for SULmax/liver improved test specificity (94% vs. 87%, P < 0.05) on early and (93% vs. 88%, P < 0.05) on delayed imaging.

Conclusion: Qualitative interpretation of 18F-FDG PET/CT discriminates MPNSTs from BNFs in NF1 patients with similar accuracy on both early and delayed imaging. Quantitative data showed better sensitivity on delayed acquisition and best test specificity with lesion SULmax normalization to liver activity, more so than with delayed imaging at 4 h.

VISUAL AND STATISTICAL ANALYSIS OF $^{18}$F-FDG PET IN PRIMARY PROGRESSIVE APHASIA.


Abstract

**Purpose:** Diagnosing progressive primary aphasia (PPA) and its variants is of great clinical importance, and fluorodeoxyglucose (FDG) positron emission tomography (PET) may be a useful diagnostic technique. The purpose of this study was to evaluate interobserver variability in the interpretation of FDG PET images in PPA as well as the diagnostic sensitivity and specificity of the technique. We also aimed to compare visual and statistical analyses of these images.

**Methods:** There were 10 raters who analysed 44 FDG PET scans from 33 PPA patients and 11 controls. Five raters analysed the images visually, while the other five used maps created using Statistical Parametric Mapping software. Two spatial normalization procedures were performed: global mean normalization and cerebellar normalization. Clinical diagnosis was considered the gold standard.

**Results:** Inter-rater concordance was moderate for visual analysis (Fleiss' kappa 0.568) and substantial for statistical analysis (kappa 0.756-0.881). Agreement was good for all three variants of PPA except for the nonfluent/agrammatic variant studied with visual analysis. The sensitivity and specificity of each rater's diagnosis of PPA was high, averaging 87.8 and 89.9% for visual analysis and 96.9 and 90.9% for statistical analysis using global mean normalization, respectively. In cerebellar normalization, sensitivity was 88.9% and specificity 100%.

**Conclusion:** FDG PET demonstrated high diagnostic accuracy for the diagnosis of PPA and its variants. Inter-rater concordance was higher for statistical analysis, especially for the nonfluent/agrammatic variant. These data support the use of FDG PET to evaluate patients with PPA and show that statistical analysis methods are particularly useful for identifying the nonfluent/agrammatic variant of PPA.


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CHANGES IN REGIONAL BRAIN GLUCOSE METABOLISM MEASURED WITH F-18-FDG-PET IN ESSENTIAL TREMOR.

Ha SW, Yang YS, Song IU, Chung YA, Oh JK, Chung SW.

Abstract

**Background:** There is growing evidence that essential tremor (ET) is a multiple-system disorder. Previous PET studies in ET typically have measured brain oxygen consumption and cerebral blood flow.

**Purpose:** To compare ET patients with control subjects to investigate any regional change in cerebral glucose metabolism through statistical parametric mapping (SPM) analysis of F-18-fluorodeoxyglucose positron emission tomography (F-18-FDG-PET).

**Materials and methods:** We studied 17 patients with ET (17 men; mean age, 67.3 ± 4.8 years) and age-sex matched normal subjects. All subjects underwent FDG-PET imaging, and evaluated severity of tremor symptoms was measured as score on the Fahn-Tolosa-Marin rating scale (FTM). We also evaluated detailed the medical history and neurological examinations in all patients.
Results: The mean age of tremor onset was $57.6 \pm 12.9$ years and the mean FTM score was $15.1 \pm 4.9$. Brain FDG-PET analysis demonstrated hypometabolism in the medial frontal lobe, medial temporal lobe, and the precuneus of parietal lobe. However, there was no significant difference of glucose metabolism in the cerebellum.

Conclusion: We propose that motor symptom of ET are caused by electrophysiological disturbances within cortical-cerebellar networks, rather than degenerative process of cerebellum, because the metabolism of the cerebellum was normal at rest. Furthermore, the abnormal glucose metabolism in the cerebral regions that do not mainly participate in motor function suggest that these regions may play a role as early markers of non-motor manifestations.


High-resolution $^{18}$F-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging for pituitary adenoma detection in Cushing disease.

Chittiboina P, Montgomery BK, Millo C, Herscovitch P, Lonser RR.

Abstract

Objective: High-resolution PET (hrPET) performed using a high-resolution research tomograph is reported as having a resolution of 2 mm and could be used to detect corticotroph adenomas through uptake of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). To determine the sensitivity of this imaging modality, the authors compared $^{18}$F-FDG hrPET and MRI detection of pituitary adenomas in Cushing disease (CD).

Methods: Consecutive patients with CD who underwent preoperative $^{18}$F-FDG hrPET and MRI (spin echo [SE] and spoiled gradient recalled [SPGR] sequences) were prospectively analyzed. Standardized uptake values (SUVs) were calculated from hrPET and were compared with MRI findings. Imaging findings were correlated to operative and histological findings.

Results: Ten patients (7 females and 3 males) were included (mean age 30.8 ± 19.3 years; range 11-59 years). MRI revealed a pituitary adenoma in 4 patients (40% of patients) on SE and 7 patients (70%) on SPGR sequences. $^{18}$F-FDG hrPET demonstrated increased $^{18}$F-FDG uptake consistent with an adenoma in 4 patients (40%; adenoma size range 3-14 mm). Maximum SUV was significantly higher for $^{18}$F-FDG hrPET-positive tumors (difference = 5.1, 95% CI 2.1-8.1; p = 0.004) than for $^{18}$F-FDG hrPET-negative tumors. $^{18}$F-FDG hrPET positivity was not associated with tumor volume (p = 0.2) or dural invasion (p = 0.5). Midnight and morning ACTH levels were associated with $^{18}$F-FDG hrPET positivity (p = 0.01 and 0.04, respectively) and correlated with the maximum SUV (R = 0.9; p = 0.001) and average SUV (R = 0.8; p = 0.01). All $^{18}$F-FDG hrPET-positive adenomas had a less than a 180% ACTH increase and $^{18}$F-FDG hrPET-negative adenomas had a greater than 180% ACTH increase after CRH stimulation (p = 0.03). Three adenomas were detected on SPGR MRI sequences that were not detected by $^{18}$F-FDG hrPET imaging. Two adenomas not detected on SE (but no adenomas not detected on SPGR) were detected on $^{18}$F-FDG hrPET.

Conclusions: While $^{18}$F-FDG hrPET imaging can detect small functioning corticotroph adenomas and is more sensitive than SE MRI, SPGR MRI is more sensitive than $^{18}$F-FDG hrPET and SE MRI in the detection of CD-associated pituitary adenomas. Response to CRH stimulation can predict $^{18}$F-FDG hrPET-positive adenomas in CD.

Clinical course of primary progressive aphasia: clinical and FDG-PET patterns.


Abstract
Primary progressive aphasia (PPA) may be the onset of several neurodegenerative diseases. This study evaluates a cohort of patients with PPA to assess their progression to different clinical syndromes, associated factors that modulate this progression, and patterns of cerebral metabolism linked to different clinical evolutionary forms. Thirty-five patients meeting PPA criteria underwent a clinical and neuroimaging $^{18}$F-Fluorodeoxyglucose PET evaluation. Survival analysis was performed using time from clinical onset to the development of a non-language symptom or deficit (PPA-plus). Cerebral metabolism was analyzed using Statistical Parametric Mapping. Patients classified into three PPA variants evolved to atypical parkinsonism, behavioral disorder and motor neuron disease in the agrammatic variant; to behavioral disorder in the semantic; and to memory impairment in the logopenic. Median time from the onset of symptoms to PPA-plus was 36 months (31-40, 95 % confidence interval).

Right laterality, and years of education were associated to a lower risk of progression, while logopenic variant to a higher risk. Different regions of hypometabolism were identified in agrammatic PPA with parkinsonism, motor neuron disease and logopenic PPA-plus. Clinical course of PPA differs according to each variant. Left anterior temporal and frontal medial hypometabolism in agrammatic variant is linked to motor neuron disease and atypical parkinsonism, respectively. PPA variant, laterality and education may be associated to the risk of progression. These results suggest the possibility that clinical and imaging data could help to predict the clinical course of PPA.


Preoperative brain metabolism and quality of life after subthalamic nucleus stimulation in Parkinson's disease.


Abstract
Subthalamic nucleus deep brain stimulation (STN-DBS) has been proven to improve health-related quality of life (HRQoL) in patients with Parkinson's disease (PD) presenting medically refractory motor complications and dyskinesia. However, some patients fail to benefit from STN-DBS despite rigorous preoperative selection. We postulated that they have a particular, clinically ineluctable, brain metabolism before surgery.

We divided 40 stimulated PD patients into two groups (responders vs. nonresponders) depending on whether they reported or not a clinically significant improvement in their quality of life 1 year after surgery. We retrospectively compared their preoperative brain metabolism on the basis of $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) scans. We also analyzed their neuropsychological and psychiatric profiles before and after surgery.

We expected that nonresponders would show distinctive brain functioning pre-surgery, in regions involved in associative and limbic circuits, as a result of PD-related degeneration.
STN-DBS may have interfered with this already abnormal circuitry, leading to the occurrence of complex nonmotor symptoms reducing quality of life. Preoperative brain metabolism could be a useful biomarker for anticipating STN-DBS efficacy in terms of HRQoL in the context of advanced PD.

DOES A NOVEL PENALIZED LIKELIHOOD RECONSTRUCTION OF $^{18}$F-FDG PET-CT IMPROVE SIGNAL-TO-BACKGROUND IN COLORECTAL LIVER METASTASES?

Parvizi N, Franklin JM, McGowan DR, Teoh EJ, Bradley KM, Gleeson FV.

Abstract

Purpose: Iterative reconstruction algorithms are widely used to reconstruct positron emission tomography computerised tomography (PET/CT) data. Lesion detection in the liver by $^{18}$F-fluorodeoxyglucose PET/CT ($^{18}$F-FDG-PET/CT) is hindered by $^{18}$F-FDG uptake in background liver arechyma. The aim of this study was to compare semi-quantitative parameters of histologically-proven colorectal liver metastases detected by $^{18}$F-FDG-PET/CT using data based on a Bayesian penalised likelihood (BPL) reconstruction, with data based on a conventional time-of-flight (ToF) ordered subsets expectation maximisation (OSEM) reconstruction.

Methods: A BPL reconstruction algorithm was used to retrospectively reconstruct sinogram PET data. This data was compared with OSEM reconstructions. A volume of interest was placed within normal background liver parenchyma. Lesions were segmented using automated thresholding. Lesion maximum standardised uptake value (SUV$_{\text{max}}$), standard deviation of background liver parenchyma SUV, signal-to-background ratio (SBR), and signal-to-noise ratio (SNR) were collated. Data was analysed using paired Student's t-tests and the Pearson correlation.

Results: Forty-two liver metastases from twenty-four patients were included in the analysis. The average lesion SUV$_{\text{max}}$ increased from 8.8 to 11.6 (p<0.001) after application of the BPL algorithm, with no significant difference in background noise. SBR increased from 4.0 to 4.9 (p<0.001) and SNR increased from 10.6 to 13.1 (p<0.001) using BPL. There was a statistically significant negative correlation between lesion size and the percentage increase in lesion SUV$_{\text{max}}$ (p=0.03).

Conclusions: This BPL reconstruction algorithm improved SNR and SBR for colorectal liver metastases detected by $^{18}$F-FDG-PET/CT, increasing the lesion SUV$_{\text{max}}$ without increasing background liver SUV or image noise. This may improve the detection of FDG-avid focal liver lesions and the diagnostic performance of clinical $^{18}$F-FDG-PET/CT in this setting, with the largest impact for small foci.


Slight uptake of $^{18}$F-FDG on positron emission tomography in pulmonary hamartoma: A case report.


Abstract

The present study reports the case of a 77-year-old female that was asymptomatic at presentation and was found to possess a lesion that was incidentally identified on a computed tomography (CT) scan. The CT scan revealed a non-homogeneous, hypodense, non-lobulated solid mass, ~1.2 cm in diameter, in the left upper lobe of the lung that demonstrated minimal contrast enhancement. The following CT scan was performed only two years later.

This scan revealed that the non-homogeneous round mass had increased in size to ~1.7 cm in diameter, and possessed an irregular margin, in addition to being slightly lobulated with no calcification or fat. Combined positron emission tomography and CT revealed a lobulated mass that was ~1.9 cm in diameter, demonstrating an irregular margin with involvement of the mediastinal pleura.
Slight uptake of $^{18}$F-fluorodeoxyglucose was also detected. The final histological diagnosis was pulmonary hamartoma.


FEASIBILITY OF PET-CT BASED HYPOFRACTIONATED ACCELERATED DOSE ESCALATION IN OROPHARYNGEAL CANCERS: FINAL DOSIMETRIC RESULTS OF THE VORTIGERN STUDY. (SECONDARY ENDPOINT OF UK NCRI PORTFOLIO: MREC NO: 08/H0907/127, UKCRN ID 7341).

Chatterjee S, Kelly C, Arunsingh M, Chakrabarty C, Mott J.

Abstract

Objective: Technological advances have enabled clinicians to explore dose escalation strategies in various tumor sites. Intermediate and high risk oropharyngeal cancers have poor 5 year outcomes. This study aimed to assess the feasibility and dosimetric safety of 9% dose escalation in these tumors and compare the dose received by organs at risk (OAR) in escalated plans (67.2 Gy/28 fractions) versus (65 Gy/30 fractions) standard dose plans.

Materials and methods: FDG-PET fused datasets were used to delineate gross, clinical and planning target volumes. Standard dose plans were created using two non IMRT techniques (conventional and field in field plans) whilst the patient was treated using a helical tomotherapy plan. A fourth dose escalation plan was obtained allowing comparison between the 20 plans of oropharyngeal cancer patients.

Results: It was feasible to escalate dose to the FDG-PET avid tumor within the set constraints to that of planning target volume and OAR. Comparison of the escalated dose to that of standard plans showed a statistically significant ($P < 0.05$) sparing of the mastication apparatus (MA) with escalated plans. Dose to the other critical and functional organs were comparable between the four plans.

Conclusion: Hypofractionated, slightly accelerated dose escalation in oropharyngeal cancers is likely to be safe and the chance of trismus is not any higher than when standard dose radiotherapy is used. Active measures to reduce dose to the MA achieves acceptable dose volume parameters even at escalated doses.


Clinical value of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography in evaluating relapsed and refractory nasopharyngeal carcinoma: A case report.


Abstract

For patients with locoregionally advanced nasopharyngeal carcinoma (NPC), radiotherapy, chemotherapy and even targeted therapy are widely accepted treatments. These treatments, although they mostly achieve locoregional tumor control, they may also be associated with complex post-treatment changes, such as edema, loss of tissue planes, fibrosis, mucositis and scarring, which may interfere with the detection of local recurrence and the response to therapy. However, timely detection is crucial for deciding whether treatment modification or discontinuation is required. This is the case report of A 51-year-old nasopharyngeal carcinoma patient with cervical nodal metastases (ONM). Following radiotherapy, chemotherapy and targeted therapy, multislice spiral enhanced computed tomography (CT), enhanced magnetic resonance imaging (MRI) and $^{18}$F-
fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT of the neck were performed to compare the extent of the CNM. The enhanced CT and MRI images were unremarkable, whereas the $^{18}$F-FDG PET/CT images revealed the exact recurrence or remission. Therefore, $^{18}$F-FDG PET/CT exhibits a better sensitivity and specificity for evaluating the response to combined treatment compared to CT and/or MRI.


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**IDENTIFICATION OF BIOMARKERS INCLUDING $^{18}$FDG-PET/CT FOR EARLY PREDICTION OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN TRIPLE NEGATIVE BREAST CANCER.**


**Abstract**

**Purpose:** To investigate the value of the metabolic tumor response assessed with $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET), compared with clinico-biological markers to predict pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in women with triple-negative breast cancer (TNBC).

**Experimental design:** Fifty consecutive women with TNBC and an indication for NAC were prospectively included. Different pre-treatment clinical, biological and pathological biomarkers, including SBR grade, the Ki-67 proliferation index, androgen receptor expression, epidermal growth factor receptor (EGFR) and cytokeratin 5/6 staining, were assessed. Tumor glucose metabolism at baseline and its change after the first cycle of NAC ($\Delta$SUVmax) were assessed using FDG-PET.

**Results:** The pCR rate was 42%. High Ki-67 proliferation index ($p=0.016$), negative EGFR status ($p=0.042$), and high $\Delta$SUVmax ($p=0.002$) were significantly associated with pCR. In multivariate logistic regression, both negative EGFR status (Odds ratio=6.4; $p=0.043$) and high $\Delta$SUVmax (Odds ratio=7.1; $p=0.014$) were independent predictors of pCR. Using a threshold at -50%, tumor $\Delta$SUVmax predicted pCR with a negative, a positive predictive value and an accuracy of 79%, 70% and 75%, respectively. Combining a low $\Delta$SUVmax and positive EGFR status could predict non-pCR with an accuracy of 92%.

**Conclusions:** It is important to define the chemo sensitivity of TNBC to NAC early. Combining EGFR status and the metabolic response assessed with FDG-PET can help the physician to early predict the probability of achieving pCR or not. Given these results, the interest of response-guided tailoring of the chemotherapy might be tested in multicenter trials.


**SU-E-J-249: CHARACTERIZATION OF GYNECOLOGICAL TUMOR HETEROGENEITY USING TEXTURE ANALYSIS IN THE CONTEXT OF AN $^{18}$F-FDG PET ADAPTIVE PROTOCOL.**

Nawrocki J, Chino J, Das S, Craciunescu O.

**Abstract**

**Purpose:** We propose a method to examine gynecological tumor heterogeneity using texture analysis in the context of an adaptive PET protocol in order to establish if texture metrics from baseline PET-CT predict tumor response better than SUV metrics alone as well as determine texture features correlating with tumor response during radiation therapy.
Methods: This IRB approved protocol included 29 women with node positive gynecological cancers visible on FDG-PET treated with EBRT to the PET positive nodes. A baseline and intra-treatment PET-CT was obtained. Tumor outcome was determined based on RECIST on posttreatment PET-CT. Primary GTVs were segmented using 40% threshold and a semi-automatic gradient-based contouring tool, PET Edge (MIM Software Inc., Cleveland, OH). SUV histogram features, Metabolic Volume (MV), and Total Lesion Glycolysis (TLG) were calculated. Four 3D texture matrices describing local and regional relationships between voxel intensities in the GTV were generated: co-occurrence, run length, size zone, and neighborhood difference. From these, 39 texture features were calculated. Prognostic power of baseline features derived from gradient-based and threshold GTVs were determined using the Wilcoxon rank-sum test. Receiver Operating Characteristics and logistic regression was performed using JMP (SAS Institute Inc., Cary, NC) to find probabilities of predicting response. Changes in features during treatment were determined using the Wilcoxon signed-rank test.

Results: Of the 29 patients, there were 16 complete responders, 7 partial responders, and 6 non-responders. Comparing CR/PR vs. NR for gradient-based GTVs, 7 texture values, TLG, and SUV kurtosis had a p < 0.05. Threshold GTVs yielded 4 texture features and TLG with p < 0.05. From baseline to intra-treatment, 14 texture features, SUVmean, SUVmax, MV, and TLG changed with p < 0.05.

Conclusion: Texture analysis of PET imaged gynecological tumors is an effective method for early prognosis and should be used complimentary to SUV metrics, especially when using gradient based segmentation.


IMPACT OF 4D-18FDG-PET/CT IMAGING ON TARGET VOLUME DELINEATION IN SBRT PATIENTS WITH CENTRAL VERSUS PERIPHERAL LUNG TUMORS. MULTI-READER COMPARATIVE STUDY.


Abstract

Purpose: Evaluation of the effect of co-registered 4D-18FDG-PET/CT for SBRT target delineation in patients with central versus peripheral lung tumors.

Methods: Analysis of internal target volume (ITV) delineation of central and peripheral lung lesions in 21 SBRT-patients. Manual delineation was performed by 4 observers in 2 contouring phases: on respiratory gated 4DCT with diagnostic 3DPET available aside (CT-ITV) and on co-registered 4DPET/CT (PET/CT-ITV). Comparative analysis of volumes and inter-reader agreement.

Results: 11 cases of peripheral and 10 central lesions were evaluated. In peripheral lesions, average CT-ITV was 6.2cm³ and PET/CT-ITV 8.6cm³, resembling a mean change in hypothetical radius of 2mm. For both CT-ITVs and PET/CT-ITVs inter reader agreement was good and unchanged (0.733 and 0.716; p=0.58). All PET/CT-ITVs stayed within the PTVs derived from CT-ITVs. In central lesions, average CT-ITVs were 42.1cm³, PET/CT-ITVs 44.2cm³, without significant overall volume changes. Inter-reader agreement improved significantly (0.665 and 0.750; p<0.05). 2/10 PET/CT-ITVs exceeded the PTVs derived from CT-ITVs by >1ml in average for all observers.

Conclusion: The addition of co-registered 4DPET data to 4DCT based target volume delineation for SBRT of centrally located lung tumors increases the inter-observer agreement and may help to avoid geographic misses.

FDG-PET findings of Ameloblastoma: a case report.


Abstract

Introduction: Ameloblastoma is a benign odontogenic neoplasm of the jaw, rarely presenting as a malignant tumor. Although it is very important to discriminate ameloblastoma from ameloblastic carcinoma in order to decide the appropriate operative procedure, this is difficult using conventional CT and MRI.

Case descriptions: We report a case of maxillary ameloblastoma in a 78-year-old man where FDG-PET/CT was useful for making this discrimination. CT demonstrated a $31 \times 43 \times 46$-mm mass in the left posterior maxillary sinus with destruction of its posterior and lateral wall and alveolar bone. MRI demonstrated a hypo- to isointense heterogeneous pattern on T1WI, heterogeneous hyperintensity with a prominent high-signal spot on T2WI, high signal intensity on DWI reflecting restricted diffusion, and strong heterogeneous enhancement. Because FDG-PET/CT showed mild FDG uptake (SUVmax 2.40) by the mass, ameloblastoma, rather than ameloblastic carcinoma, was considered to be the correct diagnosis.

Discussion and evaluation: It appears that ameloblastic carcinoma shows intense FDG uptake, whereas ameloblastoma shows mild or moderate FDG uptake, and only rarely intense FDG uptake. Our experience suggests that FDG-PET/CT may be effective for discriminating ameloblastoma from ameloblastic carcinoma. Especially, in cases showing mild FDG uptake, benign ameloblastoma would seem the most likely diagnosis.

Conclusions: FDG-PET/CT may be useful as an adjunctive modality for diagnosis, treatment planning and surveillance of ameloblastoma and ameloblastic carcinoma.


FDG PET/CT in Pancreatic and Hepatobiliary Carcinomas: Value to Patient Management and Patient Outcomes.

Parikh U, Marcus C, Sarangi R, Taghipour M, Subramaniam RM.

Abstract

Fludeoxyglucose F-18 (18F-FDG) PET/CT has not been shown to offer additional benefit in the initial diagnosis of pancreatic cancer, but studies show benefit of 18F-FDG PET/CT in initial staging and patient prognosis.

There is evidence for 18F-FDG PET and 18F-FDG PET/CT in staging and prognosis of cholangiocarcinoma and gallbladder cancer. 18F-FDG PET/CT has shown promise in staging liver malignancies by detecting extrahepatic metastasis. There is evidence supporting the ability of PET/CT in predicting prognosis in patients with hepatocellular carcinoma. Evidence is evolving for the role of 18F-FDG PET/CT in predicting prognosis and survival in patients with colorectal liver metastasis.

PRIMARY TUMOR DELINEATION BASED ON $^{18}$FDG PET FOR LOCALLY ADVANCED HEAD AND NECK CANCER TREATED BY CHEMO-RADIOThERAPY.

Leclerc M, Lartigau E, Lacornerie T, Daisne JF, Kramar A, Grégoire V.

**Abstract**

**Purpose:** The use of FDG-PET for target volume delineation has been validated by our group for patients with locally advanced head and neck squamous cell carcinoma (HNSCC) treated by concomitant chemo-radiotherapy providing a strict methodology for image acquisition and segmentation. The aims of this study were (1) to confirm these results in a multicentric setting, and (2) to evaluate the clinical outcome in a prospective series of patients treated with FDG-PET scan-based radiotherapy planning.

**Materials and methods:** Forty-one patients with stage III or IV HNSCC were included in this prospective multicentric study from 2007 to 2009. Before treatment, each patient underwent head and neck endoscopy, contrast enhanced CT or MRI and FDG PET scan. Patients were treated with invert or forward planning IMRT (using dose-volume constraints on PTVs and OARs). Primary tumor GTV$^{PET}$ were automatically delineated using a gradient based method and were registered on the planning CT. A prophylactic (50Gy) and a therapeutic (70Gy) primary tumor CTV$^{PET}$ were contoured using GTV$^{PET}$ volume along with data provided by endoscopy and pre-treatment imaging. Nodal CTV were delineated on the planning CT using internationally accepted guidelines. PTV was created by adding a security margin of 4-5mm around CTV$^{PET}$ (PTV$^{PET}$). At the end of the inclusion period after a minimal follow-up of 2years, target volumes (GTV$^{CT}$, CTV$^{CT}$, PTV$^{CT}$) for the primary tumors were re-delineated on the planning CT-scan using anatomic imaging only to perform a volumetric and a dosimetric comparison.

**Results:** Mean age of the population was 59years. Oropharynx was the most common tumor location (68%), followed by oral cavity (17%), larynx (7%) and hypopharynx (7%). GTV$^{PET}$ contours were significantly smaller than GTV$^{CT}$ contours in all cases but one (average volume 28.8ml vs 40.4ml, p<0.0001). The prophylactic primary tumor target volumes (CTV 50Gy and PTV 50Gy) based on PET scan were significantly smaller (p<0.0001) in oropharynx cases. The boost target volumes (CTV 70Gy and PTV 70Gy) contoured on PET scan were also significantly smaller than the ones contoured on CT scan in all cases (p<0.0001). The dosimetry comparison showed a significant decrease in parotid and oral cavity mean dose from the PET-based plans. After completion of chemo-radiotherapy, 5 patients had selective node dissection for suspicious lymph nodes on MRI and/or PET scan; only one had a positive pathological node. At a median follow-up of 3years, the relapse-free and overall survival rates were respectively 32% and 43%. No marginal recurrence (in the CTV$^{CT}$ but outside the CTV$^{PET}$) was observed.

**Conclusion:** This study confirms that the use of $^{18}$FDG-PET translated into smaller GTV, CTV and PTV for the primary tumor volumes in comparison with the use of CT. PET planning also demonstrated an improvement on dosimetry by lowering dose to certain organs at risk.

PROGNOSTIC ROLE OF METABOLIC PARAMETERS OF $^{18}$F-FDG PET-CT SCAN PERFORMED DURING RADIATION THERAPY IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA.

Min M, Lin P, Lee MT, Shon IH, Lin M, Forstner D, Bray V, Chicco A, Tieu MT, Fowler A.

Abstract

Purpose: To evaluate the prognostic value of $^{18}$F-FDG PET-CT performed in the third week (iPET) of definitive radiation therapy (RT) in patients with newly diagnosed locally advanced mucosal primary head and neck squamous-cell-carcinoma (MPHNSCC).

Methodology: Seventy-two patients with MPHNSCC treated with radical RT underwent staging PET-CT and iPET. The maximum standardised uptake value ($SUV_{\text{max}}$), metabolic tumour volume (MTV) and total lesional glycolysis (TLG) of primary tumour (PT) and index node (IN) [defined as lymph node(s) with highest TLG] were analysed, and results were correlated with loco-regional recurrence-free survival (LRFS), disease-free survival (DFS), metastatic failure-free survival (MFFS) and overall survival (OS), using Kaplan-Meier analysis.

Results: Optimal cutoffs (OC) were derived from receiver operating characteristic curves: $SUV_{\text{max}}^{\text{PT}} = 4.25$ g/mL, $MTV_{\text{PT}} = 3.3$ cm$^3$, $TLG_{\text{PT}} = 9.4$ g, for PT, and $SUV_{\text{max}}^{\text{IN}} = 4.05$ g/mL, $MTV_{\text{IN}} = 1.85$ cm$^3$, and $TLG_{\text{IN}} = 7.95$ g for IN. Low metabolic values in iPET for PT below OC were associated with statistically significant better LRFS and DFS. TLG was the best predictor of outcome with 2-year LRFS of 92.7 % vs. 71.1 % [$p = 0.005$, compared with $SUV_{\text{max}}$ (p = 0.03) and MTV (p = 0.022)], DFS of 85.9 % vs. 60.8 % [$p = 0.005$, compared with $SUV_{\text{max}}$ (p = 0.025) and MTV (p = 0.018)], MFFS of 85.9 % vs. 83.7 % [$p = 0.488$, compared with $SUV_{\text{max}}$ (p = 0.52) and MTV (p = 0.436)], and OS of 81.1 % vs. 75.0 % [$p = 0.279$, compared with $SUV_{\text{max}}$ (p = 0.345) and MTV (p = 0.512)]. There were no significant associations between the percentage reduction of primary tumour metabolic parameters and outcomes. In patients with nodal disease, metabolic parameters below OC (for both PT and IN) were significantly associated with all oncological outcomes, while TLG was again the best predictor: LRFS of 84.0 % vs. 55.3 % [$p = 0.017$], DFS of 79.4 % vs. 38.6 % [$p = 0.001$], MFFS 86.4 % vs. 68.2 % [$p = 0.034$] and OS 80.4 % vs. 55.7 % [$p = 0.045$].

Conclusion: The metabolic parameters of iPET can be useful predictors of patient outcome and potentially have a role in adaptive therapy for MPHNSCC. Among the three parameters, TLG was found to be the best prognostic indicator of oncological outcomes.


Tubercular Meningitis and Lymphadenitis Mimicking a Relapse of Burkitt's Lymphoma on $^{18}$F-FDG-PET/CT: A Case Report.


Abstract

Tuberculosis (TB) can present with various forms and can occasionally be mistaken for malignancy. Hereby, we report a 53-year-old man diagnosed and treated for Burkitt's lymphoma in 2009 who achieved a complete remission confirmed by a computed tomography (CT) scan. During the follow-up 2 years later, he complained of left hip pain that warranted investigation with magnetic resonance imaging and whole-body $^{18}$F-fludeoxyglucose-positron emission tomography (FDG-PET)/CT which showed a benign lesion in the left hip associated with multiple lymph nodes in the chest and abdomen not amenable for biopsy. A follow-up PET/CT scan a few months later showed intense tracer uptake in the lymph nodes with size progression and appearance of new lymph nodes suspicious of lymphoma relapse. The patient was asymptomatic, and all investigations including viral and connective tissue disease studies were negative. Also the tuberculin skin test and QuantIFERON were negative. Lymph node biopsy was planned; however, the patient presented a few days earlier with fever, headache and photophobia. Cerebrospinal fluid (CSF) examination confirmed meningitis with lymphocytic pleocytosis.
and elevated protein. The CSF Gram stain, culture, viral and acid-fast bacilli were negative. CSF flow
cytometry and cytopathology confirmed polyclonal lymphocytosis and suggested reactive causes. CSF
TB culture grew Mycobacterium tuberculosis. Mediastinal lymph node biopsy also confirmed TB
lymphadenitis. Four antituberculosis drugs were started. One year later, a PET/CT scan showed
regression of all the involved lymph nodes. This case highlights the importance of excluding TB in
patients with suspected malignancy, especially if they belong to endemic regions, and the increasing
role of $^{18}$F-FDG-PET/CT in the early detection of extrapulmonary TB.


**METABOLIC TUMOR VOLUME (MTV) AT $^{18}$F-FLUORODEOXYGLUCOSE
POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY ($^{18}$F-FDG-PET/CT) IMPROVES PREOPERATIVE IDENTIFICATION OF HIGH-RISK
ENDOMETRIAL CARCINOMA PATIENTS.**

Husby JA, Reitan BC, Biermann M, Trovik J, Bjørge L, Magnussen IJ, Salvesen ØO, Salvesen HB, Haldorsen IH.

**Abstract**

**Objectives:** Prospectively explore the diagnostic value of 2-deoxy-2-$^{18}$F-fluoroglucose positron
emission tomography/computed tomography ($^{18}$F-FDG-PET/CT) for preoperative staging in
endometrial carcinomas. Investigate if $^{18}$F-FDG-PET specific quantitative tumor parameters reflect
clinical and histological characteristics.

**Methods:** Preoperative $^{18}$F-FDG-PET/CT was prospectively performed in 129 consecutive
endometrial carcinoma patients. Two physicians, blinded for clinical findings and staging results,
independently reviewed the images assessing primary tumor, cervical stroma involvement and
metastatic spread, and measured tumor standardized uptake value (SUV)$_{\text{max}}$, SUV$_{\text{mean}}$ and
metabolic tumor volume (MTV) with calculation of total lesion glycolysis (TLG). All parameters were
analysed in relation to histomorphological and clinical tumor characteristics. Receiver operating
characteristics (ROC) curves for identification of deep myometrial invasion and lymph node
metastases were generated and MTV cut-off values for predicting deep myometrial invasion and
lymph node metastases were calculated.

**Results:** Sensitivity (specificity) and accuracy of $^{18}$F-FDG-PET/CT for the detection of lymph node
metastases were 77-85% (91-96%) and 89-93%, respectively. SUV$_{\text{max}}$, SUV$_{\text{mean}}$, MTV and TLG
were significantly related to deep myometrial invasion, presence of lymph node metastases and high
histological grade (P < 0.015 for all), and independently predicted deep myometrial invasion (P <
0.015) and lymph node metastases (P < 0.025) after adjusting for preoperative histological risk (based
on subtype and grade) in endometrial biopsies. Optimal cut-off values for MTV in predicting deep
myometrial invasion (20 ml) and presence of lymph node metastases (30 ml), yielded ORs of 7.8 (P <
0.001) and 16.5 (P = 0.001), respectively.

**Conclusion:** $^{18}$F-FDG-PET/CT represents a clinically valuable tool to evaluate presence of lymph
node metastases preoperatively for endometrial carcinoma patients. Applying MTV cut-off values for
the prediction of deep myometrial invasion and lymph node metastases may increase diagnostic
accuracy and aid preoperative identification of high-risk patients, enabling restriction of
lymphadenectomy for patients with low risk of aggressive disease.


**F-18-FDG PET-CT IN CHILDREN AND YOUNG ADULTS WITH EWING SARCOMA DIAGNOSED IN NORWAY DURING 2005-2012: A NATIONAL POPULATION-BASED STUDY.**

**Johnsen B, Boye K, Rosendahl K, Biermann M, Trovik C, Aukland SM.**

**Abstract**

**Background:** To examine national imaging strategies regarding the use of F-18-FDG PET-CT in patients with Ewing sarcoma and study factors that might influence the use of PET-CT, such as tumour biology (Picci grade of operation specimen), clinical disease stage and age.

**Methods:** We examined the medical records including pathology and imaging of all patients below 30 years diagnosed with Ewing sarcoma in Norway in 2005-2012.

**Results:** Of 61 patients treated at one of the two national sarcoma treatment service centres (Oslo: 35, Bergen: 26), 29 patients had localized disease, 8 had tumour extending to organs nearby and 24 had metastases. Among 35 operated patients with neoadjuvant chemotherapy, 15 had Picci grades II and III (good responders) and 20 grade I (poor responders). We found a significant difference in the use of PET-CT (Oslo/Bergen 0·9 versus 2·0 scans per patient, P = 0·010) and in the use of MRI (Oslo/Bergen: eight versus 13, P = 0·006). No differences were proven for ultrasound, radiography, CT or skeletal scintigraphy. The number of PET-CTs was associated with clinical disease stage at diagnosis (P = 0·041) but not with Picci grade or age. The number of PET studies was not correlated to the number of MR studies.

**Conclusions:** The use of PET-CT in children and young adults diagnosed with Ewing sarcoma in Norway during 2005-2012 at the two national sarcoma treatment service centres differed significantly. The use of PET-CT imaging was related to the clinical disease stage at diagnosis but unrelated to patient age and tumour biology (Picci grade).


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**BENEFITS OF FLUORINE-18 FLUDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY IN SECONDARY CYTOREDUCTIVE SURGERY FOR PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER.**


**Abstract**

**Objective:** To investigate the benefits of fluorine-18 fludeoxyglucose positron emission tomography (\(^{18}\)F-FDG-PET) in patients undergoing secondary cytoreductive surgery (SCRS) for recurrent epithelial ovarian cancer.

**Methods:** Patients were identified, and their clinical information was extracted by review of the gynaecologic oncology database of Peking Union Medical College Hospital. \(^{18}\)F-FDG-PET scan and analysis were performed by nuclear medicine experts at our hospital.

**Results:** The PET group and the control group of patients evaluated by conventional imaging methods differed significantly with respect to the proportion of patients who underwent complete SCRS and the number of residual lesions (p = 0.002 and 0.006, respectively). A Cox model showed that longer progression-free survival (PFS) correlated significantly with \(^{18}\)F-FDG-PET evaluation [relative risk (RR) = 0.432; p = 0.001], sensitivity to platinum-based chemotherapies (RR = 0.604; p = 0.034) and resection completeness (RR = 0.679; p = 0.039). Longer overall survival (OS) correlated significantly with sensitivity to platinum-based chemotherapy (RR = 0.317; p = 0.000) and the CA-125
level after two cycles of chemotherapy (RR = 2.663; p = 0.003). Surgical safety and complications did not significantly differ between the two groups of patients.

**Conclusion:** $^{18}$F-FDG-PET is useful for evaluating patients with recurrent epithelial ovarian carcinoma. Patients who undergo PET-guided SCRS have a greater chance of complete tumour resection and a longer PFS. Advances in knowledge: SCRS guided by PET results in fewer residual lesions. PET-guided SCRS is safe and can prolong PFS and OS in patients with recurrent ovarian cancer.


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**FEASIBILITY OF A MULTIMODAL $^{18}$F-FDG-DIRECTED LYMPH NODE SURGICAL EXCISIONAL BIOPSY APPROACH FOR APPROPRIATE DIAGNOSTIC TISSUE SAMPLING IN PATIENTS WITH SUSPECTED LYMPHOMA.**

Povoski SP, Hall NC, Murrey DA Jr, Wright CL, Martin EW Jr.

**Abstract**

**Background:** $^{18}$F-FDG PET/CT imaging is widely utilized in the clinical evaluation of patients with suspected or documented lymphoma. The aim was to describe our cumulative experience with a multimodal $^{18}$F-FDG-directed lymph node surgical excisional biopsy approach in patients with suspected lymphoma.

**Methods:** Thirteen patients (mean age 51 (± 16;22-76) years), with suspected new or suspected recurrent lymphoma suggested by $^{18}$F-FDG-avid lesions seen on prior diagnostic whole-body PET/CT imaging, were injected IV with $^{18}$F-FDG prior to undergoing same-day diagnostic lymph node surgical excisional biopsy in the operating room. Various $^{18}$F-FDG detection strategies were used on the day of surgery, including, (1) same-day pre-resection patient PET/CT; (2) intraoperative gamma probe assessment; (3) clinical scanner specimen PET/CT imaging of whole surgically excised tissue specimens; (4) specimen gamma well counts; and/or (5) same-day post-resection patient PET/CT.

**Results:** Same-day $^{18}$F-FDG injection dose was 14.8 (± 2.4;12.5-20.6) millicuries or 548 (± 89;463-762) megabecquerels. Sites of $^{18}$F-FDG-avid lesions were 4 inguinal, 3 cervical, 3 abdominal/retroperitoneal, 2 axillary, and 1 gluteal region subcutaneous tissue. Same-day pre-resection patient PET/CT was performed on 6 patients. Intraoperative gamma probe assessment was performed on 13 patients. Clinical scanner PET/CT imaging of whole surgically excised tissue specimens was performed in 10 cases. Specimen gamma well counts were performed in 6 cases. Same-day post-resection patient PET/CT imaging was performed on 8 patients. Time from $^{18}$F-FDG injection to same-day pre-resection patient PET/CT, intraoperative gamma probe assessment, and same-day post-resection patient PET/CT were 76 (± 8;64-84), 240 (± 63;168-304), and 487 (± 104;331-599) minutes, respectively. Time from $^{18}$F-FDG injection to clinical scanner PET/CT of whole surgically excised tissue specimens was 363 (± 60;272-446) minutes. Time from $^{18}$F-FDG injection to specimen gamma well counts was 591 (± 96;420-689) minutes. Intraoperative gamma probe assessment successfully identified $^{18}$F-FDG-avid lesions in 12/13 patients. Histopathologic evaluation confirmed lymphoma in 12/13 patients and benign disease in 1/13 patients.

**Conclusion:** A multimodal approach to $^{18}$F-FDG-directed lymph node surgical excisional biopsy for suspected lymphoma is technically feasible for guiding appropriate diagnostic tissue sampling of lymph nodes seen as $^{18}$F-FDG-avid lesions on diagnostic $^{18}$F-FDG PET/CT imaging.

**18F-FDG PET/CT AND COLORECTAL CANCER: VALUE OF FOURTH AND SUBSEQUENT POSTTHERAPY FOLLOW-UP SCANS FOR PATIENT MANAGEMENT.**

Marcus C, Marashdeh W, Ahn SJ, Taghipour M, Subramaniam RM.

**Abstract**

The purpose of this study was to evaluate the added value of a fourth and subsequent follow-up PET/CT scans to clinical assessment and impact on patient management in patients with colorectal cancer.

**Methods:** This was an institutional review board-approved, retrospective study. Eight hundred twenty-two patients with biopsy-proven colorectal cancer, who underwent 18F-FDG PET/CT, were identified from 2000 to 2012. Among these, 73 (8.9%) patients underwent 4 or more follow-up PET/CT scans, with a total of 313 fourth and subsequent follow-up PET/CT scans. Median follow-up from the fourth follow-up PET/CT scan was 41.7 mo. The added value of each follow-up PET/CT scan, for clinical assessment and the treatment changes subsequent to each follow-up PET/CT scan, was established. Overall survival prediction was established using Kaplan-Meier plots with a Mantel-Cox log-rank test.

**Results:** Of the 313 fourth and subsequent follow-up PET/CT scans, 174 (55.6%) were interpreted as positive and 139 (44.4%) were interpreted as negative for recurrence or metastases. Thirty-four (46.6%) patients died during the study period. PET/CT identified recurrence or metastasis in 40.0% of scans obtained without prior clinical suspicion and ruled out disease in 23.6% of scans obtained with prior clinical suspicion. The PET/CT scan resulted in treatment change after 34.2% (107/313) of the scans. New treatment was initiated after 24.0% (75/313) of the scans, and treatment was changed after 8.0% (25/313) scans. There was a statistically significant difference in the overall survival between patients with a positive and all negative fourth and subsequent follow-up PET/CT scans at the patient level (log-rank, \( P = 0.001 \)).

**Conclusion:** The fourth and subsequent 18F-FDG PET/CT scans obtained after primary treatment completion add value to clinical assessment and the management plan and provide prognostic information in patients with colorectal cancer.


**KIKUCHI-FUJIMOTO LYMPHADENITIS IMITATING METASTATIC MELANOMA ON POSITRON EMISSION TOMOGRAPHY: A CASE REPORT.**

Urbanellis P, Chin-Lenn L, Teman CJ, McKinnon JG.

**Abstract**

**Background:** Accurate staging is critical for decision-making for the treatment of malignant conditions. Fluoro-deoxy-glucose positron emission tomography-computed tomography (FDG PET-CT) is a highly sensitive imaging modality for the assessment of distant metastases; however false positive results are possible due to its lower specificity with detection of other hypermetabolic pathologies.

**Case presentation:** A patient with high-risk thigh melanoma was staged with FDG PET-CT. Four ipsilateral inguinal nodes (three superficial, one deep) demonstrated intense hypermetabolic activity. Metastatic melanoma was confirmed in the largest superficial inguinal node with ultrasound-guided fine needle aspiration. Histopathology demonstrated metastatic melanoma in one superficial node and
histiocytic necrotizing lymphadenitis, also known as Kikuchi-Fujimoto disease in five deep inguinal nodes.

**Conclusion:** This case illustrates a false positive FDG PET-CT due to coincidental, synchronous melanoma and Kikuchi-Fujimoto disease in the same draining lymph node basin.


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**Early Metabolic Response to Neoadjuvant Treatment: FDG PET/CT Criteria according to Breast Cancer Subtype.**


**Abstract**

**Purpose:** To investigate parameters based on fluorine-18 fluorodeoxyglucose (FDG) positron emission tomographic (PET) imaging that are best correlated with pathologic complete response (PCR) in human epidermal growth factor receptor type 2 (HER2)-positive cancer and triple-negative breast cancer (TNBC) and with partial or complete response in ER-positive/HER2-negative breast cancer.

**Materials and methods:** This study was approved by institutional review board with waivers of informed written consent and included consecutive patients treated by neoadjuvant chemotherapy. Five PET examination-derived parameters were tested: standard uptake value (SUV) maximum (SUV<sub>max</sub>), peak (SUV<sub>peak</sub>), and mean (SUV<sub>mean</sub>), metabolically active tumor volume, and total lesion glycolysis (TLG). Absolute values at baseline PET, at PET imaging after two cycles of chemotherapy, and variation (ie, change) were measured. Correlations with pathologic response (Wilcoxon rank-sum test) and predictive power assessed (area under the curve [AUC] on the basis of receiver operating characteristic analysis) were examined.

**Results:** Included were 169 consecutive patients (mean age, 50 years). PCR was more frequent in HER2-positive tumors (16 of 33 patients [48.5%]) and TNBCs (20 of 54 patients [37%]) than in ER positive/HER2-negative tumors (four of 82 [4.9%]) (P < .001). Among patients with ER-positive/HER2-negative cancers, 33 patients had partial response. In TNBC, best association with PCR was obtained with change in SUV<sub>max</sub> (AUC, 0.86) or change in TLG (AUC, 0.88). In HER2-positive phenotype, absolute SUV<sub>max</sub> or (SUV<sub>peak</sub>) values at PET imaging after two cycles of chemotherapy (AUC for each cycle, 0.93) were better correlated with PCR than change in SUV<sub>max</sub> (AUC, 0.78; P = .11) or change in TLG (AUC, 0.62; P = .005). Regarding ER-positive/HER2-negative cancers, change in SUV<sub>max</sub> or change in TLG (AUC, 0.75) were parameters best correlated with partial or complete response. Baseline SUV<sub>max</sub> was higher in lymph nodes than in primary tumor in 31 patients. Findings were similar considering the site with highest FDG uptake.

**Conclusion:** Quantitative indexes of tumor glucose use that are best correlated with pathologic response vary by phenotype: change in SUV<sub>max</sub> or TLG are most adequate for TNBCs and ER-positive/HER2-negative cancers and absolute SUV<sub>max</sub> after two cycles of chemotherapy for HER2-positive breast cancers.

FDG-PET/CT FOR PRE-OPERATIVE STAGING AND PROGNOSTIC STRATIFICATION OF PATIENTS WITH HIGH-GRADE PROSTATE CANCER AT BIOPSY.


Abstract

Background: The role of $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in prostate cancer (PCa) has not been well defined yet. Because high-grade PCa tends to exhibit increased glycolytic rate, FDG-PET/CT could be useful in this setting. The aim of this study was to assess the value of FDG-PET/CT for pre-operative staging and prognostic stratification of patients with high-grade PCa at biopsy.

Methods: Fifty-four patients with a Gleason sum $\geq 8$ PCa at biopsy underwent FDG-PET/CT as part of the staging workup. Thirty-nine patients underwent radical prostatectomy (RP) and pelvic lymph node (LN) dissection, 2 underwent LN dissection only, and 13 underwent non-surgical treatments. FDG-PET/CT findings from clinical reports, blinded reading and quantitative analysis were correlated with clinico-pathological characteristics at RP.

Results: Suspicious foci of increased FDG uptake were found in the prostate, LNs and bones in 44, 13 and 6% of patients, respectively. Higher clinical stage, post-RP Gleason sum and pattern, and percentage of cancer involvement within the prostate were significantly associated with the presence of intraprostatic FDG uptake (IPFU) ($P<0.05$ in all cases). Patients without IPFU who underwent RP were downgraded to Gleason $\leq 7$ in 84.6% of cases, as compared to 30.8% when IPFU was reported ($P=0.003$). Qualitative and quantitative IPFU were significantly positively correlated with post-RP Gleason pattern and sum, and pathological T stage. Absence and presence of IPFU were associated with a median 5-year cancer-free survival probability of 70.2 and 26.9% ($P=0.0097$), respectively, using the CAPRA-S prognostic tool.

Conclusion: These results suggest that, among patients with a high-grade PCa at biopsy, FDG-PET/CT could improve pre-treatment prognostic stratification by predicting primary PCa pathological grade and survival probability following RP.


SAFETY AND COST ANALYSIS OF AN $^{18}$FDG-PET-CT RESPONSE BASED FOLLOW-UP STRATEGY FOR HEAD AND NECK CANCERS TREATED WITH PRIMARY RADIATION OR CHEMORADIATION.


Abstract

Background: Prognostic information can rationalise clinical follow-up after radical cancer treatment. This retrospective cohort study of radical head and neck (chemo)radiotherapy patients examines the clinical safety and cost implications of stratifying follow-up intensity by post-treatment ($^{18}$FDG-PET-CT response.

Methods: In 2008 clinical review after radical head and neck radiotherapy was reduced from 3- to 6-monthly for patients with complete ($^{18}$FDG-PET-CT response at 3months. 184 patients treated after this change ("PET Stratified", 2009-11) were compared to 178 patients treated before ("Standard", 2005-7). Clinical safety was assessed by the time to detection of recurrence, overall survival and
potential for radical treatment of recurrence. A hospital cost analysis was performed using individual patient data.
Results: 127 of 178 Standard and 148 of 184 PET Stratified patients achieved complete response on post-treatment imaging. Baseline clinical characteristics were comparable. Median follow-up from response assessment was 4.8 years in the Standard cohort and 2.1 years for PET Stratified. PET Stratified patients had a mean 4.4 outpatient visits in 2 years, compared to 7.0 among Standard patients. Over 90% of patients remained free of recurrence at 2 years in both cohorts. Time to detection of recurrence was similar between two cohorts (HR 1.05, 95% CI 0.45-2.52), as was overall survival (HR 0.91, 95% CI 0.36-2.29). The proportion of radically treatable recurrences was also similar (42% Standard vs. 47% PET Stratified). The hospital cost savings per patient from reduced review were AUD$2606 over 2 years, AUD$5012 over five.

Conclusion: (18)FDG-PET-CT to stratify follow-up intensity after radical radiotherapy for head and neck cancer reduces costs with no apparent clinical detriment.

BRAIN $^{18}$F-DOPA PET AND COGNITION IN DE NOVO PARKINSON'S DISEASE.


Abstract

Purpose: The role of mesocortical dopaminergic pathways in the cognitive function of patients with early Parkinson's disease (PD) needs to be further clarified.

Methods: The study groups comprised 15 drug-naive patients with de novo PD and 10 patients with essential tremor (controls) who underwent $^{18}$F-DOPA PET (static acquisition, normalization on mean cerebellar counts) and an extended neuropsychological test battery. Factor analysis with varimax rotation was applied to the neuropsychological test scores, to yield five factors from 16 original scores, which explained 82% of the total variance. Correlations between cognitive factors and $^{18}$F-DOPA uptake were assessed with SPM8, taking age and gender as nuisance variables.

Results: $^{18}$F-DOPA uptake was significantly lower in PD patients than in controls in the bilateral striatum, mainly in the more affected (right) hemisphere, and in a small right temporal region. Significant positive correlations were found only in PD patients between the executive factor and $^{18}$F-DOPA uptake in the bilateral anterior cingulate cortex (ACC) and the middle frontal gyrus, between the verbal fluency factor and $^{18}$F-DOPA uptake in left BA 46 and the bilateral striatum, and between the visuospatial factor and $^{18}$F-DOPA uptake in the left ACC and bilateral striatum. No correlations were found between $^{18}$F-DOPA uptake and either the verbal memory factor or the abstraction-working memory factor.

Conclusion: These data clarify the role of the mesocortical dopaminergic pathways in cognitive function in early PD, highlighting the medial frontal lobe, anterior cingulate, and left BA 46 as the main sites of cortical correlation with executive and language functions.


VOLUMETRIC ASSESSMENT OF RECURRENT OR PROGRESSIVE GLIOMAS: COMPARISON BETWEEN F-DOPA PET AND PERFUSION-WEIGHTED MRI.


Abstract

Purpose: To compare the diagnostic information obtained with $6-[^{18}$F]-fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) PET and relative cerebral blood volume (rCBV) maps in recurrent or progressive glioma.

Methods: All patients with recurrent or progressive glioma referred for F-DOPA imaging at our institution between May 2010 and May 2014 were retrospectively included, provided that macroscopic disease was visible on conventional MRI images and that rCBV maps were available for comparison. The final analysis included 50 paired studies (44 patients). After image registration, automatic tumour segmentation of both sets of images was performed using the average signal in a large reference VOI including grey and white matter multiplied by 1.6. Tumour volumes identified by both modalities were compared and their spatial congruence calculated. The distances between F-DOPA uptake and rCBV hot spots, tumour-to-brain ratios (TBRs) and normalized histograms were also computed.

Results: On visual inspection, 49 of the 50 F-DOPA and 45 of the 50 rCBV studies were classified as positive. The tumour volume delineated using F-DOPA (F-DOPAvol 1.6) greatly exceeded that of rCBV maps (rCBVvol 1.6). The median F-DOPAvol 1.6 and rCBVvol 1.6 were 11.44 ml (range 0 -
220.95 ml) and 1.04 ml (range 0 - 26.30 ml), respectively (p < 0.00001). Overall, the median overlapping volume was 0.27 ml, resulting in a spatial congruence of 1.38 % (range 0 - 39.22 %). The mean hot spot distance was 27.17 mm (±16.92 mm). F-DOPA uptake TBR was significantly higher than rCBV TBR (1.76 ± 0.60 vs. 1.15 ± 0.52, respectively; p < 0.0001). The histogram analysis showed that F-DOPA provided better separation of tumour from background. In 6 of the 50 studies (12 %), however, physiological uptake in the striatum interfered with tumour delineation.

**Conclusion:** The information provided by F-DOPA PET and rCBV maps are substantially different. Image interpretation is easier and a larger tumour extent is identified on F-DOPA PET images than on rCBV maps. The clinical impact of such differences needs to be explored in future studies.


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Molecular imaging in hereditary succinate dehydrogenase mutation-related paragangliomas.

Marzola MC, Rubello D.

### Abstract

Multiple paraganglioma (PGL) syndromes related to succinate dehydrogenase (SDH) gene mutations are rare hereditary conditions. These present with heterogeneous clinical signs and symptoms and in many cases are difficult to classify.

We summarize the pathophysiological, clinical, laboratory, and morphological and functional imaging characteristics of SDH gene mutation PGLs, emphasizing F-FDG and F-DOPA PET/CT. We correlate clinical and genetic features of SDH-related PGLs with specific PET radiopharmaceuticals, with the aim to obtain an "individualized" diagnostic approach.


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18F-Fluorocholine PET-CT enables minimal invasive parathyroidectomy in patients with negative sestamibi SPECT-CT and ultrasound: A case report.

Kluijfhout WP, Vriens MR, Valk GD, Barth RE, Borel Rinkes IH, de Keizer B.

Abstract

Introduction: Primary hyperparathyroidism is a common endocrine disorder for which the primary treatment is surgery. For minimal invasive parathyroidectomy adequate pre-operative imaging is essential. Conventional imaging is often inconclusive. There are reports that 18F-fluorocholine PET-CT might be a superior imaging modality, however evidence is still very scarce. This is the first report of a case with negative ultrasound and sestamibi SPECT-CT imaging that underwent successful minimal invasive surgery because of 18F-fluorocholine PET-CT.

Presentation of case: A 57 year-old man presented to us with complaints of fatigue. Laboratory results showed a biochemical primary hyperparathyroidism and an additional DEXA-scan revealed osteopenia of the lumbar spine. Conventional imaging consisting of neck ultrasound and Tc-99m-sestamibi SPECT-CT was however unable to localize the pathological gland. Subsequent 18F-fluorocholine PET-CT did clearly localize an adenoma dorsally of the left thyroid lobe which was removed at that exact location using minimal invasive parathyroidectomy. Histological examination confirmed the diagnosis adenoma and calcium levels remained normal at follow-up.

Discussion: There is clinical need for a superior imaging modality to detect pathological parathyroid glands to enable minimal invasive surgery. 18F-Fluorocholine is widely available.

Conclusion: 18F-Fluorocholine PET-CT is a promising new imaging modality for localizing parathyroid adenomas and enabling minimal invasive parathyroidectomy when conventional imaging fails to do. Clinicians should consider its use as a second line modality for optimal patient care.


Changes in Skeletal Tumor Activity on 18F-choline PET/CT in Patients Receiving 223Radium Radionuclide Therapy for Metastatic Prostate Cancer.

Miyazaki KS, Kuang Y, Kwee SA.

Abstract

Radium-223 dichloride is an alpha-emitting radiopharmaceutical shown to prolong survival in patients with castrate-resistant prostate cancer (CRPC) and symptomatic skeletal metastases. This report describes in two patients the acute changes in bone metastatic activity detected by F-18 choline PET/CT imaging midway during treatment with radium-223 dichloride. In addition to visual and standardized uptake value analysis, changes in the whole-body tumor burden were quantified by measuring the difference in net metabolically active tumor volume (MATV) and total lesion activity (TLA) between pre- and mid-treatment PET scans.

After the third dose of radium-223 dichloride, near-total disappearance of abnormal skeletal activity was observed in one case (net MATV change from 260.7 to 0.8 cc; net TLA change from 510.7 to 2.1), while a heterogeneous tumor response was observed in the other (net MATV change from 272.2 to 241.3 cc; net TLA change from 987.1 to 779.4). Corresponding normalization and persistent elevation in serum alkaline phosphatase levels were observed in these cases, respectively. Further research is needed to determine the predictive value of serial F-18 choline PET/CT imaging in patients receiving radium-223 dichloride for CRPC.

Incidental Neurofibroma on $^{18}$F-Fluorocholine PET/MR.

Agrawal K, Sajjan RS, Gavra M, Fraioli F, Bomanji J, Syed R.

Abstract

Neurofibromas are benign peripheral nerve sheath tumors. We described a unique case of recurrent prostate cancer with coexisting neurofibroma diagnosed on F-fluorocholine PET/MRI.


State of the PET/CT with $^{11}$C-choline and $^{18}$F-fluorocholine in the diagnosis and follow-up of localized and locally advanced prostate cancer.


Abstract

Objective: To provide an updated state of the art about the role of positron emission tomography/computed tomography (PET/CT) with $^{11}$C-Choline and $^{18}$F-fluorocholine in the localized and locally advanced Prostate Cancer (PCa) in the staging and restaging setting.

Methods: We performed a non-systematic review of the literature based on a free-text search in the National Library of Medicine Database (MEDLINE) to select English-language published papers evaluating PET and PET/CT imaging with radiolabelled choline in initial diagnosis and in post-treatment phase in PCa patients.

Results: PET and PET/CT with $^{11}$C-choline and $^{18}$F-fluorocholine have been largely investigated as non-invasive diagnostic tools in PCa. Actually, the relatively high rate of false negative findings due to the small dimension of neoplastic lesions and the available spatial resolution of PET tracers limits the routine use of choline PET and PET/CT in staging setting; moreover, it cannot reliably replace the lymph node (LN) dissection for detecting LN involvement. On restaging setting, Choline PET/CT showed a higher accuracy than conventional imaging modalities, especially in the detection of LN and systemic metastases, while it is less accurate than magnetic resonance imaging in the detection of local relapse.

Conclusion: In the Prostate Specific Antigen (PSA) era with a large number of localized disease, the diagnostic performance of choline PET and PET/CT lack of reliability in initial diagnosis of PCa. The major clinical role of choline PET/CT is the re-staging of patients with a biochemical relapse after radical treatment; the promising performance of choline PET/CT scan in patients with low levels of PSA could also lead the clinicians for to perform PET-guided adjuvant curative therapies or palliative treatments in patients already treated radically for PCa.

The role of radionuclide imaging in the surgical management of primary hyperparathyroidism.

Hindié E, Zanotti-Fregonara P, Tabarin A, Rubello D, Morelec I, Wagner T, Henry JF, Taïeb D.

Abstract
Primary hyperparathyroidism is a frequent and potentially debilitating endocrine disorder for which surgery is the only curative treatment. The modalities of parathyroid surgery have changed over the last 2 decades, as conventional bilateral neck exploration is no longer the only surgical approach. Parathyroid scintigraphy plays a major role in defining the surgical strategy, given its ability to orient a targeted (focused) parathyroidectomy and to recognize ectopic locations or multiglandular disease.

This review, which represents a collaborative effort between nuclear physicians, endocrinologists, and endocrine surgeons, emphasizes the importance of performing imaging before any surgery for primary hyperparathyroidism, even in the case of conventional bilateral neck exploration. We discuss the advantages and drawbacks of targeted parathyroidectomy and the performance of various scintigraphic protocols to guide limited surgery.

We also discuss the optimal strategy to localize the offending gland before reoperation for persistent or recurrent hyperparathyroidism. Finally, we describe the potential applications of novel PET tracers, with special emphasis on $^{18}$F-fluorocholine.


Oncocytic Adenoma of Thyroid Incidentally Detected by 18F-Fluorocholine PET/CT.

Aziz AL, Courbon F, Dierickx LO, Pascal P, Zerdoud S.

Abstract
A 58-old-man underwent $^{18}$F-fluorocholine PET/CT for restaging of prostate cancer because of a rising level of prostate-specific antigen. $^{18}$F-fluorocholine showed no significant tracer uptake at the site of the prostatectomy or the pelvic lymph nodes. Incidental high tracer uptake was observed in a 26 × 23 mm left thyroid nodule. A benign tumor of the thyroid (oncocytic adenoma of thyroid) was diagnosed after left loboisthmectomy.


Asymptomatic metastasis to cricoid from prostate carcinoma: an incidental finding detected on $^{18}$F-choline PET/CT.

Ng SJ, Sinha AK, Loi HY, Khor LK.

Abstract
Metastases to the larynx from prostate carcinoma are rare. We describe a case of asymptomatic prostate carcinoma metastasis to the right cricoid cartilage detected on $^{18}$F-fluorocholine PET/CT. This was histologically proven on open biopsy and the patient was offered local radiotherapy.

Usefulness of MRI-assisted metabolic volumetric parameters provided by simultaneous $^{18}$F-fluorocholine PET/MRI for primary prostate cancer characterization.


Abstract

Purpose: The aim of this study was to determine the usefulness of MRI-assisted positron emission tomography (PET) parameters provided by simultaneous $^{18}$F-fluorocholine (FCH) PET/MRI for characterization of primary prostate cancer.

Methods: Thirty patients with localized prostate cancer (mean age 69.4 ± 6.7 years) confirmed by biopsy were prospectively enrolled for simultaneous PET/MRI imaging. The patients underwent ($^{18}$)F-FCH PET/MRI 1 week before undergoing total prostatectomy. Multiple parameters of diffusion-weighted MRI [minimum and mean apparent diffusion coefficient (ADCmin and ADCmean)], metabolic PET [maximum and mean standardized uptake value (SUVmax and SUVmean)], and metabolic volumetric PET [metabolic tumor volume (MTV) and uptake volume product (UVP)] were compared with laboratory, pathologic, and immunohistochemical (IHC) features of the prostate cancer specimen. PET parameters were divided into two categories as follows: volume of interest (VOI) of prostate by SUV cutoff 2.5 (SUVmax, SUVmean, MTVSUV, and UVPSUV) and MRI-assisted VOI of prostate cancer (SUVmaxMRI, SUVmeanMRI, MTVMRI, and UVPMRI).

Results: The rates of prostate cancer-positive cases identified by MRI alone, $^{18}$F-FCH PET alone, and $^{18}$F-FCH PET/MRI were 83.3, 80.0, and 93.3 %, respectively. Among the multiple PET/MRI parameters, MTVMRI showed fair correlation with serum prostate-specific antigen (PSA; $r = 0.442$, $p = 0.014$) and highest correlation with tumor volume ($r = 0.953$, $p < 0.001$). UVPMRI showed highest correlation with serum PSA ($r = 0.531$, $p = 0.003$), good correlation with tumor volume ($r = 0.908$, $p < 0.001$), and it was significantly associated with Gleason score ($p = 0.041$). High MTVMRI and UVPMRI values were significant for perineural invasion, lymphatic invasion, extracapsular extension, seminal vesicle invasion, and positive B-cell lymphoma 2 (Bcl-2) expression (all $p < 0.05$).

Conclusion: Simultaneous $^{18}$F-FCH PET/MRI demonstrated a better diagnostic value for localized prostate cancer detection than each individual modality. MRI-assisted metabolic volumetric PET parameters (MTVMRI and UVPMRI) provided more accurate characterization of prostate cancer than conventional PET and MRI parameters.

**Methods:** The study group comprised 36 patients with a median age of 72 years (range 48-90 years) who were treated with enzalutamide 160 mg once daily after at least one chemotherapeutic regimen with docetaxel. Patients were evaluated monthly for serological prostate-specific antigen (PSA) response. FCH PET/CT was performed at baseline and repeated after 3-6 weeks. Univariate and multivariate Cox regression models addressed potential predictors of progression-free survival (PFS) and overall survival (OS).

**Results:** At a median follow-up of 24.2 months (range 1.8-27.3 months), 34 patients were evaluable for early FCH PET/CT evaluation of response, and of these 17 showed progressive disease (PD) and 17 had stable disease or a partial response. A decrease in PSA level of more than 50 % was observed in 21 patients. Early FCH PET/CT PD predicted radiological PD 3 months in advance of CT in 12 of 18 patients (66 %) and was discordant with the decrease in PSA level in 13 patients. In 6 of these, biochemical PD was confirmed in 2 months. In multivariate analysis, only decrease in PSA level and FCH PET/CT were significant predictors of PFS ($p=0.0005$ and $p=0.029$, respectively), whereas decrease in PSA level alone was predictive of OS ($p=0.007$).

**Conclusion:** This is one of the first studies to evaluate the role of FCH PET/CT as an early predictor of outcome in mCRPC patients treated with enzalutamide. Our preliminary results suggest that the combination of FCH PET/CT and decrease in PSA level could be a valid tool to predict PFS in mCRPC patients. PSA remains the single most important prognostic factor, while FCH PET/CT does not add more information on OS beyond that obtained from PSA. Further studies in larger populations are needed to confirm these data and to clarify the role of FCH PET/CT in predicting response to enzalutamide in mCRPC patients.


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**Unusual lymph node metastases of prostate cancer detected by $^{18}$F-fluorocholine PET/CT.**

Pinaquy JB, Allard JB, Cornelis F, Pasticier G, De Clermont H.

**Abstract**
A 65-year-old patient with prostate adenocarcinoma was explored by $^{18}$F-fluorocholine (FCH) PET/CT for pretreatment staging because of a high risk of prostate cancer. Images showed multiple foci with increased uptake of $^{18}$F-FCH within some pelvic and retroperitoneal lymph nodes, osseous foci (iliac bones and sacrum), and much more unusual, increased uptake foci within some left supraclavicular and left axillary lymph nodes. Owing to the rarity of spread to supraclavicular lymph nodes, surgical removal was performed and revealed prostate cancer metastases.


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**$^{18}$F-Fluorocholine PET/CT as a complementary tool in the follow-up of low-grade glioma: diagnostic accuracy and clinical utility.**


**Abstract**

**Purpose:** The follow-up of treated low-grade glioma (LGG) requires the evaluation of subtle clinical changes and MRI results. When the result is inconclusive, additional procedures are required to assist...
decision-making, such as the use of advanced MRI (aMRI) sequences and nuclear medicine scans (SPECT and PET). The aim of this study was to determine whether incorporating $^{18}$F-fluorocholine PET/CT in the follow-up protocol for treated LGG improves diagnostic accuracy and clinical utility.

**Methods:** This was a prospective case-series study in patients with treated LGG during standard follow-up with indeterminate clinical and/or radiological findings of tumour activity. All patients underwent clinical evaluation, aMRI, (201)TI-SPECT and $^{18}$F-fluorocholine PET/CT. Images were interpreted by visual evaluation complemented with semiquantitative analysis.

**Results:** Between January 2012 and December 2013, 18 patients were included in this study. The final diagnosis was established by histology (five surgical specimens, one biopsy specimen) or by consensus of the Neuro-Oncology Group (11 patients) after a follow-up of >6 months (mean 14.9 ± 2.72 months). The global diagnostic accuracies were 90.9% for aMRI (38.8% inconclusive), 69.2% for (201)TI-SPECT (11.1% inconclusive), and 100% for $^{18}$F-fluorocholine PET/CT. (201)TI-SPECT led correctly to a change in the initial approach in 38.9% of patients but might have led to error in 27.8%. The use of $^{18}$F-fluorocholine PET/CT alone rather than (201)TI-SPECT led correctly to a change in the approach suggested by routine follow-up in 72.2% of patients and endorsed the approach in the remaining 27.8%.

**Conclusion:** Our results support the need to complement structural MRI with aMRI and nuclear medicine procedures in selected patients. $^{18}$F-Fluorocholine PET/CT can be useful in the individualized management of patients with treated LGG with uncertain clinical and/or radiological evidence of tumour activity.


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**Clinical utility of $^{18}$F-fluorocholine positron-emission tomography/computed tomography (PET/CT) in biochemical relapse of prostate cancer after radical treatment: results of a multicentre study.**


**Abstract**

**Objective:** To evaluate $^{18}$F-fluorocholine positron-emission tomography (PET)/computed tomography (CT) in restaging patients with a history of prostate adenocarcinoma who have biochemical relapse after early radical treatment, and to correlate the technique's disease detection rate with a set of variables and clinical and pathological parameters.

**Patients and methods:** This was a retrospective multicentre study that included 374 patients referred for choline-PET/CT who had biochemical relapse. In all, 233 patients who met the following inclusion criteria were analysed: diagnosis of prostate cancer; early radical treatment; biochemical relapse; main clinical and pathological variables; and clinical, pathological and imaging data needed to validate the results. Criteria used to validate the PET/CT: findings from other imaging techniques, clinical follow-up, treatment response and histological analysis. Different statistical tests were used depending on the distribution of the data to correlate the results of the choline-PET/CT with qualitative [T stage, N stage, early radical prostatectomy (RP) vs other treatments, hormone therapy concomitant to choline-PET/CT] and quantitative [age, Gleason score, prostate-specific antigen (PSA) levels at diagnosis, PSA nadir, PSA level on the day of the choline-PET/CT (Trigger PSA) and PSA doubling time (PSADT)] variables. We analysed whether there were independent predictive factors associated with positive PET/CT results.

**Results:** Choline-PET/CT was positive in 111 of 233 patients (detection rate 47.6%) and negative in 122 (52.4%). Disease locations: prostate or prostate bed in 26 patients (23.4%); regional and/or distant lymph nodes in 52 (46.8%); and metastatic bone disease in 33 (29.7%). Positive findings were
validated by: results from other imaging techniques in 35 patients (15.0%); at least 6 months of clinical follow-up in 136 (58.4%); treatment response in 24 (10.3%); histological analysis of lesions in 17 (7.3%); and follow-up plus imaging results in 21 (9.0%).

The statistical analysis of qualitative variables, corresponding to patients’ clinical characteristics, and the positive/negative final PET/CT results revealed that only whether or not early treatment with RP was done was statistically significant (P < 0.001), with the number of positive results higher in patients who did not undergo a RP. Among the quantitative variables, Gleason score, Trigger PSA and PSADT clearly differentiated the two patient groups (positive and negative choline-PET/CT: P = 0.010, P = 0.001 and P = 0.025, respectively).

A Gleason score of <5 or ≥8 clearly differentiated positive from negative PET. Trigger PSA: mean of 8 ng/mL for positive PET/CT vs 2.8 ng/mL for negative PET/CT; PSADT: mean of 8 months for positive vs 12.6 months for negative. The optimal threshold values were: 3 ng/mL for Trigger PSA level and 6 months for PSADT (Youden index/receiver operating characteristic curve).

Analysing these two variables together showed that PSADT was more conclusive in patients with lower Trigger PSA levels. Analysing variables by location showed that only PSADT was able to differentiate between those with disease confined to the prostate compared with the other two locations (lymph nodes and bone), with shorter PSADT in these two, which was statistically significant (P < 0.002). In the patient group with a PSA level of <1.5 ng/mL, 30.8% had the disease, 7% of whom had metastatic bone disease. In the multivariate logistic regression, the risks factors that were clearly independent for those with positive PET/CT were: PSA level of >3 ng/mL, no early RP, and Gleason score of ≥8.

**Conclusion:** Our results support the usefulness of $^{18}$F-fluorocholine PET/CT in biochemical relapse of prostate cancer after radical treatment, with an overall disease detection rate close to 50%, and it can be recommended as first-line treatment. As mentioned above, besides Trigger PSA levels, there are other clinical and pathological variables that need to be considered so as to screen patients properly and thus minimise the number of nodular lesions and increase the diagnostic accuracy of the examination.

The use of dynamic O-(2-18F-fluoroethyl)-L-tyrosine PET in the diagnosis of patients with progressive and recurrent glioma.


Abstract

Background: We evaluated the diagnostic value of static and dynamic O-(2-18F][fluoroethyl]-L-tyrosine (18F-FET) PET parameters in patients with progressive or recurrent glioma.

Methods: We retrospectively analyzed 132 dynamic 18F-FET PET and conventional MRI scans of 124 glioma patients (primary World Health Organization grade II, n = 55; grade III, n = 19; grade IV, n = 50; mean age, 52 ± 14 y). Patients had been referred for PET assessment with clinical signs and/or MRI findings suggestive of tumor progression or recurrence based on Response Assessment in Neuro-Oncology criteria. Maximum and mean tumor/brain ratios of 18F-FET uptake were determined (20-40 min post-injection) as well as tracer uptake kinetics (ie, time to peak and patterns of the time-activity curves). Diagnoses were confirmed histologically (95%) or by clinical follow-up (5%). Diagnostic accuracies of PET and MR parameters for the detection of tumor progression or recurrence were evaluated by receiver operating characteristic analyses/chi-square test.

Results: Tumor progression or recurrence could be diagnosed in 121 of 132 cases (92%). MRI and 18F-FET PET findings were concordant in 84% and discordant in 16%. Compared with the diagnostic accuracy of conventional MRI to diagnose tumor progression or recurrence (85%), a higher accuracy (93%) was achieved by 18F-FET PET when a mean tumor/brain ratio ≥2.0 or time to peak <45 min was present (sensitivity, 93%; specificity, 100%; accuracy, 93%; positive predictive value, 100%; P < .001).

Conclusion: Static and dynamic 18F-FET PET parameters differentiate progressive or recurrent glioma from treatment-related nonneoplastic changes with higher accuracy than conventional MRI.


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Dual-time-point O-(2-18F-fluoroethyl)-L-tyrosine PET for grading of cerebral gliomas.


Abstract

Objective: We aimed to evaluate the diagnostic potential of dual-time-point imaging with positron emission tomography (PET) using O-(2-18F][fluoroethyl]-L-tyrosine (18F-FET) for non-invasive grading of cerebral gliomas compared with a dynamic approach.

Methods: Thirty-six patients with histologically confirmed cerebral gliomas (21 primary, 15 recurrent; 24 high-grade, 12 low-grade) underwent dynamic PET from 0 to 50 min post-injection (p.i.) of 18F-FET, and additionally from 70 to 90 min p.i. Mean tumour-to-brain ratios (TBRmean) of 18F-FET uptake were determined in early (20-40 min p.i.) and late (70-90 min p.i.) examinations. Time-activity curves (TAC) of the tumours from 0 to 50 min after injection were assigned to different patterns. The diagnostic accuracy of changes of 18F-FET uptake between early and late examinations for tumour grading was compared to that of curve pattern analysis from 0 to 50 min p.i. of 18F-FET.
**Results:** The diagnostic accuracy of changes of the TBR_{mean} of $^{18}$F-FET PET uptake between early and late examinations for the identification of HGG was $81\%$ (sensitivity $83\%$; specificity $75\%$; cutoff - $8\%$; $p < 0.001$), and $83\%$ for curve pattern analysis (sensitivity $88\%$; specificity $75\%$; $p < 0.001$).

**Conclusion:** Dual-time-point imaging of $^{18}$F-FET uptake in gliomas achieves diagnostic accuracy for tumour grading that is similar to the more time-consuming dynamic data acquisition protocol.


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$^{18}$F-fluoro-ethyl-tyrosine positron emission tomography for grading and estimation of prognosis in patients with intracranial gliomas.

Gempt J^1, Bette S^2, Ryan YM^2, Buchmann N^2, Peschke P^2, Pyka T^3, Wester HJ^3, Förster S^3, Meyer B^2, Ringel F^2.

**Abstract**

**Introduction:** Histopathological examination is the standard for grading and determination of diagnosis in intrinsic brain tumors though the possibility of malignization and tumor heterogeneity always bears the possibility of tumor under-grading or misjudgement regarding the estimation of prognosis. The aim of the present study was to evaluate the use of $^{18}$F-FET-PET (FET-PET) for the grading and estimation of prognosis in newly diagnosed patients with intracranial gliomas in a clinical setting.

**Methods:** Patients who were treated for a newly diagnosed intracranial glioma between January 2007 and May 2012, and had a preoperative FET-PET and MRI scan between were included. The ratio of counts in a tumor VOI (volume of interest) with maximum uptake to the respective counts in a background VOI was calculated to provide the tumor-to-normal (T/N) ratio. The clinical and histopathological data (tumor grading, pre- and postoperative neurological status, Karnofsky Performance Status Scale scores, and overall survival rates) were recorded.

**Results:** One hundred fifty-two patients (39 WHO II, 26 WHO III, 87 WHO IV) were included. The median T/N ratio was 2.81 (1.1-8.1). The median T/N ratio of low-grade glioma patients was 1.65 (1.1-3.7), and 3.14 (1.61-8.1, $p<0.001$) in high-grade glioma patients.

The median survival for patients with WHO III tumors was 22.8 months (95% CI: 15.87%-NA) and 13.23 months (95% CI: 10.83-15.6) for patients with WHO IV tumors ($p=0.0001$). For T/N$\leq$1.6, no deaths were recorded; for 1.6<T/N$\leq$3, median survival was 25.6 months (95% CI: 16.5%-NA), while for T/N>3, median survival was 14.0 months (95% CI: 11.7-16.2, $p<0.001$). The test of the maximally selected log-rank statistic resulted in a T/N ratio of 1.88 as the cut-off value, with the greatest difference in overall survival between patients with longer and shorter survival.

The ROC curve for differentiation of low- vs. high-grade tumors with regard to the T/N ratio showed an area under the curve (AUC) of 0.903. Regarding the prognostic validity for overall survival ROC-curves for 12-month, 24-month and 48-month survival display a higher validity for the WHO-classification than for the imaging modalities though with an AUC of 0.847 for the 48-month survival T/N ratio and MRI contrast-enhancement have a high prognostic value as well.

**Conclusion:** Our study suggests that FET-PET can predict prognosis and survival in patients harboring intracranial gliomas and serves as a valuable tool to supplement the established clinical and histopathological parameters.


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Uptake and tracer kinetics of $O$-(2-$^{18}$F-fluoroethyl)-$L$-tyrosine in meningiomas: preliminary results.


Abstract

**Purpose:** $O$-(2-[$^{18}$F]fluoroethyl)-$L$-tyrosine ($^{18}$F-FET) is a well-established PET tracer for the imaging of cerebral gliomas, but little is known about $^{18}$F-FET uptake in meningiomas. The aim of this study was to explore $^{18}$F-FET kinetics and tumour-to-background contrast in meningiomas of various histologies.

**METHODS:** A group of 24 patients with suspected cerebral meningioma on MRI/CT had an additional dynamic $^{18}$F-FET PET scan prior to surgery. Time-activity curves (TAC) of $^{18}$F-FET uptake in the tumours and tumour-to-brain ratios (TBR) for early (3 - 14 min after injection) and late $^{18}$F-FET uptake (20 - 40 min after injection) were analysed and compared with histological subtypes and WHO grade. $^{18}$F-FET uptake in critical structures in the skull base was also evaluated in terms of tumour-to-tissue (T/Tis) ratio.

**RESULTS:** TBR of $^{18}$F-FET uptake in meningiomas was significantly higher in the early phase than in the late phase (3.5 ± 0.8 vs. 2.2 ± 0.3; P < 0.001). The difference in TBR between low-grade meningiomas (WHO grade I, 18 patients) and high-grade meningiomas (WHO grade II or III, 6 patients) was significant in the late phase of $^{18}$F-FET uptake (2.1 ± 0.2 vs. 2.5 ± 0.2, P = 0.003) while there was no significant difference in the early phase. ROC analysis showed that TBR of $^{18}$F-FET uptake in the late phase had significant power to differentiate low-grade from high-grade meningiomas (AUC 0.87 ± 0.18, sensitivity 83 %, specificity 83 %, optimal cut-off 2.3; P < 0.01). Evaluation of TAC yielded three different curve patterns of $^{18}$F-FET PET uptake.

Combination of TBR (cut-off value 2.3) and TAC pattern slightly improved the differentiation of high-grade from low-grade meningiomas (accuracy 92 %; P = 0.001). Analysis of background radioactivity in the skull base indicated that $^{18}$F-FET uptake may be helpful in distinguishing meningioma tissue in the late phase. T/Tis ratios were >1.2 in all patients for the periorbita, sphenoidal sinus, pituitary gland, tentorium, bone and brain, in more than 90 % of patients for the mucosa and dura, but in only 63 % of patients for the cavernous sinus.

**CONCLUSION:** $^{18}$F-FET PET may provide additional information for noninvasive grading of meningiomas and possibly for the discrimination of tumour in critical areas of the skull base. A further evaluation of $^{18}$F-FET PET in meningiomas appears to be justified.

**TU-AB-BRA-05: Repeatability of $[^{18}\text{F}]-\text{NaF} \text{ PET Imaging Biomarkers for Bone Lesions: A Multicenter Study.}**

**Lin C, Bradshaw T, Perk T, Harmon S, Liu G, Jeraj R.**

**Abstract**

**Purpose:** Quantifying the repeatability of imaging biomarkers is critical for assessing therapeutic response. While therapeutic efficacy has been traditionally quantified by SUV metrics, imaging texture features have shown potential for use as quantitative biomarkers. In this study we evaluated the repeatability of quantitative $[^{18}\text{F}]-\text{NaF} \text{ PET-derived SUV metrics and texture features in bone lesions from patients in a multicenter study.}**

**Methods:** Twenty-nine metastatic castrate-resistant prostate cancer patients received whole-body test-retest NaF PET/CT scans from one of three harmonized imaging centers. Bone lesions of volume greater than 1.5 cm$^3$ were identified and automatically segmented using a SUV$>$15 threshold. From each lesion, 55 NaF PET-derived texture features (including first-order, co-occurrence, grey-level run-length, neighbor gray-level, and neighbor gray-tone difference matrix) were extracted. The test-retest repeatability of each SUV metric and texture feature was assessed with Bland-Altman analysis.

**Results:** A total of 315 bone lesions were evaluated. Of the traditional SUV metrics, the repeatability coefficient (RC) was 12.6 SUV for SUVmax, 2.5 SUV for SUVmean, and 4.3 cm$^3$ for volume. Their respective intralesion coefficients of variation (COVs) were 12%, 17%, and 6%. Of the texture features, COV was lowest for entropy (0.03%) and highest for kurtosis (105%). Lesion intraclass correlation coefficient (ICC) was lowest for maximum correlation coefficient (ICC=0.848), and highest for entropy (ICC=0.985). Across imaging centers, repeatability of texture features and SUV varied. For example, across imaging centers, COV for SUVmax ranged between 11-23%.

**Conclusion:** Many NaF PET-derived SUV metrics and texture features for bone lesions demonstrated high repeatability, such as SUVmax, entropy, and volume. Several imaging texture features demonstrated poor repeatability, such as SUVtotal and SUVstd. These results can be used to establish response criteria for NaF PET-based treatment response assessment. Prostate Cancer Foundation (PCF).


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**SU-C-BRA-01: $^{18}\text{F}-\text{NaF} \text{ PET/CT-Directed Dose Escalation in Stereotactic Body Radiotherapy for Spine Oligometastases From Prostate Cancer.}**


**Abstract**

**Purpose:** To investigate the technical feasibility of SBRT dose painting using $^{18}\text{F}-\text{NaF} \text{ PET scans guidance in patients with spine oligometastases from prostate cancer.}**

**Methods:** As a proof of concept, six patients with 14 spine oligometastatic lesions from prostate cancer who had $^{18}\text{F}-\text{NaF} \text{ PET/CT scan prior to treatment were retrospectively included. GTVreg was delineated according to the regular tumor boundary shown on PET and/or CT images; and GTVMATV was contoured based on a net metabolically active tumor volume (MATV) defined by 60% of the SUVmax values on $^{18}\text{F}-\text{NaF} \text{ PET images. The PTVs (PTVreg and PTVMATV) were defined as respective GTVs (plus involved entire vertebral body for PTVreg) with a 3-mm isotropic expansion.}**
margin. Three 1-fraction SBRT plans using VMAT technique along with 10 MV FFF beams (Plan24Gy, Plan24-27Gy, and Plan24-30Gy) were generated for each patient. All plans included a dose of 24 Gy prescribed to PTVreg. The Plan24-27Gy and Plan24-30Gy also included a simultaneous boost dose of 27 Gy or 30 Gy prescribed to the PTVMATV, respectively. The feasibility of $^{18}$F-NaF PET-guided SBRT dose escalation was evaluated by its ability to achieve the prescription dose objectives while adhering to organ-at-risk (OAR) dose constraints. The normal tissue complication probabilities (NTCP) calculated by radiological models were also compared between the plans.

**Results:** In all 33 SBRT plans generated, the planning objectives and dose constraints were met without exception. Plan24-27Gy and Plan24-30Gy had a significantly higher dose in PTVMATV than Plan24Gy ($p < 0.05$), respectively, while maintaining a similar OAR sparing profile and NTCP values.

**Conclusion:** Using VMAT with FFF beams to incorporate a simultaneous $^{18}$F-NaF PET-guided radiation boost dose up to 30 Gy into a SBRT plan is technically feasible. The relationship between local control and normal tissue toxicity in SBRT dose painting should be validated in clinical trials.


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**Prognostic factors in patients treated with radium-223: the role of skeletal tumor burden on baseline $^{18}$F-fluoride-PET/CT in predicting overall survival.**

Etchebehere E, Araujo JC, Fox PS, Swanston NM, Macapinlac HA, Rohren EM.

**Abstract**

**Purpose:** To evaluate outcome after radium-223 dichloride therapy (Ra-223) and to determine if skeletal tumor burden on whole-body $^{18}$F-Fluoride-PET/CT can be used as a predictive biomarker of survival in patients treated Ra-223.

**Patients and methods:** Forty-two patients with hormone-refractory prostate cancer underwent Ra-223 and a baseline fluoride-PET/CT scan. Fluoride-PET/CT parameters were generated, including maximum SUV of the hottest lesion ($h$SUV\textsubscript{max}), average SUV of disease (Mean10), and skeletal tumor burden indices of total fluoride skeletal metastatic lesion uptake (TLF10) and total volume of fluoride avid bone metastases (FTV10). Overall survival (OS) was the primary end point. Secondary end points were progression-free survival (PFS) and skeletal related event (SRE).

**Results:** Skeletal tumor burden indices (TLF10 and FTV10) derived from fluoride-PET/CT at baseline were highly correlated and significant independent predictors of OS ($P = 0.0212$; HR = 5.990; 95%CI $= 1.306$- 27.475). A TLF10 cutoff value of 8000 discriminated survivors from non-survivors after Ra-223 (with TLF10 values below 8000 the median OS was not estimated while with TLF10 > 8000, the median OS was 6.67 months). Visual analysis, Mean10, and hSUV\textsubscript{max} were not predictors of OS or PFS. Mean10 was found to be a significant univariate predictor of the odds of having a SRE ($P =0.0445$; OR=1.30; 95%CI = 1.006- 1.681), with a Mean10 $>$19 increasing the risk of SRE.

**Conclusion:** Skeletal tumor burden on baseline fluoride-PET/CT is a predictive biomarker of OS and the risk of a SRE in patients treated with Ra-223.


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**Ann Hematol.** 2015 Jun 13. [Epub ahead of print]

**Is there any complimentary role of F-18 NaF PET/CT in detecting of osseous involvement of multiple myeloma? A comparative study for F-18 FDG PET/CT and F-18 FDG NaF PET/CT.**

**Ak I, Onner H, Akay OM.**

**Abstract**

Multiple myeloma (MM) is a disease characterized by a monoclonal plasma cell population in the bone marrow whereby osseous involvement is a predominant feature. The aim of this prospective study was to investigate the combined use of F-18 FDG and F-18 NaF PET/CT in the skeletal assessment of patients with MM and to compare the efficacy of these two PET tracers regarding detection of myeloma-indicative osseous lesions.

A total of 26 patients (14 females and 12 males, mean age 61.8 ± 1.8 years (range 40-81 years)) with MM diagnosed according to standard criteria. All patients underwent both F-18 FDG PET/CT and F-18 NaF PET/CT scans within 1 week after the completion of the usual staging workup for MM. In total, approximately 128 focal F-18 FDG avid skeletal lesions were detected; the stage I (n = 5) patients had 10 bone lesions, the stage II (n = 11) patients had 43 lesions, and the stage III (n = 10) patients demonstrated 75 focal bone lesions.

F-18 NaF PET/CTs demonstrated fewer myeloma indicative lesions than F-18 FDG PET/CTs. Totally, 57 focal bone lesions were detected with whole body F-18 NaF PET/CT (mean 2.19 ± 0.34, between 1 and 9 lesions); the five stage I patients had 6 bone lesions, the 11 stage II pts had 18 lesions, and the ten stage III patients demonstrated 33 focal bone lesions. On the other hand, F-18 NaF PET/CT demonstrated additional 135 bone lesions defined as rib fractures and other findings due to degenerative changes. In conclusion, our study implies that F-18 NaF PET/CT scan did not actually aid for assessing the myelomatous bone lesions in patients with MM. Therefore, a complementary F-18 NaF PET/CT may be an accurate modality for detecting of bone fracture in patients with MM.


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**Clin Nucl Med.** 2015 Jun 6. [Epub ahead of print]

**Combined 18F-NaF and 18F-FDG PET/CT in the Evaluation of Sarcoma Patients.**


**Abstract**

**Purpose:** The combined administration of 18F-NaF and 18F-FDG in a single PET/CT scan has the potential to improve patient convenience and cancer detection. Here we report the use of this approach for patients with sarcomas.

**Patients and methods:** This is a retrospective review of 21 patients (12 men, 9 women; age, 19-66 years) with biopsy-proven sarcomas who had separate 18F-NaF PET/CT, 18F-FDG PET/CT, and combined 18F-NaF/18F-FDG PET/CT scans for evaluation of malignancy. Two board-certified nuclear medicine physicians and 1 board-certified musculoskeletal radiologist were randomly assigned to review the scans. Results were analyzed for sensitivity and specificity, using linear regression and receiver operating characteristics.

**Results:** A total of 13 patients had metastatic disease on 18F-NaF PET/CT, 18F-FDG PET/CT, and combined 18F-NaF/18F-FDG PET/CT. Skeletal disease was more extensive on the 18F-NaF PET/CT scan than on the 18F-FDG PET/CT in 3 patients, whereas in 1 patient, 18F-FDG PET/CT showed skeletal disease and the 18F-NaF PET/CT was negative. Extraskeletal lesions were detected on both 18F-FDG and combined 18F-NaF/18F-FDG PET/CT in 20 patients, with 1 discordant finding in the lung.
Conclusions: The combined $^{18}$F-NaF/$^{18}$F-FDG PET/CT scan allows for accurate evaluation of sarcoma patients. Further evaluation of this proposed imaging modality is warranted to identify the most suitable clinical scenarios, including initial treatment strategy and evaluation of response to therapy.


$^{18}$F-sodium fluoride PET/CT for the in vivo visualization of Mönckeberg's sclerosis in a diabetic patient.


Abstract
Diabetes is a major frequent cause of atherosclerosis vascular disease. Arterial calcification in diabetic patients is responsible for peripheral vascular involvement. Molecular imaging using $^{18}$F-sodium fluoride ($^{18}$F-NaF) positron emission tomography (PET)/computed tomography (CT) has been recently proposed as a marker to study the in vivo mineralization process in the atheroma plaque.

A 69-year-old man with a history of type 2 diabetes and no clinical evidence of peripheral arterial disease underwent an $^{18}$F-NaF PET/CT scan. A linear, well-defined $^{18}$F-NaF uptake was detected along the femoral arteries. In addition, the CT component of the PET/CT identified an unsuspected "tram-track" calcification in his femoral arteries, suggestive of medial calcification (Mönckeberg's sclerosis). In other vascular territories, focal $^{18}$F-NaF uptake was also detected in carotid and aorta atheroma plaques. Molecular imaging with $^{18}$F-NaF PET/CT might provide new functional information about the in vivo vascular calcification process in diabetic patients.


$^{18}$F-NaF Uptake by Atherosclerotic Plaque on PET/CT Imaging: Inverse Correlation Between Calcification Density and Mineral Metabolic Activity.


Abstract
Several studies have highlighted the role of vascular $^{18}$F-NaF uptake as a marker of ongoing calcium deposition. However, accumulation of $^{18}$F-NaF is often inconsistent with localization of arterial plaque. Calcification activity and thus $^{18}$F-NaF uptake might prevail in the earlier plaque stages. To test this hypothesis, we evaluated $^{18}$F-NaF uptake in plaque of 3 different densities, using density as a marker of calcification progression. We also tested whether attenuation-weighted image reconstruction affects $^{18}$F-NaF uptake in the different plaque stages.

Methods: Sixty-four oncologic patients (14 men and 50 women; mean age, 65.3 ± 8.2 y; range, 26-81 y) underwent $^{18}$F-NaF PET/CT. A volume of interest was drawn on each plaque within the infrarenal aorta to assess mean standardized uptake value and attenuation (in Hounsfield units [HU]). Plaque was then categorized as light (<210 HU), medium (211-510 HU), or heavy (>510 HU). Standardized uptake value was normalized for blood $^{18}$F-NaF activity to obtain the plaque target-to-background ratio (TBR). During this process, several focal, noncalcified areas of $^{18}$F-NaF were identified (hot spots). The TBR of the hot spots was computed after isocountour thresholding. The TBR of a noncalcified
control region was also calculated. In 35 patients, the TBR of non-attenuation-corrected images was calculated.

**Results:** The average TBR was highest in light plaque (2.21 ± 0.88), significantly lower in medium plaque (1.59 ± 0.63, P < 0.001), and lower still in heavy plaque (1.14 ± 0.37, P < 0.0001 with respect to both light and medium plaque). The TBR of the control region was not significantly different from that of heavy plaque but was significantly lower than that of light and medium plaque (P < 0.01). Hot spots had the highest absolute TBR (3.89 ± 1.87, P < 0.0001 vs. light plaque). TBRs originating from non-attenuation-corrected images did not significantly differ from those originating from attenuation-corrected images.

**Conclusion:** Our results support the concept that $^{18}$F-NaF is a feasible option in imaging molecular calcium deposition in the early stages of plaque formation, when active uptake mechanisms are the main determinants of calcium presence, but that retention of $^{18}$F-NaF progressively decreases with increasing calcium deposition in the arterial wall. Our data suggest that non-attenuation-corrected reconstruction does not significantly affect evaluation of plaque of any thickness.


Semiquantitative Analysis of the Biodistribution of the Combined $^{18}$F-NaF and $^{18}$F-FDG Administration for PET/CT Imaging.


**Abstract**

In this study, we evaluated the biodistribution of the $[^{18}\text{F}]$F/$^{18}$F-FDG administration, compared with separate $^{18}$F-NaF and $^{18}$F-FDG administrations. We also estimated the interaction of $^{18}$F-NaF and $^{18}$F-FDG in the $[^{18}\text{F}]$F/$^{18}$F-FDG administration by semiquantitative analysis.

**Methods:** We retrospectively analyzed the data of 49 patients (39 men, 10 women; mean age ± SD, 59.3 ± 15.2 y) who underwent separate $^{18}$F-FDG PET/CT and $^{18}$F-NaF PET/CT scans as well as $[^{18}\text{F}]$F/$^{18}$F-FDG PET/CT sequentially. The most common primary diagnosis was prostate cancer (n = 28), followed by sarcoma (n = 9) and breast cancer (n = 6). The mean standardized uptake values (SUVs) were recorded for 18 organs in all patients, and maximum SUV and mean SUV were recorded for all the identified malignant lesions. We also estimated the $[^{18}\text{F}]$F/$^{18}$F-FDG uptake as the sum of $^{18}$F-FDG uptake and adjusted $^{18}$F-NaF uptake based on the ratio of $^{18}$F-NaF injected dose in $[^{18}\text{F}]$F/$^{18}$F-FDG PET/CT. Lastly, we compared the results to explore the interaction of $^{18}$F-FDG and $^{18}$F-NaF uptake in the $[^{18}\text{F}]$F/$^{18}$F-FDG scan.

**Results:** The $[^{18}\text{F}]$F/$^{18}$F-FDG uptake in the cerebral cortex, cerebellum, parotid gland, myocardium, and bowel mostly reflected the $^{18}$F-FDG uptake, whereas the uptake in the other analyzed structures was influenced by both the $^{18}$F-FDG and the $^{18}$F-NaF uptake. The $[^{18}\text{F}]$F/$^{18}$F-FDG uptake in extraskeletal lesions showed no significant difference when compared with the uptake from the separate $^{18}$F-FDG scan. The $[^{18}\text{F}]$F/$^{18}$F-FDG uptake in skeletal lesions reflected mostly the $^{18}$F-NaF uptake. The tumor-to-background ratio of $[^{18}\text{F}]$F/$^{18}$F-FDG in extraskeletal lesions showed no significant difference when compared with that from $^{18}$F-FDG alone (P = 0.73). For skeletal lesions, the tumor-to-background ratio of $[^{18}\text{F}]$F/$^{18}$F-FDG was lower than that from $^{18}$F-NaF alone (P < 0.001); however, this difference did not result in missed skeletal lesions on the $[^{18}\text{F}]$F/$^{18}$F-FDG scan.

**Conclusion:** The understanding of the biodistribution of radiopharmaceuticals and the lesion uptake of the $[^{18}\text{F}]$F/$^{18}$F-FDG scan as well as the variations compared with the uptake on the separate $^{18}$F-FDG PET/CT and $^{18}$F-NaF PET/CT are valuable for more in-depth evaluation of the combined scanning technique.


**Added value of using a cocktail of F-18 sodium fluoride and F-18 fluorodeoxyglucose in positron emission tomography/computed tomography for detecting bony metastasis: a case report.**

Chan HP, Hu C, Yu CC, Huang TC, Peng NJ.

**Abstract**

Current nuclear imaging of the skeletal system is achieved using technetium-99m (Tc-99m) methylene diphosphonate (MDP), F-18 sodium fluoride (NaF), or F-18 fluorodeoxyglucose (FDG). However, comparisons of these are rare in the literature.

We present a case of a 51-year-old female with suspicious lung cancer due to main symptoms of dyspnea, nonproductive cough, and pleural pain. Tc-99m MDP whole-body bone scan (WBBS) showed multiple bony metastases. Five days later, positron emission tomography/computed tomography (PET/CT) images using both F-18 NaF and a cocktail of F-18 NaF and F-18 FDG were obtained on the same day 2 hours apart. The former showed more foci and precisely showed bony lesions compared to those obtained using Tc-99m MDP WBBS.

However, the latter demonstrated more extensive radiotracer uptake, especially in osteolytic lesions, and additional soft tissue lesions in the left axillary and surraclavicular nodes as well as the left pleura. Surgical biopsy was performed in left axillary nodes, and the metastatic carcinoma was found to be of breast origin. This case demonstrated that a cocktail of F-18 NaF and F-18 FDG could be useful in PET/CT for not only detecting more skeletal lesions but also guiding biopsies accurately to the affected tissue.


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**Prospective evaluation of planar bone scintigraphy, SPECT, SPECT/CT, 18F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial.**


**Abstract**

**Purpose:** Detection of bone metastases in breast and prostate cancer patients remains a major clinical challenge. The aim of the current trial was to compare the diagnostic accuracy of 99mTc-hydroxymethane diphosphonate (99mTc-HDP) planar bone scintigraphy (BS), 99mTc-HDP SPECT, 99mTc-HDP SPECT/CT, 18F-NaF PET/CT and whole body 1.5 Tesla magnetic resonance imaging (MRI), including diffusion weighted imaging, (wbMRI+DWI) for the detection of bone metastases in high risk breast and prostate cancer patients.

**Materials and methods:** Twenty-six breast and 27 prostate cancer patients at high risk of bone metastases underwent 99mTc-HDP BS, 99mTc-HDP SPECT, 99mTc-HDP SPECT/CT, 18F-NaF PET/CT and wbMRI+DWI. Five independent reviewers interpreted each individual modality without the knowledge of other imaging findings. The final metastatic status was based on the consensus reading, clinical and imaging follow-up (minimal and maximal follow-up time was 6, and 32 months, respectively). The bone findings were compared on patient-, region-, and lesion-level.
Results: $^{99m}$Tc-HDP BS was false negative in four patients. In the region-based analysis, sensitivity values for $^{99m}$Tc-HDP BS, $^{99m}$Tc-HDP SPECT, $^{99m}$Tc-HDP SPECT/CT, $^{18}$F-NaF PET/CT, and wbMRI+DWI were 62%, 74%, 85%, 93%, and 91%, respectively. The number of equivocal findings for $^{99m}$Tc-HDP BS, $^{99m}$Tc-HDP SPECT, $^{99m}$Tc-HDP SPECT/CT, $^{18}$F-NaF PET/CT and wbMRI+DWI was 50, 44, 5, 6, and 4, respectively.

Conclusions: wbMRI+DWI showed similar diagnostic accuracy to $^{18}$F-NaF PET/CT and outperformed $^{99m}$Tc-HDP SPECT/CT, and $^{99m}$Tc-HDP BS.


Detection of osseous metastasis by $^{18}$F-NaF/$^{18}$F-FDG PET/CT versus CT alone.


Abstract

Purpose: Sodium fluoride PET ($^{18}$F-NaF) has recently reemerged as a valuable method for detection of osseous metastasis, with recent work highlighting the potential of coadministered $^{18}$F-NaF and $^{18}$F-FDG PET/CT in a single combined imaging examination. We further examined the potential of such combined examinations by comparing dual tracer $^{18}$F-NaF/$^{18}$F-FDG PET/CT with CT alone for detection of osseous metastasis.

Patients and methods: Seventy-five participants with biopsy-proven malignancy were consecutively enrolled from a single center and underwent combined $^{18}$F-NaF/$^{18}$F-FDG PET/CT and diagnostic CT scans. PET/CT as well as CT only images were reviewed in blinded fashion and compared with the results of clinical, imaging, or histological follow-up as a truth standard.

Results: Sensitivity of the combined $^{18}$F-NaF/$^{18}$F-FDG PET/CT was higher than that of CT alone (97.4% vs 66.7%). CT and $^{18}$F-NaF/$^{18}$F-FDG PET/CT were concordant in 73% of studies. Of 20 discordant cases, $^{18}$F-NaF/$^{18}$F-FDG PET/CT was correct in 19 (95%). Three cases were interpreted concordantly but incorrectly, and all 3 were false positives. A single case of osseous metastasis was detected by CT alone, but not by $^{18}$F-NaF/$^{18}$F-FDG PET/CT.

Conclusions: Combined $^{18}$F-NaF/$^{18}$F-FDG PET/CT outperforms CT alone and is highly sensitive and specific for detection of osseous metastases. The concordantly interpreted false-positive cases demonstrate the difficulty of distinguishing degenerative from malignant disease, whereas the single case of metastasis seen on CT but not PET highlights the need for careful review of CT images in multimodality studies.

**Abstract**

**Purpose:** Conventional MRI based on contrast enhancement is often not sufficient in differentiating grade II from grade III and grade III from grade IV diffuse gliomas. We assessed advanced MRI, MR spectroscopy and [(18)F]-fluoro-l-thymidine [(18)F]-FLT PET as tools to overcome these limitations.

**Methods:** In this prospective study, thirty-nine patients with diffuse gliomas of grades II, III or IV underwent conventional MRI, perfusion, diffusion, proton MR spectroscopy ((1)H-MRS) and [(18)F]-FLT-PET imaging before surgery. Relative cerebral blood volume (rCBV), apparent diffusion coefficient (ADC), Cho/Cr, NAA/Cr, Cho/NAA and FLT-SUV were compared between grades.

**Results:** Cho/Cr showed significant differences between grade II and grade III gliomas (p = 0.03). To discriminate grade II from grade IV and grade III from grade IV gliomas, the most relevant parameter was the maximum value of [(18)F]-FLT uptake FLTmax (respectively, p < 0.001 and p < 0.0001). The parameter showing the best correlation with the grade was the mean value of [(18)F]-FLT uptake FLTmean (R(2) = 0.36, p < 0.0001) and FLTmax (R(2) = 0.5, p < 0.0001).

**Conclusion:** Whereas advanced MRI parameters give indications for the grading of gliomas, the addition of [(18)F]-FLT-PET could be of interest for the accurate preoperative classification of diffuse gliomas, particularly for identification of doubtful grade III and IV gliomas.


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**TU-G-BRA-07: Characterization of Tumor Proliferation During Successive Cycles of Anti-Angiogenic Therapy Using [(18)F]FLT PET/CT.**

**Abstract**

**Purpose:** Studies have shown cessation of anti-angiogenic treatment during the first cycle of therapy resulted in rebound of tumor proliferation (flare). This study characterized proliferation dynamics during the first and third cycle of anti-angiogenic treatment using [(18)F]FLT PET.

**Methods:** Thirteen patients with various solid cancers were treated with Axitinib (Pfizer, Inc) at a dose of 5mg orally, twice daily, on contiguous three-week cycles with intermittent dosing (two-weeks-on/one-week-off). All patients received three FLT PET/CT scans during cycle 1 (C1): at baseline (C1D0), peak Axitinib concentration (C1D14), and the end of washout (C1D21). Ten patients received up to an additional three scans at corresponding time points during cycle 3 (C3). Lesions were identified by a nuclear medicine physician and manually contoured. Tumor burden was quantified using standard SUV metrics. Correlations between imaging metrics across C1 and C3 were calculated using the Spearman correlation.

**Results:** At C1 peak drug concentration 11/13 patients had decreases in SUVtotal, with median decrease of 50% (change from C1D0 to C1D14). At C3 peak drug concentration 7/7 patients had decreases in SUVtotal, with median decrease of 20% (C3D0 to C3D14). Proliferative flare during C1 washout (>20% increase from C1D14 to C1D21) occurred in 9/13 patients, with median SUVtotal...
increase of 190%. Flare was also seen in C3 for 5/5 patients, with median SUVtotal increase of 70% (change from C3D14 to C3D21).

Correlations were found between changes in imaging metrics across C1 and C3, notably the change in SUVtotal from C1D0 to C1D21 and the change in SUVtotal from C1D0 to C3D0 (ρ = 0.80).

**Conclusion:** Measurements of SUVtotal showed that both patient response to treatment and flare were evident in both cycles of treatment. Correlation between changes in SUVtotal across C1 and C3 suggest early time points could be used to characterize patient response in later cycles. Research funded in part by Pfizer.


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**Predicting location of recurrence using FDG, FLT, and Cu-ATSM PET in canine sinonasal tumors treated with radiotherapy.**

Bradshaw T, Fu R, Bowen S, Zhu J, Forrest L, Jeraj R.

**Abstract**

Dose painting relies on the ability of functional imaging to identify resistant tumor subvolumes to be targeted for additional boosting. This work assessed the ability of FDG, FLT, and Cu-ATSM PET imaging to predict the locations of residual FDG PET in canine tumors following radiotherapy. Nineteen canines with spontaneous sinonasal tumors underwent PET/CT imaging with radiotracers FDG, FLT, and Cu-ATSM prior to hypofractionated radiotherapy. Therapy consisted of 10 fractions of 4.2 Gy to the sinonasal cavity with or without an integrated boost of 0.8 Gy to the GTV. Patients had an additional FLT PET/CT scan after fraction 2, a Cu-ATSM PET/CT scan after fraction 3, and follow-up FDG PET/CT scans after radiotherapy.

Following image registration, simple and multiple linear and logistic voxel regressions were performed to assess how well pre- and mid-treatment PET imaging predicted post-treatment FDG uptake. R(2) and pseudo R(2) were used to assess the goodness of fits. For simple linear regression models, regression coefficients for all pre- and mid-treatment PET images were significantly positive across the population (P < 0.05). However, there was large variability among patients in goodness of fits: R(2) ranged from 0.00 to 0.85, with a median of 0.12. Results for logistic regression models were similar.

Multiple linear regression models resulted in better fits (median R(2) = 0.31), but there was still large variability between patients in R(2). The R(2) from regression models for different predictor variables were highly correlated across patients (R = 0.8), indicating tumors that were poorly predicted with one tracer were also poorly predicted by other tracers. In conclusion, the high inter-patient variability in goodness of fits indicates that PET was able to predict locations of residual tumor in some patients, but not others. This suggests not all patients would be good candidates for dose painting based on a single biological target.

Pharmacodynamic study of axitinib in patients with advanced malignancies assessed with $^{18}$F-3'deoxy-3'fluoro-L-thymidine positron emission tomography/computed tomography.

Bruce JY, Scully PC, Carmichael LL, Eickhoff JC, Perlman SB, Kolesar JM, Heideman JL, Jeraj R, Liu G.

Abstract

**Purpose:** Rapid disease progression associated with increased tumor proliferation has been observed during withdrawal of anti-angiogenic therapy. We characterize the dynamics of withdrawal flare for axitinib.

**Methods:** Thirty patients with metastatic solid malignancies received axitinib for 2 weeks, followed by a 1-week drug holiday. Twenty patients suitable for PET imaging received scans with $^{18}$F-3'deoxy-3'fluoro-L-thymidine (FLT), a marker of proliferation. Plasma VEGF and axitinib pharmacokinetic levels were also assessed at specified time points.

**Results:** During axitinib withdrawal, significant increases in both SUVmax (+22%; p = 0.006) and SUVmean (+20%; p = 0.001) were observed. Significant increases relative to peak axitinib concentration were observed at day 2 withdrawal for SUVmax and SUVmean, with no further significant increase from day 2 to day 7 of withdrawal. No significant change in SUVmax or SUVmean was observed during the treatment period, relative to baseline. VEGF concentration significantly increased when on drug (p < 0.001) and decreased back to a level indistinguishable from baseline by day 7 of drug washout (p = 0.448). No correlation between change in VEGF and change in imaging metrics was observed.

**Conclusion:** A significant increase in tumor proliferation was observed during withdrawal of axitinib therapy, and this flare occurred within 2 days of axitinib withdrawal. An exploratory analysis indicated that this flare may be associated with poor clinical outcome.


Effectiveness of PET/CT with $^{18}$F-fluorothymidine in the staging of patients with squamous cell head and neck carcinomas before radiotherapy.

Vojtíšek R, Ferda J, Finek J.

Abstract

**Aim:** The aim of our study was to compare the staging of the disease declared before anticancer treatment was begun with the staging that was found after the planning PET/CT scanning with $^{18}$F-FLT was performed.

**Background:** PET/CT in radiotherapy planning of head and neck cancers can facilitate the contouring of the primary tumour and the definition of metastatic lymph nodes.

**Materials and methods:** Between November 2010 and November 2013, 26 patients suffering from head and neck carcinomas underwent planning PET/CT examination with $^{18}$F-FLT. We compared the staging of the disease and the treatment strategy declared before and after $^{18}$F-FLT-PET/CT was performed.
**Results:** The findings from $^{18}$FLT-PET/CT led in 22 patients to a change of staging: in 19 patients it led to upstaging of the disease and in 3 patients it led to downstaging of the disease. In one patient, a secondary malignancy was found.

**Conclusions:** We have confirmed in this study that the use of $^{18}$F-FLT-PET/CT scanning in radiotherapy planning of squamous cell head and neck carcinomas has a great potential in the precise evaluation of disease staging and consequently in the precise determination of target volumes.


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**Metabolically active tumour volume segmentation from dynamic $[^{18}]$FLT PET studies in non-small cell lung cancer.**

**Abstract**

**Background:** Positron emission tomography (PET) with $^{18}$F-3'-deoxy-3'-fluorothymidine ($^{[18]}$FLT) can be used to assess tumour proliferation. A kinetic-filtering (KF) classification algorithm has been suggested for segmentation of tumours in dynamic $^{[18]}$FLT PET data. The aim of the present study was to evaluate KF segmentation and its test-retest performance in $^{[18]}$FLT PET in non-small cell lung cancer (NSCLC) patients.

**Method:** Nine NSCLC patients underwent two 60-min dynamic $^{[18]}$FLT PET scans within 7 days prior to treatment. Dynamic scans were reconstructed with filtered back projection (FBP) as well as with ordered subsets expectation maximisation (OSEM). Twenty-eight lesions were identified by an experienced physician. Segmentation was performed using KF applied to the dynamic data set and a source-to-background corrected 50% threshold (A50%) was applied to the sum image of the last three frames (45- to 60-min p.i.). Furthermore, several adaptations of KF were tested. Both for KF and A50% test-retest (TRT) variability of metabolically active tumour volume and standard uptake value (SUV) were evaluated.

**Results:** KF performed better on OSEM- than on FBP-reconstructed PET images. The original KF implementation segmented 15 out of 28 lesions, whereas A50% segmented each lesion. Adapted KF versions, however, were able to segment 26 out of 28 lesions. In the best performing adapted versions, metabolically active tumour volume and SUV TRT variability was similar to those of A50%. KF misclassified certain tumour areas as vertebrae or liver tissue, which was shown to be related to heterogeneous $^{[18]}$FLT uptake areas within the tumour.

**Conclusions:** For $^{[18]}$FLT PET studies in NSCLC patients, KF and A50% show comparable tumour volume segmentation performance. The KF method needs, however, a site-specific optimisation. The A50% is therefore a good alternative for tumour segmentation in NSCLC $^{[18]}$FLT PET studies in multicentre studies. Yet, it was observed that KF has the potential to subsegment lesions in high and low proliferative areas.


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Exploring spatial overlap of high-uptake regions derived from dual tracer positron emission tomography-computer tomography imaging using $^{18}$F-fluorodeoxyglucose and $^{18}$F-fluorodeoxythymidine in non-small cell lung cancer patients: a prospective pilot study.


Abstract

Interest is growing in radiotherapy to nonuniformly boost radioresistant regions within non-small cell lung cancer (NSCLC) using molecular imaging techniques. The complexity of tumor behavior is beyond the ability of any single radiotracer to reveal. We hold dual tracer positron emission tomography-computer tomography (PET/CT) imaging with fluorodeoxyglucose (FDG) and fluorodeoxythymidine (FLT) for NSCLC patients to offer an integrated overlook of tumor biological behaviors quantitatively and localizationally, which may help biological target volume delineation and subvolume boost. Pathological confirmed that NSCLC patients were eligible.

FDG and FLT PET/CT were performed for each patient before anticancer treatment and coregistrated for analysis. Maximum and mean standardized uptake values (SUVmax and SUVmean) were calculated automatically. Metabolic volumes (MVs) were delineated by a fixed 50% of SUVmax in FDG PET/CT and proliferative volumes (PVs) were delineated by 50% to 90% of SUVmax with 10% interval in FLT PET/CT. Overlap ratio (OR) were determined as overlapped volume between MV and PV divided PV. Conventional contrast-enhanced CT-based intensity-modulated radiotherapy (IMRT) plans with and without additional PET/CT-guided subtarget boost were made for each of the 5 typical NSCLC patients. Dosimetric parameters derived from dose-volume histogram, tumor control probability (TCP), and normal tissue complication probability (NTCP) of lung, esophagus, heart, and spinal cord were calculated and compared.

Thirty-one patients were prospectively included and 23 were selected for analysis. Totally, 23 primary diseases, 41 metastatic lymph nodes, and 15 metastatic lesions were positive in dual PET/CTs and included for analysis. Median ORs increased from 58.61% to 93.12% under thresholds of 50% of SUVmax in FDG PET/CT and increased thresholds from 50% to 90% of SUVmax in FLT PET/CT. Based on conventional IMRT, additional boost to union of high FDG (determined by 50% SUVmax) and FLT (determined by 80% SUVmax) uptake subtargets exhibited higher TCP without significant elevated NTCP of lung, esophagus, spinal cord, and heart. Dual tracer PET/CT of FDG and FLT is suggested for NSCLC patients to guide tumor target delineation in clinical practice. FDG PET/CT is necessary whereas FLT PET/CT may be optional when guiding tumor target delineation clinically. Additional information from randomized trials is required to validate.


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FDG-PET/CT and FLT-PET/CT for differentiating between lipid-poor benign and malignant adrenal tumours.


Abstract

Objective: To compare F-18-fluorodeoxyglucose (FDG) and F-18-fluorothymidine (FLT) PET/CT examinations for differentiating between benign and malignant adrenal tumours.

Methods: Thirty lipid-poor benign and 11 malignant tumours of 40 patients were included. FDG- and FLT-based indices including visual score, maximum standardized uptake value (SUVmax) and FDG
adrenal lesion/liver SUVmax (A/L SUVmax) or FLT adrenal lesion/back muscle SUVmax (A/B SUVmax) ratio were compared between benign and malignant tumours using the Mann-Whitney's U test or Wilcoxon signed-rank test, and their diagnostic performances were evaluated by means of the area under the curve (AUC) values derived from the receiver operating characteristic analysis.

**Results:** All indices were significantly higher in malignant than benign tumours on both images (p < 0.05 each). On FDG-PET/CT, the sensitivity, specificity, and accuracy were 91 %, 63 % and 71 % for visual score, 91 %, 67 % and 73 % for SUVmax, and 100 %, 70 % and 78 % for A/L SUVmax ratio, respectively. On FLT-PET/CT, they were 100 %, 97 % and 98 % for visual score, SUVmax and A/B SUVmax ratio, respectively. All FLT indices were significantly higher than those of FDG in AUC (p < 0.05 each).

**Conclusion:** FLT-PET/CT may be superior to FDG-PET/CT in differentiating lipid-poor benign from malignant adrenal tumours because of higher specificity and accuracy.


**[18]F-FLT PET to predict early response to neoadjuvant therapy in KRAS wild-type rectal cancer: a pilot study.**


**Abstract**

**OBJECT:** This pilot study evaluated the utility of 3'-deoxy-3'[^18]F]-fluorothymidine ([^18]F-FLT) positron emission tomography (PET) to predict response to neoadjuvant therapy that included cetuximab in patients with wild-type KRAS rectal cancers.

**METHODS:** Baseline[^18]F-FLT PET was collected prior to treatment initiation. Follow-up ([18]F-FLT was collected after three weekly infusions of cetuximab, and following a combined regimen of cetuximab, 5-FU, and radiation. Imaging-matched biopsies were collected with each PET study.

**RESULTS:** Diminished[^18]F-FLT PET was observed in 3/4 of patients following cetuximab treatment alone and in all patients following combination therapy. Reduced[^18]F-FLT PET following combination therapy predicted disease-free status at surgery. Overall,[^18]F-FLT PET agreed with Ki67 immunoreactivity from biopsy samples and surgically resected tissue, and was predictive of treatment-induced rise in p27 levels.

**CONCLUSION:** These results suggest that[^18]F-FLT PET is a promising imaging biomarker to predict response to neoadjuvant therapy that included EGFR blockade with cetuximab in patients with rectal cancer.


Performance of FLT-PET for pulmonary lesion diagnosis compared with traditional FDG-PET: A meta-analysis.


Abstract

Purpose: Widely used 18F-2'-deoxy-2'-fluoro-d-glucose (FDG) positron emission tomography (PET) can be problematic with false positives in cancer imaging. This study aims to investigate the diagnostic accuracy of a candidate PET tracer, 18F-2',3'-dideoxy-3'-fluoro-2-thiothymidine (FLT), in diagnosing pulmonary lesions compared with FDG.

Materials and methods: After comprehensive search and study selection, a meta-analysis was performed on data from 548 patients pooled from 17 studies for evaluating FLT accuracy, in which data from 351 patients pooled from ten double-tracer studies was used for direct comparison with FDG. Weighted sensitivity and specificity were used as main indicators of test performance. Individual data was extracted and patient subgroup analyses were performed.

Results: Overall, direct comparisons showed lower sensitivity (0.80 vs. 0.89) yet higher specificity (0.82 vs. 0.66) for FLT compared with FDG (both p<0.01). Patient subgroup analysis showed FLT was less sensitive than FDG in detecting lung cancers staged as T1 or T2, and those ≤2.0cm in diameter (0.81 vs. 0.93, and 0.53 vs. 0.78, respectively, both p<0.05), but was comparable for cancers staged as T3 or T4, and those >2.0cm in diameter (0.95 vs. 1.00, 0.96 vs. 0.88, both p>0.05). For benignities, FLT performed better compared with FDG in ruling out inflammation-based lesions (0.57 vs. 0.32, p<0.05), and demonstrated greater specificity regardless of lesion sizes.

Conclusions: Although FLT cannot replace FDG in detecting small and early lung cancers, it may help to prevent patients with larger or inflammatory lesions from cancer misdiagnosis or even overtreatment.


Comparison of 4'-[methyl-11C]thiothymidine (11C-4DST) and 3'-deoxy-3'-[18F]fluorothymidine (18F-FLT) PET/CT in human brain glioma imaging.


Abstract

Background: 3'-deoxy-3'-[18F]fluorothymidine (18F-FLT) has been used to evaluate tumor malignancy and cell proliferation in human brain gliomas. However, 18F-FLT has several limitations in clinical use. Recently, 11C-labeled thymidine analogue, 4'-[methyl-11C]thiothymidine (11C-4DST), became available as an in vivo cell proliferation positron emission tomography (PET) tracer. The present study was conducted to evaluate the usefulness of 11C-4DST PET in the diagnosis of human brain gliomas by comparing with the images of 18F-FLT PET.

Methods: Twenty patients with primary and recurrent brain gliomas underwent 18F-FLT and 11C-4DST PET scans. The uptake values in the tumors were evaluated using the maximum standardized uptake value (SUVmax), the tumor-to-normal tissue uptake (T/N) ratio, and the tumor-to-blood uptake (T/B) ratio. These values were compared among different glioma grades. Correlation between the Ki-67 labeling index and the uptake values of 11C-4DST and 18F-FLT in the tumor was evaluated using linear regression analysis. The relationship between the individual 18F-FLT and 11C-4DST uptake values in the tumors was also examined.
Results: $^{11}$C-4DST uptake was significantly higher than that of $^{18}$F-FLT in the normal brain. The uptake values of $^{11}$C-4DST in the tumor were similar to those of $^{18}$F-FLT resulting in better visualization with $^{18}$F-FLT. No significant differences in the uptake values of $^{18}$F-FLT and $^{11}$C-4DST were noted among different glioma grades. Linear regression analysis showed a significant correlation between the Ki-67 labeling index and the T/N ratio of $^{11}$C-4DST ($r = 0.50$, $P < 0.05$) and $^{18}$F-FLT ($r = 0.50$, $P < 0.05$). Significant correlations were also found between the Ki-67 labeling index and the T/B ratio of $^{11}$C-4DST ($r = 0.52$, $P < 0.05$) and $^{18}$F-FLT ($r = 0.55$, $P < 0.05$). A highly significant correlation was observed between the individual T/N ratio of $^{11}$C-4DST and $^{18}$F-FLT in the tumor ($r = 0.79$, $P = 0.0001$).

Conclusions: The present study demonstrates that $^{11}$C-4DST is useful for the imaging of human brain gliomas with PET. A relatively higher background uptake of $^{11}$C-4DST in the normal brain compared to $^{18}$F-FLT limits the detection of low-tracer-uptake tumors. Moreover, no superiority was found in $^{11}$C-4DST over $^{18}$F-FLT in the evaluation of cell proliferation.


$^{18}$F-Fluorothymidine PET-CT for resected malignant gliomas before radiotherapy: tumor extent according to proliferative activity compared with MRI.

Zhao F, Li M, Wang Z, Fu Z, Cui Y, Chen Z, Yu J.

Abstract

Objective: To compare the presence of post-operative residual disease by magnetic resonance imaging (MRI) and $[^{18}F]$fluorothymidine (FLT)-positron emission tomography (PET)-computer tomography (CT) in patients with malignant glioma and to estimate the impact of $^{18}$F-FLT PET on the delineation of post-operative target volumes for radiotherapy (RT) planning.

Methods: Nineteen patients with post-operative residual malignant gliomas were enrolled in this study. For each patient, $^{18}$F- FLT PET-CT and MRI were acquired in the same week, within 4 weeks after surgery but before the initiation of RT. The PET-CT and MRI data were co-registered based on mutual information. The residual tumor volume defined on the $^{18}$F-PET PET (Vol-PET) was compared with that of gadolinium [Gd] enhancement on T1-weighted MRI (Vol-T1) and areas of hyperintensity on T2-weighted MRI (Vol-T2).

Results: The mean Vol-PET (14.61 cm³) and Vol-T1 (13.60 cm³) were comparable and smaller than the mean Vol-T2 (32.93 cm³). The regions of $^{18}$F-FLT uptake exceeded the contrast enhancement and the hyperintense area on the MRI in 14 (73.68%) and 8 patients (42.11%), respectively. In 5 (26.32%) of the 19 patients, Vol-PET extended beyond 25 mm from the margin of Vol-T1; in 2 (10.53%) patients, Vol-PET extended 20 mm from the margin of Vol-T2. Vol-PET was detected up to 35 mm away from the edge of Vol-T1 and 24 mm away from the edge of Vol-T2. In 16 (84.21%) of the 19 patients, the Vol-T1 extended beyond the Vol-PET. In all of the patients, at least some of the Vol-T2 was located outside of the Vol-PET.

Conclusions: The volumes of post-operative residual tumor in patients with malignant glioma defined by $^{18}$F-FLT uptake on PET are not always consistent with the abnormalities shown on post-operative MRI. Incorporation of $^{18}$F-FLT-PET in tumor delineation may have the potential to improve the definition of target volume in post-operative radiotherapy.

Applications of PET imaging with the proliferation marker $^{18}$F-FLT.


Abstract

$^{18}$F-3'-fluoro-3'-deoxythymidine (FLT) is a nucleoside-analog imaging agent for quantifying cellular proliferation that was first reported in 1998. It accumulates during the S-phase of the cell cycle through the action of cytosolic thymidine kinase, TK1. Since TK1 is primarily expressed in dividing cells, FLT uptake is essentially limited to dividing cells. Thus FLT is an effective measure of cell proliferation.

FLT uptake has been shown to correlate with the more classic proliferation marker, the monoclonal antibody to Ki-67. Increased cellular proliferation is known to correlate with worse outcome in many cancers. However, the Ki-67 binding assay is performed on a sampled preparation, ex vivo, whereas FLT can be quantitatively measured in vivo using positron emission tomography (PET). FLT is an effective and quantitative marker of cell proliferation, and therefore a useful prognostic predictor in the setting of neoplastic disease. This review summarizes clinical studies from 2011 forward that used FLT-PET to assess tumor response to therapy. The paper focuses on our recommendations for a standardized clinical trial protocol and components of a report so multi center studies can be effectively conducted, and different studies can be compared. For example, since FLT is glucuronidated by the liver, and the metabolite is not transported into the cell, the plasma fraction of FLT can be significantly changed by treatment with particular drugs that deplete this enzyme, including some chemotherapy agents and pain medications.

Therefore, the plasma level of metabolites should be measured to assure FLT uptake kinetics can be accurately calculated. This is important because the flux constant (KFLT) is a more accurate measure of proliferation and, by inference, a better discriminator of tumor recurrence than standardized uptake value (SUVFLT). This will allow FLT imaging to be a specific and clinically relevant prognostic predictor in the treatment of neoplastic disease.


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3'-Deoxy-3'-$^{18}$F-fluorothymidine positron emission tomography as an early predictor of disease progression in patients with advanced and metastatic pancreatic cancer.

Challapalli A, Barwick T, Pearson RA, Merchant S, Mauri F, Howell EC, Sumpter K, Maxwell RJ, Aboagye EO, Sharma R.

Abstract

Purpose: 3'-Deoxy-3'-$^{18}$F-fluorothymidine (FLT) positron emission tomography (PET) has limited utility in abdominal imaging due to high physiological hepatic uptake of tracer. We evaluated FLT PET/CT combined with a temporal-intensity information-based voxel-clustering approach termed kinetic spatial filtering (FLT PET/CTKSF) for early prediction of response and survival outcomes in locally advanced and metastatic pancreatic cancer patients receiving gemcitabine-based chemotherapy.

Methods: Dynamic FLT PET/CT data were collected before and 3 weeks after the first cycle of chemotherapy. Changes in tumour FLT PET/CT variables were determined. The primary end point was RECIST 1.1 response on contrast-enhanced CT after 3 months of therapy.
Results: Twenty patients were included. Visual distinction between tumours and normal pancreas was seen in FLT PETKSF images. All target lesions (>2 cm), including all primary pancreatic tumours, were visualised. Of the 11 liver metastases, 3 (<2 cm) were not visible after kinetic filtering. Of the 20 patients, 7 progressed (35%). Maximum standardised uptake value at 60 min post-injection (SUV60,max) significantly increased in patients with disease progression ($p = 0.04$). Receiver-operating characteristic curve analysis indicated that a threshold of SUV60,max increase of ≥12% resulted in sensitivity, specificity and positive predictive value (PPV) of 71, 100 and 100%, respectively [area under the curve (AUC) 0.90, $p = 0.0001$], to predict patients with disease progression. Changes in SUV60,max were not predictive of survival.

Conclusions: FLT PET/CT detected changes in proliferation, with early increase in SUV60,max predicting progressive disease with a high specificity and PPV. Therefore, FLT PET/CT could be used as an early response biomarker for gemcitabine-based chemotherapy, to select a poor prognostic group who may benefit from novel therapeutic agents in advanced and metastatic pancreatic cancer.


¹⁸F-FLT PET/CT as an imaging tool for early prediction of pathological response in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy: a pilot study.


Abstract

Purpose: We evaluated whether $¹⁸F$-3’-deoxy-3’-fluorothymidine positron emission tomography (FLT PET) can predict the final postoperative histopathological response in primary breast cancer after the first cycle of neoadjuvant chemotherapy (NCT).

Methods: In this prospective cohort study of 15 patients with locally advanced operable breast cancer, FLT PET evaluations were performed before NCT, after the first cycle of NCT, and at the end of NCT. All patients subsequently underwent surgery. Variables from FLT PET examinations were correlated with postoperative histopathological results.

Results: At baseline, median of maximum standardized uptake values (SUVmax) in the groups showing a complete pathological response (pCR) + residual cancer burden (RCB) I, RCB II or RCB III did not differ significantly for the primary tumour (5.0 vs. 2.9 vs. 8.9, $p = 0.293$) or for axillary nodes (7.9 vs. 1.6 vs. 7.0, $p = 0.363$), whereas the Spearman correlation between SUVmax and Ki67 proliferation rate index was significant ($r = 0.69$, $p < 0.001$).

Analysis of the relative percentage change of SUVmax in the primary tumour ($\Delta$SUVTmax(t₁)) and axillary nodes ($\Delta$SUVNmax(t₁)) after the first NCT cycle showed that the power of $\Delta$SUVTmax(t₁) to predict pCR + RCB I responses (AUC = 0.91, $p < 0.001$) was statistically significant, whereas $\Delta$SUVNmax(t₁) had a moderate ability (AUC = 0.77, $p = 0.119$) to separate subjects with $\Delta$SUVTmax(t₁) >-52.9 % into two groups: RCB III patients and a heterogeneous group that included RCB I and RCB II patients. A predictive score $\mu$ based on $\Delta$SUVTmax(t₁) and $\Delta$SUVNmax(t₁) parameters is proposed.

Conclusions: The preliminary findings of the present study suggest the potential utility of FLT PET scans for early monitoring of response to NCT and to formulate a therapeutic strategy consistent with the estimated efficacy of NCT. However, these results in a small patient population need to be validated in a larger independent cohort.


Prognostic value comparison between $^{18}$F-FLT PET/CT and $^{18}$F-FDG PET/CT volume-based metabolic parameters in patients with head and neck cancer.

Hoshikawa H, Mori T, Yamamoto Y, Kishino T, Fukumura T, Samukawa Y, Mori N, Nishiyama Y.

Abstract

**Purpose:** The present study compared the potential of pretreatment 3'-deoxy-3'-[18F]-fluorothymidine (F-FLT) uptake parameters and those of F-FDG to predict the clinical outcome of head and neck squamous cell carcinoma treated with chemoradiotherapy.

**Methods:** A total 53 patients undergoing pretreatment F-FLT PET/CT and F-FDG PET/CT from May 2006 to April 2013 were evaluated. The SUVmax, metabolic tumor volume (MTV), total lesion glycolysis, and total lesion proliferation (TLP) were determined semiquantitatively. Associations between clinical factors and PET/CT parameters and prognostic value were analyzed.

**Results:** In univariate analyses, F-FLT SUVmax, MTV, TLP, F-FDG MTV, and total lesion glycolysis correlated with locoregional control ($P = 0.02, P = 0.0007, P = 0.0001, P = 0.007,$ and $P = 0.013,$ respectively). Clinical T stage, F-FLT SUVmax, MTV, TLP, and F-FDG SUVmax correlated with overall survival ($P = 0.012, P = 0.0057, P = 0.0018, P = 0.0012,$ and $P = 0.047,$ respectively). On multivariate analyses, F-FLT TLP was an independent factor for locoregional control ($P = 0.002;$ hazards ratio [HR], 5.13; 95% confidence interval [CI], 1.81-14.54), as were F-FLT SUVmax and MTV for overall survival ($P = 0.021; HR, 3.47; 95% CI, 1.2-10.01$ and $P = 0.029; HR, 3.17; 95% CI, 1.12-8.95$).

**Conclusions:** Pretreatment F-FLT PET/CT volume-based metabolic parameters are superior prognostic predictors to those of F-FDG PET/CT. F-FLT SUVmax and MTV can provide important prognostic information for patients with head and neck squamous cell carcinomas administered with chemoradiotherapy.


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$^{18}$F-FLT PET imaging in a patient with sarcoidosis with cardiac involvement.

Norikane T, Yamamoto Y, Maeda Y, Noma T, Nishiyama Y.

Abstract

FDG PET has been proposed to play a role in the diagnosis and therapy monitoring of sarcoidosis including cardiac involvement. However, assessing inflammatory lesions in cardiac sarcoidosis using FDG can be challenging because the FDG accumulates in normal myocardium.

We report a case of sarcoidosis with cardiac involvement that underwent 3'-deoxy-3'-F-fluorothymidine (FLT) PET. FLT PET images demonstrated increased uptake in the lymph nodes and left ventricle. After immunosuppressive therapy, a follow-up PET scan showed disappearance of FLT uptake in the lymph nodes and left ventricle.


Monitoring Tumor Response After Histone Deacetylase Inhibitor Treatment Using 3'-Deoxy-3'-[\(^{18}\)F]-fluorothymidine PET.


Abstract

Purpose: This study employed 3'-deoxy-3'-[\(^{18}\)F]-fluorothymidine ([\(^{18}\)F]FLT) microPET scanning to assess the treatment response of histone deacetylase inhibitors (HDACi), e.g., N1-hydroxy-N8-phenyloctanediadime (SAHA) and its iodinated derivative ISAHA, in a hepatoma mouse model.

Procedures: The in vitro cytotoxicity of HDACi in various hepatoma cell lines was determined by MTT assay and flow cytometry. ISAHA and SAHA were used to treat HepG2 hepatoma xenograft-bearing mice. The treatment responses were characterized in terms of tumor burden, microPET imaging, and immunohistochemical staining of tumor sections.

Results: ISAHA effectively inhibited HepG2 hepatoma cell survival and tumor growth. A significantly reduced tumor uptake during HDACi treatment was noticed in [\(^{18}\)F]FLT microPET imaging, which was consistent with the findings in immunohistochemical staining.

Conclusions: ISAHA can suppress tumor cell proliferation both in vitro and in vivo. [\(^{18}\)F]FLT PET is a promising modality for evaluating the in vivo therapeutic efficacy of HDACi at the early stage of treatment.

**Abstract**

$^{18}\text{F}$-FMISO is the most widely used PET agent for imaging hypoxia, a condition associated with resistance to tumor therapy. $^{18}\text{F}$-FMISO equilibrates in normoxic tissues, but is retained under hypoxic conditions because of reduction and binding to macromolecules. A simple tissue-to-blood ratio (TB) is suitable for quantifying hypoxia. A threshold of $\text{TB} \geq 1.2$ is useful in discriminating the hypoxic volume (HV) of tissue; $\text{TB}_{\text{max}}$ is the maximum intensity of the hypoxic region and does not invoke a threshold. Because elimination of blood sampling would simplify clinical use, we tested the validity of using imaging regions as a surrogate for blood sampling.

**Methods:** Patients underwent 20 min $^{18}\text{F}$-FMISO scans during the 90-140 min interval post-injection with venous blood sampling. 223 $^{18}\text{F}$-FMISO patient studies had detectable surrogate blood regions in the field-of-view. Quantitative parameters of hypoxia ($\text{TB}_{\text{max}}$, HV) derived from blood samples were compared to values using surrogate blood regions derived from heart, aorta and/or cerebellum. In a subset of brain cancer patients, parameters from blood samples and from cerebellum were compared for their ability to independently predict outcome.

**Results:** Vascular regions of heart showed the highest correlation to measured blood activity ($R^2 = 0.84$). For brain studies, cerebellar activity was similarly correlated to blood samples. In brain cancer patients, Kaplan-Meier analysis showed that image-derived reference regions had nearly identical predictive power as parameters derived from blood, thus obviating the need for venous sampling in these patients.

**Conclusions:** Simple static analysis of $^{18}\text{F}$-FMISO PET captures both the intensity ($\text{TB}_{\text{max}}$) and spatial extent (HV) of tumor hypoxia. An image-derived region to assess blood activity can be used as a surrogate for blood sampling in quantification of hypoxia.


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**Assessing Biological Response to Bevacizumab Using $^{18}\text{F}$-Fluoromisonidazole PET/MR Imaging in a Patient with Recurrent Anaplastic Astrocytoma.**

**Abstract**

We present our initial experience in using single modality fluoromisonidazole (FMISO) PET/MR imaging to noninvasively evaluate the biological effects induced by bevacizumab therapy in a patient treated for recurrent high grade glioma. In this index patient, bevacizumab therapy resulted in the development of nonenhancing tumor characterized by reduced diffusion and markedly decreased FMISO uptake in the setting of maintained CBF and CBV.

These observations suggest that the dynamic biological interplay between tissue hypoxia and vascular normalization occurring within treated recurrent high grade glioma can be captured utilizing FMISO PET/MR imaging.

Tumor Hypoxia Response After Targeted Therapy in EGFR-Mutant Non-Small Cell Lung Cancer: Proof of Concept for FMISO-PET.

Arvold ND, Heidari P, Kunawudhi A, Sequist LV, Mahmood U.

Abstract
Hypoxia is associated with resistance to radiotherapy and chemotherapy. Functional imaging of hypoxia in non-small cell lung cancer (NSCLC) could allow early assessment of tumor response and guide subsequent therapies.

Epidermal growth factor receptor (EGFR) inhibition with erlotinib reduces hypoxia in vivo. $\text{[^{18}F]}$-Fluoromisonidazole (FMISO) is a radiolabeled tracer that selectively accumulates in hypoxic cells. We sought to determine whether FMISO positron emission tomography (FMISO-PET) could detect changes in hypoxia in vivo in response to EGFR-targeted therapy.

In a preclinical investigation, nude mice with human EGFR-mutant lung adenocarcinoma xenografts underwent FMISO-PET scans before and 5 days after erlotinib or empty vehicle initiation. Descriptive statistics and analysis of variance (ANOVA) tests were used to analyze changes in standardized uptake value (SUV), with pooled analyses for the mice in each group (baseline, postvehicle, and posterlotinib).

In a small correlative pilot human study, patients with EGFR-mutant metastatic NSCLC underwent FMISO-PET scans before and 10 to 12 days after erlotinib initiation. Changes in SUV were compared to standard chest computed tomography (CT) scans performed 6 weeks after erlotinib initiation.

The mean ($\pm$standard error of the mean; SUV$_\text{mean}$) of the xenografts was 0.17 ± 0.014, 0.14 ± 0.008, and 0.06 ± 0.004 for baseline, postvehicle, and posterlotinib groups, respectively, with lower SUV$_\text{mean}$ among the posterlotinib group compared to other groups (P < .05). Changes on preclinical PET imaging were striking, with near-complete disappearance of FMISO uptake after erlotinib initiation.

Two patients were enrolled on the pilot study. In the first patient, SUV$_\text{mean}$ increased by 21% after erlotinib, with progression on 6-week chest CT followed by death after 4.8 months. In the second patient, SUV$_\text{mean}$ decreased by 7% after erlotinib, with regression on 6-week chest CT accompanied by clinical improvement; the patient had stable disease at 14.5 months.

In conclusion, we observed that FMISO-PET can detect changes in hypoxia levels after EGFR-directed therapy in EGFR-mutant NSCLC. Further study is warranted to determine its utility as an imaging biomarker of early response to EGFR-directed therapy.

F-18 fluoromisonidazole for imaging tumor hypoxia: imaging the microenvironment for personalized cancer therapy.

Rajendran JG, Krohn KA.

Abstract
Hypoxia in solid tumors is one of the seminal mechanisms for developing aggressive traits and treatment resistance in solid tumors. This evolutionarily conserved biological mechanism along with derepression of cellular functions in cancer, although resulting in many challenges, provide us with opportunities to use these adversities to our advantage. Our ability to use molecular imaging to characterize therapeutic targets such as hypoxia and apply this information for therapeutic interventions is growing rapidly. Evaluation of hypoxia and its biological ramifications to effectively plan appropriate therapy that can overcome the cure-limiting effects of hypoxia provides an objective means for treatment selection and planning.

Fluoromisonidazole (FMISO) continues to be the lead radiopharmaceutical in PET imaging for the evaluation, prognostication, and quantification of tumor hypoxia, one of the key elements of the tumor microenvironment. FMISO is less confounded by blood flow, and although the images have less contrast than FDG-PET, its uptake after 2 hours is an accurate reflection of inadequate regional oxygen partial pressure at the time of radiopharmaceutical administration. By virtue of extensive clinical utilization, FMISO remains the lead candidate for imaging and quantifying hypoxia.

The past decade has seen significant technological advances in investigating hypoxia imaging in radiation treatment planning and in providing us with the ability to individualize radiation delivery and target volume coverage. The presence of widespread hypoxia in the tumor can be effectively targeted with a systemic hypoxic cell cytotoxin or other agents that are more effective with diminished oxygen partial pressure, either alone or in combination. Molecular imaging in general and hypoxia imaging in particular will likely become an important in vivo imaging biomarker of the future, complementing the traditional direct tissue sampling methods by providing a snapshot of a primary tumor and metastatic disease and in following treatment response and will serve as adjuncts to personalized therapy.


Hypoxia imaging in gliomas with $^{18}$F-fluoromisonidazole PET: toward clinical translation.

Bell C, Dowson N, Fay M, Thomas P, Puttick S, Gal Y, Rose S.

Abstract
There is significant interest in the development of improved image-guided therapy for neuro-oncology applications. Glioblastomas (GBM) in particular present a considerable challenge because of their pervasive nature, propensity for recurrence, and resistance to conventional therapies. MRI is routinely used as a guide for planning treatment strategies. However, this imaging modality is not able to provide images that clearly delineate tumor boundaries and affords only indirect information about key tumor pathophysiology. With the emergence of PET imaging with new oncology radiotracers, mapping of tumor infiltration and other important molecular events such as hypoxia is now feasible within the clinical setting. In particular, the importance of imaging hypoxia levels within the tumoral microenvironment is gathering interest, as hypoxia is known to play a central role in glioma pathogenesis and resistance to treatment. One of the hypoxia radiotracers known for its clinical utility is $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO).
In this review, we highlight the typical causes of treatment failure in gliomas that may be linked to hypoxia and outline current methods for the detection of hypoxia. We also provide an overview of the growing body of studies focusing on the clinical translation of $^{18}$F-FMISO PET imaging, strengthening the argument for the use of $^{18}$F-FMISO hypoxia imaging to help optimize and guide treatment strategies for patients with glioblastoma.


Automated synthesis and PET evaluation of both enantiomers of [^{18}F]FMISO.

Revunov E$^1$, Jørgensen JT$^2$, Jensen AE$^3$, Severin GW$^1$, Kjaer A$^4$, Zhuravlev F$^5$.

Abstract

**Introduction:** [^{18}F]FMISO, the widely used positron emission tomography (PET) hypoxia tracer, is a chiral compound clinically used as a racemic mixture. The purpose of this study was to synthesize the individual ($R$)- and the ($S$)- enantiomers of [^{18}F]FMISO and compare their PET imaging characteristics.

**Methods:** The radiosynthesis of enantiopure ($R$)- and ($S$)-[^{18}F]FMISO was based on Co(salen) (N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt)-mediated opening of enantiopure epoxides with $[^{18}]$HF. The uptake and clearance of the individual [^{18}F]FMISO antipodes were investigated using micro-PET/CT imaging performed on mice bearing FaDu tumors. Image-derived biodistribution was obtained from micro-PET/CT scans performed at 1 and 3 hours post injection (p.i.). In addition, the uptake patterns of each enantiomer were observed using two-hour dynamic micro-PET/CT scans, and the time-activity curves from different organs were compared.

**Results:** The individual ($R$)- and ($S$)-[^{18}F]FMISO enantiomers were synthesized in one step with high enantiomeric excess (ee) >99% and radiochemical purity >97% using custom-made automation module. The dynamic micro-PET/CT scanning revealed a faster initial uptake of the ($R$)-[^{18}F]FMISO enantiomer in tumor and muscle tissues, however the difference became progressively smaller with time. The tumor-to-muscle (T/M) and tumor-to-liver (T/L) ratios remained nearly identical for the ($R$)- and ($S$)-forms at all time points. The micro-PET/CT imaging at 1 and 3 hours p.i. did not show any significant enantioselective tissue uptake.

**Conclusions:** Although the ($R$)-enantiomer of [^{18}F]FMISO demonstrated a somewhat faster initial tumor and muscle uptake no significant enantioselective tissue uptake was observed at later time points. The T/M- and T/L- ratios for the ($R$)- and ($S$)-forms were the same within the experimental error at all times. Therefore, the use of enantiopure [^{18}F]FMISO is unlikely to present any practical clinical benefit for PET imaging.


A patient-specific computational model of hypoxia-modulated radiation resistance in glioblastoma using $^{18}$F-FMISO-PET.


Abstract

Glioblastoma multiforme (GBM) is a highly invasive primary brain tumour that has poor prognosis despite aggressive treatment. A hallmark of these tumours is diffuse invasion into the surrounding brain, necessitating a multi-modal treatment approach, including surgery, radiation and chemotherapy.
We have previously demonstrated the ability of our model to predict radiographic response immediately following radiation therapy in individual GBM patients using a simplified geometry of the brain and theoretical radiation dose. Using only two pre-treatment magnetic resonance imaging scans, we calculate net rates of proliferation and invasion as well as radiation sensitivity for a patient’s disease.

Here, we present the application of our clinically targeted modelling approach to a single glioblastoma patient as a demonstration of our method. We apply our model in the full three-dimensional architecture of the brain to quantify the effects of regional resistance to radiation owing to hypoxia in vivo determined by $^{18}$F-fluoromisonidazole positron emission tomography (FMISO-PET) and the patient-specific three-dimensional radiation treatment plan.

Incorporation of hypoxia into our model with FMISO-PET increases the model-data agreement by an order of magnitude. This improvement was robust to our definition of hypoxia or the degree of radiation resistance quantified with the FMISO-PET image and our computational model, respectively. This work demonstrates a useful application of patient-specific modelling in personalized medicine and how mathematical modelling has the potential to unify multi-modality imaging and radiation treatment planning.


Hypoxia imaging with $^{18}$F-FMISO-PET for guided dose escalation with intensity-modulated radiotherapy in head-and-neck cancers.


Abstract

Background and purpose: Positron emission tomography (PET) with $^{(18)}$F-fluoromisonidazole ($^{18}$F-FMISO) provides a non-invasive assessment of hypoxia. The aim of this study is to assess the feasibility of a dose escalation with volumetric modulated arc therapy (VMAT) guided by $^{18}$F-FMISO-PET for head-and-neck cancers (HNC).

Patients and methods: Ten patients with inoperable stages III-IV HNC underwent $^{18}$F-FMISO-PET before radiotherapy. Hypoxic target volumes (HTV) were segmented automatically by using the fuzzy locally adaptive Bayesian method. Retrospectively, two VMAT plans were generated delivering 70 Gy to the gross tumour volume (GTV) defined on computed tomography simulation or 79.8 Gy to the HTV.

A dosimetric comparison was performed, based on calculations of tumour control probability (TCP), normal tissue complication probability (NTCP) for the parotid glands and uncomplicated tumour control probability (UTCP).

Results: The mean hypoxic fraction, defined as the ratio between the HTV and the GTV, was 0.18. The mean average dose for both parotids was 22.7 Gy and 25.5 Gy without and with dose escalation respectively. FMISO-guided dose escalation led to a mean increase of TCP, NTCP for both parotids and UTCP by 18.1, 4.6 and 8% respectively.

Conclusion: A dose escalation up to 79.8 Gy guided by $^{18}$F-FMISO-PET with VMAT seems feasible with improvement of TCP and without excessive increase of NTCP for parotids.


Positron emission tomography of tumour $[^{18}F]$fluoroestradiol uptake in patients with acquired hormone-resistant metastatic breast cancer prior to oestradiol therapy.

van Kruchten M$^1$, Glaudemans AW, de Vries EF, Schröder CP, de Vries EG, Hospers GA.

Abstract

Purpose: Whereas anti-oestrogen therapy is widely applied to treat oestrogen receptor (ER) positive breast cancer, paradoxically, oestrogens can also induce tumour regression. Up-regulation of ER expression is a marker for oestrogen hypersensitivity. We, therefore, performed an exploratory study to evaluate positron emission tomography (PET) with the tracer $16\alpha-[^{18}F]$fluoro-$17\beta$-oestradiol ($^{18}$F-FES) as potential marker to select breast cancer patients for oestradiol therapy.

Methods: Eligible patients had acquired endocrine-resistant metastatic breast cancer that progressed after $\geq 2$ lines of endocrine therapy. All patients had prior ER-positive histology. Treatment consisted of oestradiol 2 mg, three times daily, orally. Patients underwent $^{18}$F-FES-PET/CT imaging at baseline. Tumour $^{18}$F-FES-uptake was quantified for a maximum of 20 lesions and expressed as maximum standardised uptake value (SUV$_{\text{max}}$). CT-scan was repeated every 3 months to evaluate treatment response. Clinical benefit was defined as time to radiologic or clinical progression $\geq 24$ weeks.

Results: $^{18}$F-FES uptake, quantified for 255 lesions in 19 patients, varied greatly between lesions (median 2.8; range 0.6-24.3) and between patients (median 2.5; range 1.1-15.5). Seven (37 %) patients experienced clinical benefit of oestrogen therapy, eight progressed (PD), and four were non-evaluable due to side effects. The positive and negative predictive value (PPV/NPV) of $^{18}$F-FES-PET for response to treatment were 60 % (95 % CI: 31-83 %) and 80 % (95 % CI: 38-96 %), respectively, using SUV$_{\text{max}}$ $>1.5$.

Conclusion: $^{18}$F-FES-PET may aid identification of patients with acquired antihormone resistant breast cancer that are unlikely to benefit from oestradiol therapy.


The value of PET/CT with FES or FDG tracers in metastatic breast cancer: a computer simulation study in ER-positive patients.


Abstract

Background: The aim of this study was to evaluate the effect on the number of performed biopsies and costs associated with implementing positron emission tomography (PET) and computed tomography (PET/CT) with $16\alpha-[^{18}F]$fluoro-$17\beta$-oestradiol (FES) or $2[^{18}F]$fluoro-2-deoxy-D-glucose (FDG) as an upfront imaging test for diagnosing metastatic breast cancer (MBC) in comparison with the standard work-up in oestrogen receptor-positive women with symptoms.

Methods: A published computer simulation model was adapted and validated. Three follow-up strategies were evaluated in a simulated cohort of women with primary breast cancer over a 5-year-time horizon: (1) the standard work-up, (2) upfront FES-PET/CT and (3) upfront FDG-PET/CT. The main outcome was the number of avoided biopsies to assess MBC. The costs for all three strategies
were calculated based on the number of imaging tests and biopsies. The incremental cost-effectiveness ratio (ICER) to avoid a biopsy was calculated only based on the costs of initial imaging and staging tests.

**Results:** The FES-PET/CT strategy decreased the number of biopsies by 39 ± 9%, while upfront FDG-PET/CT increased the number of biopsies by 38 ± 15% when compared with the standard work-up. Both PET/CT strategies reduced the number of imaging tests and false positives when compared with the standard work-up. The number of false negatives decreased only in the FES-PET/CT strategy. The ICER in the FES-PET/CT strategy per avoided biopsy was 12.1 ± 3.4 thousand Euro. In the FDG-PET/CT strategy, the costs were higher and there were no avoided biopsies as compared with the standard work-up, hence this was an inferior strategy in terms of cost effectiveness.

**Conclusions:** The number of performed biopsies was lower in the FES-PET/CT strategy at an ICER of 12.1 ± 3.4 thousand Euro per biopsy avoided, whereas the application of the FDG-PET/CT did not reduce the number of biopsies and was more expensive. Whether the FES-PET/CT strategy has additional benefits for patients in terms of therapy management has to be evaluated in clinical studies.

No evidence for attenuated stress-induced extrastriatal dopamine signaling in psychotic disorder.


Abstract
Stress is an important risk factor in the etiology of psychotic disorder. Preclinical work has shown that stress primarily increases dopamine (DA) transmission in the frontal cortex. Given that DA-mediated hypofrontality is hypothesized to be a cardinal feature of psychotic disorder, stress-related extrastriatal DA release may be altered in psychotic disorder. Here we quantified for the first time stress-induced extrastriatal DA release and the spatial extent of extrastriatal DA release in individuals with non-affective psychotic disorder (NAPD). Twelve healthy volunteers (HV) and 12 matched drug-free NAPD patients underwent a single infusion \[^{18}F\]fallypride positron emission tomography scan during which they completed the control and stress condition of the Montreal Imaging Stress Task.

HV and NAPD did not differ in stress-induced \[^{18}F\]fallypride displacement and the spatial extent of stress-induced \[^{18}F\]fallypride displacement in medial prefrontal cortex (mPFC) and temporal cortex (TC). In the whole sample, the spatial extent of stress-induced radioligand displacement in right ventro-mPFC, but not dorso-mPFC or TC, was positively associated with task-induced subjective stress. Psychotic symptoms during the scan or negative, positive and general subscales of the Positive and Negative Syndrome Scale were not associated with stress-induced \[^{18}F\]fallypride displacement nor the spatial extent of stress-induced \[^{18}F\]fallypride displacement in NAPD. Our results do not offer evidence for altered stress-induced extrastriatal DA signaling in NAPD, nor altered functional relevance. The implications of these findings for the role of the DA system in NAPD and stress processing are discussed.


Striatal D1- and D2-type dopamine receptors are linked to motor response inhibition in human subjects.


Abstract
Motor response inhibition is mediated by neural circuits involving dopaminergic transmission; however, the relative contributions of dopaminergic signaling via D1- and D2-type receptors are unclear. Although evidence supports dissociable contributions of D1- and D2-type receptors to response inhibition in rats and associations of D2-type receptors to response inhibition in humans, the relationship between D1-type receptors and response inhibition has not been evaluated in humans.

Here, we tested whether individual differences in striatal D1- and D2-type receptors are related to response inhibition in human subjects, possibly in opposing ways. Thirty-one volunteers participated.

Response inhibition was indexed by stop-signal reaction time on the stop-signal task and commission errors on the continuous performance task, and tested for association with striatal D1- and D2-type receptor availability [binding potential referred to nondisplaceable uptake (BPND)], measured using positron emission tomography with \[^{11}C\]NNC-112 and \[^{18}F\]fallypride, respectively. Stop-signal reaction time was negatively correlated with D1- and D2-type BPND in whole striatum, with significant
relationships involving the dorsal striatum, but not the ventral striatum, and no significant correlations involving the continuous performance task.

The results indicate that dopamine D1- and D2-type receptors are associated with response inhibition, and identify the dorsal striatum as an important locus of dopaminergic control in stopping. Moreover, the similar contribution of both receptor subtypes suggests the importance of a relative balance between phasic and tonic dopaminergic activity subserved by D1- and D2-type receptors, respectively, in support of response inhibition.

The results also suggest that the stop-signal task and the continuous performance task use different neurochemical mechanisms subserving motor response inhibition.


Relationship between dopamine deficit and the expression of depressive behavior resulted from alteration of serotonin system.


Abstract
Depression frequently accompanies in Parkinson's disease (PD). Previous research suggested that dopamine and serotonin systems are closely linked with depression in PD. However, comprehensive studies about the relationship between these two neurotransmitter systems are limited. Therefore, the purpose of this study is to evaluate the effect of dopaminergic destruction on the serotonin system. The interconnection between motor and depression was also examined.

Two PET scans were performed in the 6-hydroxydopamine (6-OHDA) lesioned and sham operated rats: [18F]FP-CIT for dopamine transporters and [18F]Mefway for serotonin 1A (5-HT1A) receptors. Here, 6-OHDA is a neurotoxin for dopaminergic neurons. Behavioral tests were used to evaluate the severity of symptoms: rotational number for motor impairment and immobility time, acquired from the forced swim test for depression. Region-of-interests were drawn in the striatum and cerebellum for the dopamine system and hippocampus and cerebellum for the 5-HT system. The cerebellum was chosen as a reference region. Non-displaceable binding potential in the striatum and hippocampus were compared between 6-OHDA and sham groups.

As a result, the degree of dopamine depletion was negatively correlated with rotational behavior ($R^2 = 0.79$, $p = 0.003$). In 6-OHDA lesioned rats, binding values for 5-HT1A receptors was 22% lower than the sham operated group. This decrement of 5-HT1A receptor binding was also correlated with the severity of depression ($R^2 = 0.81$, $p = 0.006$). Taken together, this research demonstrated that the destruction of dopaminergic system causes the reduction of the serotonergic system resulting in the expression of depressive behavior.


18F-Mefway PET imaging of serotonin 1A receptors in humans: a comparison with 18F-FCWAY.


Abstract
Introduction: The purpose of this research is to evaluate the prospects for the use of 4-(trans-18F-fluoranylmethyl)-N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-pyridin-2-ylcyclohexane-1-carboxamide (18F-Mefway) in comparison to 18F-trans-4-fluoro-N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide (18F-FCWAY) for the quantification of 5-HT1A receptors in human subjects.

Method: Five healthy male controls were included for two positron emission tomography (PET) studies: 18F-FCWAY PET after the pretreatment with 500 mg of disulfiram and two months later, 18F-Mefway PET without disulfiram. Regional time-activity curves (TACs) were extracted from nine cortical and subcortical regions in dynamic PET images. Using cerebellar cortex without vermis as reference tissue, in vivo kinetics for both radioligands were compared based on the distribution volume ratio (DVR) calculated by non-invasive Logan graphical analysis and area under the curve ratio of the TACs (AUC ratio).
**Result:** Although the pattern of regional uptakes in the $^{18}$F-Mefway PET was similar to that of the $^{18}$F-FCWAY PET (highest in the hippocampus and lowest in the cerebellar cortex), the amount of regional uptake in $^{18}$F-Mefway PET was almost half of that in $^{18}$F-FCWAY PET. The skull uptake in $^{18}$F-Mefway PET was only 25% of that in $^{18}$F-FCWAY PET with disulfiram pretreatment. The regional DVR values and AUC ratio values for $^{18}$F-Mefway were 17-40% lower than those of $^{18}$F-FCWAY. In contrast to a small overestimation of DVR values by AUC ratio values (< 10%) in $^{18}$F-FCWAY PET, the overestimation bias of AUC ratio values was much higher (up to 21%) in $^{18}$F-Mefway PET.

**Conclusion:** As $^{18}$F-Mefway showed lower DVR values and greater overestimation bias of AUC ratio values, $^{18}$F-Mefway may appear less favorable than $^{18}$F-FCWAY. However, in contrast to $^{18}$F-FCWAY, the resistance to in vivo defluorination of $^{18}$F-Mefway obviates the need for the use of a defluorination inhibitor. Thus, $^{18}$F-Mefway may be a good candidate PET radioligand for 5-HT1A receptor imaging in human.


**Synthesis and Evaluation of Mefway Analogs as Ligands for Serotonin 5HT1A Receptors.**

Thio JP, Liang C, Bajwa AK, Wooten DW, Christian BT, Mukherjee J.

**Abstract**

$^{18}$F-Mefway ($N$-[2-[4-(2’-methoxyphenyl)piperazinyl]ethyl]-$N$-(2-pyridyl)-$N$-(4’-$^{18}$F-fluoro-methylcyclohexane)carboxamide) was developed and evaluated for use as a PET ligand for imaging 5-HT$_{1A}$ receptors. Ongoing studies of $^{18}$F-Mefway have shown it to be an effective PET radiotracer.

We have synthesized isomers of Mefway by changing the position of the methyl-group in attempts to evaluate stability for imaging purposes. 2-Methyl-, 3-methyl-, and 4-methyl-cyclohexane-1-carboxylic acids and 3-carbomethoxy-, 4-carbomethoxy-cyclohexane-1-carboxylic acids were coupled with WAY-100634 to provide the methylcyclohexyl derivatives (2-, 3- and 4-methyl).

Mefway and 3-Mefway analogs were prepared by reduction of carbomethoxy-derivatives followed by fluorination. In vitro binding affinities for the methylated derivatives in rat brain homogenates was found to be 10.4 nM (2-methyl), 77 nM (3-methyl) and 21.5 nM (4-methyl).

Binding affinity of 3-Mefway and 4-Mefway was found to be 17.4 nM and 6.26 nM, respectively. Our results suggest that 3-methyl/3-fluoromethyl substituent has approx. 3-fold lower affinities compared to the 4-methyl/4-fluoromethyl substituent.

Initial Experience of 68Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy.


Abstract
Prostate-specific membrane antigen (PSMA) overexpression theoretically enables targeting of prostate cancer (PCa) metastases using gallium Ga-68 (68Ga)-labeled PSMA ligands for positron emission tomography/computed tomography (PET/CT) imaging. Promising detection rates have been reported when using this approach for functional imaging of recurrent PCa; however, until now, the diagnostic accuracy of 68Ga-PSMA PET/CT for preoperatively identifying lymph node metastases (LNMs) had not been assessed. We retrospectively compared preoperative 68Ga-PSMA PET/CT lymph node (LN) findings with histologic work-up after radical prostatectomy (RP). Overall, 608 LNs containing 53 LNMs were detected during RP. LNMs were present in 12 of 30 patients (40%). The 68Ga-PSMA-PET/CT scans identified 4 patients (33.3%) as LN true positive and 8 patients (66.7%) as false negative. Median size of 68Ga-PSMA-PET/CT-detected versus undetected LNMs was 13.6 versus 4.3mm (p<0.05).

Overall sensitivity, specificity, positive predictive value, and negative predictive value of 68Ga-PSMA PET/CT for LNM detection were 33.3%, 100%, 100%, and 69.2%, respectively. Per-side analyses revealed corresponding values of 27.3%, 100%, 100%, and 52.9%. Conversely, 68Ga-PSMA PET/CT enabled tumor visualization in the prostate. In 92.9% of patients, the intraprostatic tumor foci were correctly predicted. Overall, 68Ga-PSMA PET/CT is a promising tool for functional imaging; however, our initial experience revealed substantial influence of LNM size on the diagnostic accuracy of 68Ga-PSMA PET/CT.

Patient summary: We assessed the diagnostic accuracy of 68Ga-PSMA PET/CT in high-risk prostate cancer patients prior to radical prostatectomy. We found that lymph node metastasis detection rates were substantially influenced by lymph node metastasis size.

Prospective Comparison of the detection rate of 18F-Fluoromethylcholine and 68Ga-PSMA-HBED PET/CT in men with prostate cancer with rising PSA post curative treatment, being considered for targeted therapy.


Abstract
In prostate cancer (PCa) and biochemical failure following therapy, current imaging techniques have a low detection rate at PSA levels at which targeted salvage therapy is effective. 11C-Choline or 18F-Fluoromethylcholine (FMC), though widely used, have poor sensitivity at low PSA levels. 68Ga-PSMA-HBED (PSMA) has shown promising results in retrospective trials. Our aim is to prospectively compare detection rates of PSMA versus FMC PET/CT in men initially managed with either radical prostatectomy (RP), radiation treatment (RT) or both, being considered for targeted therapy.

Methods: A sample of men with rising PSA following treatment, eligible for targeted treatment, was prospectively included. Patients on systemic treatment were excluded. PSMA, FMC PET/CT and
diagnostic CT were undertaken in all patients sequentially between January and April 2015, and assessed by blinded experienced readers. Scan results and management impact changes, together with histological follow-up when feasible, were documented.

**Results:** 38 patients (pts) were enrolled. 34/38 pts (89%) were post-RP, 4/38 pts (11%) were post-RT. 12/38 pts (32%) had salvage RT after primary RP. Mean PSA was 1.74 ± 2.54 ng/ml. 68% of pts (26/38) had a positive scan, 32% (12/38) were negative at both tracers. Of the 26 positive pts, 54% (14/26) were positive on PSMA alone, 42% (11/26) on both FMC and PSMA and only 4% (1/26) on FMC alone. With PSA <0.5ng/ml, PSMA detection rate (DR) was 50% vs. 12.5% for FMC. At PSA between 0.5-2.0 ng/ml, DR was 69% for PSMA vs. 31% for FMC, and at PSA >2.0, DR was 86% for PSMA vs. 57% for FMC. On lesion-based follow-up, PSMA detected more lesions than FMC (59 vs. 29, P <0.001). The TBR in positive scans was higher in PSMA than in FMC (28.6 for PSMA vs 9.4 for FMC, p<0.001). There was a 63% (24/38 pts) management impact, 54% (13/24 pts) due to PSMA imaging alone. Histological follow-up was available for 9/38 pts (24%), and 9/9 PSMA positive lesions were consistent with Pca (PSMA True Positive). The one lesion positive on FMC and negative on PSMA resulted at biopsy as a false positive of FMC (PSMA true negative).

**Conclusion:** In patients with biochemical failure and low PSA, PSMA demonstrated a significantly higher detection rate with a high overall management impact.


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**68**Ga- and **177**Lu-labeled PSMA I&T: Optimization of a PSMA targeted theranostic concept and first proof of concept human studies.

Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, Kulkarni HR, Lassmann M, Klette I, Eiber M, Schwaiger M, Wester HJ.

**Abstract**

Based on the high and consistent expression of prostate-specific membrane antigen (PSMA) in metastatic prostate cancer (PC), the goal of this study was the development, preclinical evaluation and first proof of concept investigation of a PSMA inhibitor for imaging and therapy (PSMA I&T) for **68**Ga-based positron emission tomography (PET) and **177**Lu-based endoradiotherapeutic treatment in patients with metastatic and castration resistant disease.

**Methods:** PSMA I&T was synthesized in a combined solid phase and solution chemistry strategy. The PSMA-affinity of [nat]Ga/[nat]LuPSMA I&T was determined in a competitive binding assay using LNCaP cells. Internalization kinetics of [68]Ga and [177]LuPSMA I&T were investigated using the same cell line, and biodistribution studies were performed in LNCaP-tumor bearing CD-1 nu/nu mice. Initial human PET imaging studies using [68]GaPSMA I&T, as well as endoradiotherapeutic treatment of two patients with metastatic PC using [177]LuPSMA I&T were carried out.

**Results:** PSMA I&T and its cold gallium and lutetium analogs revealed nanomolar affinity towards PSMA. The DOTAGA-conjugate PSMA I&T allowed fast and high-yield labeling with [59]GaIII and [177]LuIII. Uptake of [68]Ga[177]LuPSMA I&T in LNCaP tumor cells is highly efficient and PSMA-specific, as demonstrated by competition studies both in vitro and in vivo. Tumor targeting and tracer kinetics in vivo were fast, with the highest uptake in tumor xenografts and kidneys (both PSMA specific). First human [68]GaPSMA I&T PET imaging allowed high contrast detection of bone lesions, lymph node and liver metastases. Endoradiotherapy with [177]LuPSMA I&T in two patients was found to be effective and safe with no detectable side effects.

**Conclusion:** [68]GaPSMA I&T shows potential for high-contrast PET imaging of metastatic PC, while its [177]Lu-labeled counterpart exhibits suitable targeting and retention characteristics for successful endoradiotherapeutic treatment. Prospective studies on larger cohorts of patients are warranted and planned.

**Metastatic Prostate Carcinoma Presenting as a Superscan on $^{68}$Ga-PSMA PET/CT.**

Lawal I, Vorster M, Boshomane T, Ololade K, Ebenhan T, Sathekge M.

**Abstract**

We describe the finding of a metastatic superscan detected by Ga-PSMA PET/CT imaging. A 63-year-old man with metastatic prostate carcinoma underwent Ga-PSMA PET/CT imaging for staging and evaluation of the most appropriate therapeutic option.

Images demonstrated diffuse and extensive skeletal uptake in the axial and appendicular skeleton, corresponding to the typical red marrow distribution. Intense soft tissue uptake was also seen in the prostate and multiple pelvic and abdominal lymph nodes.


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**Prostate-specific Membrane Antigen-radioguided Surgery for Metastatic Lymph Nodes in Prostate Cancer.**


**Abstract**

With the advent of $^{68}$Ga-labeled prostate-specific membrane antigen-$N,N'$-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-$N,N'$-diacetic acid ($^{68}$Ga-PSMA-HBED-CC) positron emission tomography (PET) hybrid imaging in prostate cancer (PCa), even small metastatic lymph nodes (LNs) can be visualized. However, intraoperative detection of such LNs may not be easy owing to their inconspicuous morphology and/or atypical localization. The aim of our feasibility study was to evaluate PSMA-radioguided surgery for detection of metastatic LNs. One patient with primary PCa and evidence of LN metastases and four PCa patients with evidence of recurrent disease to regional LNs on $^{68}$Ga-PSMA-HBED-CC PET hybrid imaging received an intravenous injection of an $^{111}$In-PSMA investigation and therapy agent 24h before surgery.

Metastatic LNs were tracked intraoperatively using a gamma probe with acoustic and visual feedback. All radioactive-positive LN specimens detected in vivo were confirmed by ex vivo measurements and corresponded to PSMA-avid metastatic disease according to histopathology analysis. Intraoperative use of the gamma probe detected all PSMA-positive lesions identified on preoperative $^{68}$Ga-PSMA-HBED-CC PET. Detection of small subcentimeter metastatic LNs was facilitated, and PSMA-radioguided surgery in two patients revealed additional lesions close to known tumor deposits that were not detected by preoperative $^{68}$Ga-PSMA-HBED-CC PET. However, greater patient numbers and long-term follow-up data are needed to determine the future role of PSMA-radioguided surgery.

Detection of brain metastasis with $^{68}$Ga-labeled PSMA ligand PET/CT: a novel radiotracer for imaging of prostate carcinoma.

Chakraborty PS, Kumar R, Tripathi M, Das CJ, Bal C.

Abstract
Brain metastasis in prostate cancer is rare and not expected at initial presentation especially when the patient is asymptomatic for the same. A 45-year-old male patient undergoing initial evaluation for newly diagnosed prostatic adenocarcinoma was referred to our department for 99mTc-MDP bone scintigraphy.

As part of the study protocol, he also underwent Glu-NH-CO-NH-Lys-(Ahx)-[Ga-$^{68}$(HBED-CC)] ($^{68}$Ga-PSMA) PET/CT, which revealed tracer accumulation in brain lesions, apart from localization in the primary, lymph node, and bone metastases. A subsequent MR evaluation confirmed brain metastases.


Metastatic poorly differentiated prostatic carcinoma with neuroendocrine differentiation: negative on $^{68}$Ga-PSMA PET/CT.

Chakraborty PS, Tripathi M, Agarwal KK, Kumar R, Vijay MK, Bal C.

Abstract
Glu-NH-CO-NH-Lys-(Ahx)-[Ga-$^{68}$(HBED-CC)], abbreviated as Ga-PSMA, is a novel radiotracer undergoing evaluation for PET/CT imaging of prostate carcinoma. Its major advantage is the sensitive detection of lesions even at low prostate-specific antigen level and high target-to-background ratios obtained in metastatic lesions, which is better than that obtained with F-fluoromethylcholine.

We present the case of a 28-year-old man with poorly differentiated prostate carcinoma with neuroendocrine differentiation, whose lesions did not show significant Ga-PSMA localization. As literature on utility of Ga-PSMA PET/CT for imaging prostate carcinoma grows, it is important to be aware of potential false negatives that could influence study results.

Clinical value of $^{68}$Ga-DOTATATE-PET/CT compared to stand-alone contrast enhanced CT for the detection of extra-hepatic metastases in patients with neuroendocrine tumours (NET).

Albanus DR, Apitzsch J, Erdem Z, Erdem O, Verburg FA, Behrendt FF, Mottaghy FM, Heinzel A.

Abstract

**Purpose:** To compare and outline the beneficial skills of combined $^{68}$Ga-DOTATATE positron emission tomography (PET) with concurrent contrast enhanced X-ray computed tomography (ceCT) against stand-alone ceCT in 54 patients with neuroendocrine tumours (NET).

**Methods:** Patients with histologically confirmed NET and available follow-up of at least 6 months (median 12.6 months; range 6.1-23.2) were included. PET/CT and ceCT images were initially analyzed separately by two blinded nuclear medicine physicians and two radiologists, respectively. In a second step all four physicians reviewed all detected lesions together reaching a consensus-grading for PET/ceCT. The results were then compared to the reference standard consisting of clinical follow-up data.

**Results:** With regard to true positive lesions, PET/ceCT vs. stand alone ceCT detected 139 vs. 48 bone-lesions, 106 vs. 71 lymph node metastases and 26 vs. 26 pulmonary lesions. On a per-patient basis, PET/ceCT achieved a higher sensitivity (100% vs. 47%) and specificity (89% vs. 49%) for bone lesions than ceCT. For lymph nodes the effect was similar (sensitivity 92% vs. 64% and specificity 83% vs. 59%). For the detection of pulmonary lesions the sensitivity was identical (100%) while specificity of PET/ceCT was superior to ceCT-alone (95% vs. 82%).

**Conclusion:** In summary, the use of $^{68}$Ga-DOTATATE PET/ceCT leads to an increase in sensitivity and specificity in the detection of extra-hepatic NET metastases compared to stand-alone ceCT. Therefore, $^{68}$Ga-DOTATATE PET/ceCT should be the imaging modality of choice in patients with NET.


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**Diagnostic Performance of $^{68}$Ga-DOTATATE PET/CT, $^{18}$F-FDG PET/CT and $^{131}$I-MIBG Scintigraphy in Mapping Metastatic Pheochromocytoma and Paraganglioma.**

Tan TH$^1$, Hussein Z$^2$, Saad FF$^3$, Shuaib IL$^4$.

Abstract

**Purpose:** To evaluate the diagnostic performance of $^{68}$Ga-DOTATATE $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET)/computed tomography (CT), $^{18}$F-FDG PET/CT and $^{131}$I-MIBG scintigraphy in the mapping of metastatic pheochromocytoma and paraganglioma.

**Materials and methods:** Seventeen patients (male = 8, female = 9; age range, 13-68 years) with clinically proven or suspicious metastatic pheochromocytoma or paraganglioma were included in this prospective study. Twelve patients underwent all three modalities, whereas five patients underwent $^{68}$Ga-DOTATATE and $^{131}$I-MIBG without $^{18}$F-FDG. A composite reference standard derived from
anatomical and functional imaging findings, along with histopathological information, was used to validate the findings. Results were analysed on a per-patient and on per-lesion basis. Sensitivity and accuracy were assessed using McNemar’s test.

**Results:** On a per-patient basis, 14/17 patients were detected in $^{68}$Ga-DOTATATE, 7/17 patients in $^{131}$I-MIBG, and 10/12 patients in $^{18}$F-FDG. The sensitivity and accuracy of $^{68}$Ga-DOTATATE, $^{131}$I-MIBG and $^{18}$F-FDG were (93.3 %, 94.1 %), (46.7 %, 52.9 %) and (90.9 %, 91.7 %) respectively. On a per-lesion basis, an overall of 472 positive lesions were detected; of which 432/472 were identified by $^{68}$Ga-DOTATATE, 74/472 by $^{131}$I-MIBG, and 154/300 (patient, $n = 12$) by $^{18}$F-FDG.

The sensitivity and accuracy of $^{68}$Ga-DOTATATE, $^{131}$I-MIBG and $^{18}$F-FDG were (91.5 %, 92.6 % $p < 0.0001$), (15.7 %, 26.0 % $p < 0.0001$) and (51.3 %, 57.8 % $p < 0.0001$) respectively. Discordant lesions were demonstrated on $^{68}$Ga-DOTATATE, $^{131}$I-MIBG and $^{18}$F-FDG.

**Conclusions:** $^{68}$Ga-DOTATATE PET/CT shows high diagnostic accuracy than $^{131}$I-MIBG scintigraphy and $^{18}$F-FDG PET/CT in mapping metastatic pheochromocytoma and paraganglioma.


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**INTRAPANCREATIC ACCESSORY SPLEEN MIMICKING NEUROENDOCRINE TUMOR ON $^{68}$GA-DOTATATE PET/CT.**


**Abstract**

Besides well-known physiologic uptake of Ga-DOTATATE in spleen, pituitary gland, pancreatic head, adrenals, kidney, and urinary bladder, sometimes unusual areas of uptake are found. We report a case of a 53-year-old woman who had vague pain in abdomen for which abdominal CT was done showing a contrast-enhancing lesion in the pancreatic tail. It was suspected to be of neuroendocrine origin and Ga-DOTATATE PET/CT showed a corresponding focal uptake. Spleen-preserving pancreatic tail resection was performed. Pathology revealed the diagnosis of an accessory intrapancreatic spleen (AIPS).


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**PET/COMPUTED TOMOGRAPHY IN NEUROENDOCRINE TUMOR: VALUE TO PATIENT MANAGEMENT AND SURVIVAL OUTCOMES.**

**Shamim SA, Kumar A, Kumar R.**

**Abstract**

PET/computed tomography evaluation of neuroendocrine tumors is gaining prominence with the availability of novel pet radiotracers, such as $^{18}$F-DOPA and gallium-68 somatostatin peptide derivatives. These tumors have unique properties and hence the basis of use of these new radiotracers.

Prominent centers worldwide have reported the usefulness of these PET tracers in diagnosis and clinical decision making. Portability of $^{68}$Ge/$^{68}$Ga generators has also helped in more widespread use of these somatostatin peptide derivatives as PET radiotracers. This article reviews established and potential roles of these novel PET radiotracers in diagnosis, management, and prognosis of neuroendocrine tumors.
USE OF RADIOACTIVE SUBSTANCES IN DIAGNOSIS AND TREATMENT OF NEUROENDOCRINE TUMORS.

Kjaer A, Knigge U.

Abstract

Radionuclides are needed both for nuclear medicine imaging as well as for peptide-receptor radionuclide therapy (PRRT) of neuroendocrine tumors (NET). Imaging is important in the initial diagnostic work-up and for staging NETs. In therapy planning, somatostatin receptor imaging (SRI) is used when treatment is targeted at the somatostatin receptors as with the use of somatostatin analogues or PRRT. SRI with gamma camera technique using the tracer $^{111}$In-DTPA-octreotide has for many years been the backbone of nuclear imaging of NETs. However, increasingly PET tracers for SRI are now used. $^{68}$Ga-DOTATATE, $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTANOC are the three most often used PET tracers. They perform better than SPECT tracers and should be preferred.

FDG-PET is well suited for visualization of most of the somatostatin receptor-negative tumors prognostic in NET patients. Also $^{11}$C-5-HTP, $^{18}$F-DOPA and $^{131}$I-MIBG may be used in NET. However, with FDG-PET and somatostatin receptor PET at hand we see limited necessity of other tracers.

PRRT is an important tool in the treatment of advanced NETs causing complete or partial response in 20% and minor response or tumor stabilization in 60% with response duration of up to 3 years. Grade 3-4 kidney or bone marrow toxicity is seen in 1.5% and 9.5%, respectively, but are completely or partly reversible in most patients. (177)Lu-DOTATATE seems to have less toxicity than (90)Y-DOTATOC. However, until now only retrospective, non-randomized studies have been performed and the role of PRRT in treatment of NETs remains to be established.

NUCLEAR IMAGING OF NEUROENDOCRINE TUMORS WITH UNKNOWN PRIMARY: WHY, WHEN AND HOW?


Abstract

Neuroendocrine tumors (NETs) with unknown primary (CUP-NET) are associated with a poor prognosis (10-year survival 22%), grade 1 and 2 NETs having a more favorable outcome than grade 3 (also called carcinoma). There is evidence that an effort should be made to localize the primary tumor even in the presence of metastasis because resection of the primary tumor(s) may improve disease-free and overall survival, and because the choice of chemotherapeutic agent depends on the location of the primary tumor.

Localization of the tumors remains challenging and often relies on a combination of radiological, endoscopic and functional imaging. The functional imaging protocol for evaluation of these patients has historically relied on somatostatin receptor scintigraphy (SRS). However, the sensitivity and specificity of SRS may be unsatisfactory, especially for NETs of midgut origin. Newer PET radiotracers such as $^{68}$Ga-labeled somatostatin analogs ($^{68}$Ga-DOTA-SSTa) and $^{18}$F-DOPA have shown promise. In direct comparisons between $^{68}$Ga-DOTA-SSTa PET/CT and $^{99m}$Tc-HYNIC-octreotide/$^{111}$In-pentetreotide SPECT/(CT), $^{68}$Ga-DOTA-SSTa performed better than other techniques, giving a
compelling reason for switching from SPECT/CT to PET/CT imaging. $^{18}$F-DOPA performs better than SRS and CT in well-differentiated NETs of the small intestine.

For detecting pancreatic NETs, the high background uptake of $^{18}$F-DOPA by the normal exocrine pancreas can be somewhat overcome by pretreatment with carbidopa. We have suggested a protocol in which SRS is replaced by one of the two agents (preferably with $^{68}$Ga-DOTA-SSTa, alternatively $^{18}$F-DOPA) as first-line nuclear tracer for detection of CUP-NET in patients with well-differentiated NETs and $^{18}$F-FDG PET/CT may be an additional diagnostic test for poorly differentiated tumors and for prognostication. In the near future, it is expected that patients with CUP-NET will benefit from newly developed PET approaches (radiopharmaceuticals) and intraoperative PET imaging.


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**SUPERIORITY OF $^{68}$GA-DOTATATE PET/CT TO OTHER FUNCTIONAL IMAGING MODALITIES IN THE LOCALIZATION OF SDHB-ASSOCIATED METASTATIC PHEOCHROMOCYTOMA AND PARAGANGLIOMA.**

Janssen I$^1$, Blanchet EM$^2$, Adams K$^1$, Chen CC$^3$, Millo C$^4$, Herscovitch P$^5$, Taieb D$^6$, Kebebew E$^7$, Lehnert H$^8$, Fojo AT$^9$, Pacak K$^{10}$.

**Abstract**

**Purpose:** Patients with succinate dehydrogenase subunit B (SDHB) mutation-related pheochromocytoma/paraganglioma (PHEO/PGL) are at higher risk for metastatic disease than other hereditary PHEOs/PGLs. Current therapeutic approaches are limited but the best outcomes are based on the early and proper detection of as many lesions as possible.

Because PHEOs/PGLs overexpress somatostatin receptor 2 (SSTR2), the goal of our study was to assess the clinical utility of $^{[68]}$Ga-DOTA(0)-Tyr(3)-octreotate ($^{[68]}$Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT) and to evaluate its diagnostic utility in comparison to the currently recommended functional imaging modalities $^{[18]}$F-fluorodopamine ($^{[18]}$F-FDA), $^{[18]}$F-fluorodihydroxyphenylalanine ($^{[18]}$F-FDOPA), $^{[18]}$F-fluoro-2-deoxy-D-glucose ($^{[18]}$F-FDG) PET/CT as well as CT/magnetic resonance imaging (MRI).

**Experimental design:** $^{[68]}$Ga-DOTATATE PET/CT was prospectively performed in 17 patients with SDHB-related metastatic PHEOs/PGLs. All patients also underwent $^{[18]}$F-FDG PET/CT and CT/MRI with 16 of the 17 patients also receiving $^{[18]}$F-FDOPA and $^{[18]}$F-FDA PET/CT scans. Detection rates of metastatic lesions were compared between all these functional imaging studies. A composite synthesis of all used functional and anatomical imaging studies served as the imaging comparator.

**Results:** $^{[68]}$Ga-DOTATATE PET/CT demonstrated a lesion-based detection rate of 98.6% (95% confidence interval (CI) 96.5% to 99.5%), $^{[18]}$F-FDG, $^{[18]}$F-FDOPA, $^{[18]}$F-FDA PET/CT, and CT/MRI showed detection rates of 85.8% (CI 81.3% to 89.4%) (p<0.01), 61.4% (CI 55.6% to 66.9%) (p<0.01), 51.9% (CI 46.1% to 57.7%) (p<0.01), and 84.8% (CI 80.0% to 88.5%) (p<0.01), respectively.

**Conclusions:** $^{[68]}$Ga-DOTATATE PET/CT showed a significantly superior detection rate compared to all other functional and anatomical imaging modalities and may represent the preferred future imaging modality in the evaluation of SDHB-related metastatic PHEO/PGL.

SOMATOSTATIN RECEPTOR IMAGING WITH $^{68}$GA DOTATATE PET/CT: CLINICAL UTILITY, NORMAL PATTERNS, PEARLS, AND PITFALLS IN INTERPRETATION.

Hofman MS, Lau WF, Hicks RJ.

Abstract
Gallium-68 ($^{68}$Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE, GaTate) positron emission tomography (PET)/computed tomography (CT) is an imaging technique for detecting and characterizing neuroendocrine tumors (NETs). GaTate, a somatostatin analog, has recently been accorded orphan drug status by the U.S. Food and Drug Administration, thereby increasing interest in and availability of this radiotracer. GaTate PET/CT allows whole-body imaging of cell surface expression of somatostatin receptors (SSTRs) and is rapidly evolving as the new imaging standard of reference for the detection and characterization of NETs.

The authors discuss the normal appearance at GaTate PET/CT and the utility of this modality in a variety of these tumors, including gastrointestinal, pancreatic, and bronchial NETs as well as pheochromocytoma, paraganglioma, meningioma, and oncogenic osteomalacia. In addition, they discuss potential causes of false-positive findings, including pancreatic uncinate process activity, inflammation, osteoblastic activity, and splenosis. They also highlight the complementary role of 2-[$\text{fluorine-18}$]fluoro-2-deoxy-d-glucose (FDG) PET/CT, including the advantages of using both GaTate PET/CT and FDG PET/CT to evaluate sites of well- and poorly differentiated disease.

The use of GaTate PET/CT together with FDG PET/CT allows identification of tumor heterogeneity, which provides prognostic information and can be pivotal in guiding biopsy. It also allows optimal patient management, including theranostic application of peptide receptor radionuclide therapy, and the restaging of patients following therapy.


INCREASED $^{68}$GA-DOTATATE UPTAKE IN PET IMAGING DISCRIMINATES MENINGIOMA AND TUMOR-FREE TISSUE.


Abstract
Meningiomas are known to express somatostatin receptor 2 (SSTR2). PET using the SSTR2 analog $^{68}$Ga-DOTATATE has recently been introduced for imaging of meningiomas. However, a systematic correlation between $^{68}$Ga-DOTATATE uptake, SSTR2 expression, and histology (including tumor-free scar tissue) is still lacking. For elucidation, we conducted this prospective study.

Methods: Twenty-one adult patients with primary ($n = 12$) or recurrent ($n = 9$) meningiomas were prospectively enrolled. Preoperative MR imaging and $^{68}$Ga-DOTATATE PET scans were fused and used for a spatially precise neuronavigated tissue-sampling procedure during tumor resection. Histopathologic diagnosis included immunohistochemical determination of SSTR2 expression. At each individual sampling site, the maximum standardized uptake value (SUVmax) of $^{68}$Ga-DOTATATE was correlated with MR imaging findings, histology, and semiquantitative SSTR2 expression.
Results: One hundred fifteen samples (81 tumor, 34 tumor-free) were obtained. There was a significant positive correlation between SUVmax and SSTR2 expression. Receiver-operating characteristic analysis revealed a threshold of 2.3 for SUVmax to discriminate between tumor and nontumoral tissue. Regarding the detection of tumor tissue, PET imaging showed a higher sensitivity (90% vs. 79%; P = 0.049), with specificity and positive predictive values similar to MR imaging, for both de novo and recurrent tumors.

Conclusion: $^{68}$Ga-DOTATATE uptake correlates with SSTR2 expression and offers high diagnostic accuracy to delineate meningioma from tumor-free tissue even in recurrent tumors after previous therapy. Our findings substantiate an important role for $^{68}$Ga-DOTATATE PET in meningioma management.


PARAGANGLIOMA AND PANCREATIC NEUROENDOCRINE TUMOR WITH RARE METASTATIC SITES DETECTED ON $^{68}$GA-DOTATATE PET/CT IMAGING.

Parghane RV, Mittal BR, Shukla J, Dey P, Bhattacharya A, Kochhar R.

Abstract
Pancreatic neuroendocrine tumors (PNETs) represent a small percentage of all pancreatic malignancies, and most of these present as metastatic disease. Somatostatin receptor scintigraphy had been used successfully for the assessment of patients with NET. Somatostatin receptor scintigraphy is indispensable for localization of ectopic NET and the distribution of NET throughout the body.


SOMATOSTATIN RECEPTOR SUBTYPE 2 IN HIGH-GR ADE GLIOMAS: PET/CT WITH $^{68}$GA-DOTA-PEPTIDES, CORRELATION TO PROGNOSTIC MARKERS, AND IMPLICATIONS FOR TARGETED RADIOTHERAPY.


Abstract

**Background:** High-grade gliomas (HGGs) express somatostatin receptors (SSTR), rendering them candidates for peptide receptor radionuclide therapy (PRRT). Our purpose was to evaluate the potential of $^{68}$Ga-DOTA-1-Nal(3)-octreotide ($^{68}$Ga-DOTANOC) or $^{68}$Ga-DOTA-Tyr(3)-octreotide ($^{68}$Ga-DOTATOC) to target SSTR subtype 2 (SSTR2) in HGGs, and to study the association between SSTR2 expression and established biomarkers.

**Methods:** Twenty-seven patients (mean age 52 years) with primary or recurrent HGG prospectively underwent $^{68}$Ga-DOTA-peptide positron emission tomography/computed tomography (PET/CT) before resection. Maximum standardized uptake values (SUVmax) and receptor binding potential (BP) were calculated on PET/CT and disruption of blood-brain barrier (BBB) from contrast-enhanced T1-weighted magnetic resonance imaging (MRI-T1-Gad). Tumor volume concordance between PET and MRI-T1-Gad was assessed by Dice similarity coefficient (DC) and correlation by Spearman’s rank. Immunohistochemically determined SSTR2 status was compared to receptor imaging findings,
prognostic biomarkers, and survival with Kruskal-Wallis, Pearson chi-square, and multivariate Cox regression, respectively.

**Results:** All 19 HGGs with disrupted BBB demonstrated tracer uptake. Tumor SUVmax (2.25 ± 1.33) correlated with MRI-T1-Gad (r = 0.713, P = 0.001) although DC 0.41 ± 0.19 suggested limited concordance. SSTR2 immunohistochemistry was regarded as positive in nine HGGs (32%) but no correlation with SUVmax or BP was found. By contrast, SSTR2 expression was associated with IDH1 mutation (P = 0.007), oligodendroglioma component (P = 0.010), lower grade (P = 0.005), absence of EGFR amplification (P = 0.021), and longer progression-free survival (HR 0.161, CI 0.037 to 0.704, P = 0.015).

**Conclusions:** In HGGs, uptake of 68-Ga-DOTA-peptides is associated with disrupted BBB and cannot be predicted by SSTR2 immunohistochemistry. Thus, PET/CT shows limited value to detect HGGs suitable for PRRT. However, high SSTR2 expression portends favorable outcome along with established biomarkers such as IDH1 mutation.


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**COMPARISON OF 68GA-DOTATOC BIODISTRIBUTION IN PATIENTS WITH AND WITHOUT SPLENECTOMY.**


**Abstract**

**Aim:** Ga-68 labeled somatostatin analogues such as 68Ga-DOTA0-Phe1-Tyr3-octrotide (DOTATOC) as PET tracers, have significantly improved the imaging of somatostatin receptors (SSTRs) expressing tumors. Due to unspecific parenchymal binding and the expression of SSTRs on leukocytes in the spleen this is the organ with the highest non-tumor uptake of DOTATOC. Therefore, we investigated the potential changes of normal tissue distribution and tumor concentration in patients with neuroendocrine tumors (NETs) with or without splenectomy.

**Methods:** Out of 420 patients with pancreatic NET undergoing 68GA-DOTATOC PET/CT eleven patients with and eleven patients without splenectomy were derived and matched in regard to tumor histology, tumor load, age and gender. The SUVmax of liver metastases as well as of the following normal tissues was determined: pituitary gland, thyroid gland, liver parenchyma, kidneys and suprarenal glands.

**Results:** SUVmax values with and without splenectomy were: in the liver metastasis (19.17±6.05 versus 37.67±16.31), in the thyroid gland (2.56±1.3 versus 2.66±0.94), in the pituitary gland (4.08±1.79 versus 4.92±1.93) in suprarenal glands (7.18±3.33 versus 9.73±3.46 on the left side and 7.32±3.03 versus 11.19±5.72 on the right side), in the kidneys (8.13±4.26 on the left side and 8.11±4.16 on the right side versus 8.62±2.17 on the left side and 9.79±2.18 on the right side) and in normal liver tissue (5.74±1.55 versus 6.22±1.95). The difference was statistically significant (Wilcoxon test P<0.05) in tumor lesions, adrenal and kidney tissue.

**Conclusion:** Splenectomy must be considered as a relevant factor when reporting the outcome of SSTR targeted diagnostics and therapies.


SUV OF $[^{68}\text{Ga}]$DOTATOC-PET/CT PREDICTS RESPONSE PROBABILITY OF PRRT IN NEUROENDOCRINE TUMORS.


Abstract

Purpose: The goal of our study was to quantify the expression of the somatostatin receptors (SSTR2) using the maximum standard uptake value (SUVmax) of $[^{68}\text{Ga}]$DOTA(0)-Phe(1)-Tyr(3)-octreotide (DOTATOC) positron emission tomography (PET)-computed tomography (CT) in liver metastases of patients with neuroendocrine tumors (NETs) prior to peptide receptor radiation therapy (PRRT) and compare the initial tumor uptake with the final treatment outcome.

Procedures: SSTR2 expression of the 60 liver metastases in 30 NET patients was assessed at baseline and after PRRT by measuring SUVmax, tumor to spleen ratio (T/S ratio), and tumor to liver ratio (T/L ratio). Based on morphological changes and tumor size measured at baseline and follow-up contrast-enhanced CT (after three cycles of PRRT), lesions were divided into two groups by the following: (i) responding ($n=40$) and (ii) non-responding ($n=20$).

Results: Statistically significant differences were observed in the mean SUVmax for non-responding vs. responding lesions at baseline (18.00 ± 3.59 vs. 33.55 ± 4.62, $p<0.05$) and for the mean T/S ratio (1.20 ± 0.37 vs. 1.90 ± 0.45, $p<0.05$) and the mean T/L ratio (3.15 ± 0.53 vs. 4.97 ± 0.62, $p<0.05$). Using the receiver operating characteristic curves, SUVmax was found a better metric than both T/L ratio and T/S ratio (area under the curve (AUC) of SUVmax 0.87; T/L ratio 0.78; T/S ratio 0.73) as a stratification criterion. Using a threshold value of >16.4 for SUVmax, the sensitivity and specificity in predicting responding lesions were 95 and 60 %, respectively.

Conclusion: We propose a SUVmax cutoff of >16.4 from $[^{68}\text{Ga}]$DOTATOC-PET-CT to select patients for PRRT. A T/L ratio >2.2 might present a scanner-independent criterion that enables the translation of our results to other institutions. However, the robustness of this arbitrary unit still needs to be evaluated with different PET scanners.


METASTATIC NEUROENDOCRINE TUMOUR IN A RENAL TRANSPLANT RECIPIENT: DUAL-TRACER PET-CT WITH $^{18}$F-FDG AND $^{68}$Ga-DOTANOC IN THIS RARE SETTING.


Abstract

Recipients of renal transplant are at increased risk of developing various malignancies, especially post-transplant lymphoproliferative disorder (PTLD) and skin cancers. Neuroendocrine tumours (NET) of the gastrointestinal tract have not been reported in this setting. Here we describe the case of a 75-year-old male who had undergone renal transplant 8 years back and presented with significant weight loss and backache, clinically suspected as PTLD. $^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography-computed tomography (PET-CT) showed hypermetabolic lesions in the liver and rectum, raising the suspicion of PTLD. However, biopsy from the liver lesion showed poorly
differentiated NET. $^{68}$Ga-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-NaI(3)-octreotide ($^{68}$Ga-DOTANOC) PET-CT was then done, which confirmed the primary lesion in the rectum with liver metastases.


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**SIMULTANEOUS $^{68}$GA-DOTA-TOC PET/MRI WITH GADOXETATE DISODIUM IN PATIENTS WITH NEUROENDOCRINE TUMOR.**

Hope TA, Pampaloni MH, Nakakura E, VanBrocklin H, Slater J, Jivan S, Aparici CM, Yee J, Bergslund E.

**Abstract**

**Objective:** To evaluate a simultaneous PET/MRI approach to imaging patients with neuroendocrine tumor using a combination of $^{68}$Ga-DOTA-TOC as a PET contrast agent and gadoxetate disodium as a hepatobiliary MRI contrast agent.

**Materials and methods:** Ten patients with neuroendocrine tumor with known or suspected hepatic disease were imaged using a $^{68}$Ga-DOTA-TOC PET/CT immediately followed by a 3.0T time-of-flight PET/MRI, using a combined whole body and liver specific imaging. The presence of lesions and DOTA-TOC avidity were assessed on CT, PET from PET/CT, diffusion weighted imaging, hepatobiliary phase imaging (HBP), and PET from PET/MRI. Maximum standardized uptake values (SUVmax) in hepatic lesions and nodal metastases were compared between PET/CT and PET/MRI, as were detection rates using each imaging approach.

**Results:** A total of 101 hepatic lesions were identified, 47 of which were DOTA-TOC avid and able to be individually measured on both PET/CT and PET/MRI. HBP imaging had a higher sensitivity for detection of hepatic lesions compared to CT or PET (99% vs. 46% and 64%, respectively; p values <0.001). There was a strong correlation between SUVmax of liver lesions obtained with PET/CT compared to PET/MR imaging (Pearson's correlation = 0.91). For nodal disease, CT had a higher sensitivity compared to whole body MRI (p = 0.015), although PET acquired from PET/MRI detected slightly more lesions compared to PET from PET/CT.

**Conclusions:** A simultaneous PET/MRI using both $^{68}$Ga-DOTA-TOC and gadoxetate disodium was successful in whole body staging of patients with neuroendocrine tumor. HBP imaging had an increased detection rate for hepatic metastases.


**INTRAPANCREATIC ACCESSORY SPLEEN DETECTED BY $^{68}$GA DOTANOC PET/CT AND $^{99m}$TC-COLLOID SPECT/CT SCINTIGRAPHY.**

Collarino A, del Ciello A, Perotti G, Rufini V.

**Abstract**

A 77-year-old man was referred to our center for a suspected neuroendocrine neoplasm in the pancreatic tail, incidentally detected at CT. Ga DOTANOC PET/CT showed intense tracer uptake in the pancreatic lesion. At MRI, the lesion was similar to the spleen on all sequences, suggesting the presence of intrapancreatic accessory spleen. A Tc-colloid SPECT/CT scan performed to differentiate spleen tissue from neuroendocrine tumor revealed a focal uptake in the pancreatic lesion, thus confirming the presence of ectopic spleen and avoiding unnecessary surgery.

MULTICENTER COMPARISON OF $^{18}$F-FDG AND $^{68}$GA-DOTA-PEPTIDE PET/CT FOR PULMONARY CARCINOID.


Abstract

Purpose: The aims of this study were to retrospectively evaluate and compare the detection rate (DR) of $^{68}$Ga-DOTA-peptide and $^{18}$F-FDG PET/CT in the preoperative workup of patients with pulmonary carcinoid (PC) and to assess the utility of various functional indices obtained with the 2 tracers in predicting the histological characterization of PC, that is, typical versus atypical.

Methods: Thirty-three consecutive patients with confirmed PC referred for $^{18}$F-FDG and $^{68}$Ga-DOTA-peptide PET/CT in 2 centers between January 2009 and April 2013 were included. The semiquantitative evaluation included the SUV max, the SUV of the tumor relative to the maximal liver uptake for $^{18}$F-FDG (SUV T/L) or the maximal spleen uptake for $^{68}$Ga-DOTA-peptides (SUV T/S), the ratio between SUV max of $^{68}$Ga-DOTA-peptides PET/CT, and the SUV max of $^{18}$F-FDG PET/CT (SUV max ratio). Histology was used as reference standard.

Results: Definitive diagnosis consisted of 23 typical carcinoids (TCs) and 10 atypical carcinoids. $^{18}$F-FDG PET/CT was positive in 18 cases and negative in 15 (55% DR). $^{68}$Ga-DOTA-peptide PET/CT was positive in 26 cases and negative in 7 (79% DR). In the subgroup analysis, $^{68}$Ga-DOTA-peptide PET/CT was superior in detecting TC (91% DR; P < 0.001), whereas $^{18}$F-FDG PET/CT was superior in detecting atypical carcinoid (100% DR; P = 0.04). The SUV max ratio was the most accurate semiquantitative index in identifying TC.

Conclusions: Overall diagnostic performance of PET/CT in detecting PC is optimal when integrating $^{18}$F-FDG and $^{68}$Ga-DOTA-peptide PET/CT findings. In the subgroup analysis, the SUV max ratio seems to be the most accurate index in predicting TC. Both methods should be performed when PC is suspected or when the histological subtype is undefined.