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

Special Edition
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A multimodal neuroimaging study of a case of crossed nonfluent/agrammatic primary progressive aphasia.


Crossed aphasia has been reported mainly as post-stroke aphasia resulting from brain damage ipsilateral to the dominant right hand. Here, we described a case of a crossed nonfluent/agrammatic primary progressive aphasia (nfvPPA), who developed a corticobasal syndrome (CBS). We collected clinical, cognitive, and neuroimaging data for four consecutive years from a 55-year-old right-handed lady (JV) presenting with speech disturbances. 18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) and DaT-scan with (123)I-loflupane were obtained.

Functional MRI (fMRI) during a verb naming task was acquired to characterize patterns of language lateralization. Diffusion tensor MRI was used to evaluate white matter damage within the language network. At onset, JV presented with prominent speech output impairment and right frontal atrophy. After 3 years, language deficits worsened, with the occurrence of a mild agrammatism. The patient also developed a left-sided mild extrapyramidal bradykinetic-rigid syndrome. The clinical picture was suggestive of nfvPPA with mild left-sided extrapyramidal syndrome. At this time, voxel-wise SPM analyses of ($^{18}$)F-FDG PET and structural MRI showed right greater than left frontal hypometabolism and damage, which included the Broca's area. DaT-scan showed a reduced uptake in the right striatum. FMRI during naming task demonstrated bilateral language activations, and tractography showed right superior longitudinal fasciculus (SLF) involvement.

Over the following year, JV became mute and developed frank left-sided motor signs and symptoms, evolving into a CBS clinical picture. Brain atrophy worsened in frontal areas bilaterally, and extended to temporoparietal regions, still with a right-sided asymmetry. Tractography showed an extension of damage to the left SLF and right inferior longitudinal fasciculus. We report a case of crossed nfvPPA followed longitudinally and studied with advanced neuroimaging techniques. The results highlight a complex interaction between individual premorbid developmental differences and the clinical phenotype.


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

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

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 (18)F-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.


Thalamic abnormalities in children with continuous spike-wave during slow-wave sleep: An F-18-fluorodeoxyglucose positron emission tomography perspective.

Agarwal R, Kumar A, Tiwari VN, Chugani H.

OBJECTIVE: Thalamic injury has been implicated in the development of continuous spike-wave during slow-wave sleep (CSWS) in children with epilepsy. We studied thalamic abnormalities in children with CSWS using F-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging.

METHODS: Twenty-three patients (12 male; mean age 9 years) with CSWS and normal thalami on brain magnetic resonance imaging (MRI) underwent FDG-PET. Thalamic glucose metabolism, represented by standardized uptake value normalized to whole brain (nSUV, RT for right thalamus and LT for left thalamus), and its asymmetry-absolute asymmetry index (AAI): |(RT-LT)*100/[(RT+LT)/2]| was calculated. These values were compared with those from 10 normal healthy controls (five female; mean age 11.1 years).

RESULTS: Thalamic glucose metabolism was abnormal in 18 patients (78.3%). Thalamic nSUV was decreased (n = 6) or increased (n = 1) bilaterally in seven children without any asymmetry. Abnormal thalamic symmetry [AAI = 3.7-31.5% (0.8-3.3% in controls)] was seen in 11 children. Of these, six children had a unilateral thalamic metabolic abnormality (increased metabolism, n = 3 and decreased metabolism, n = 3), whereas 5 of 14 children had abnormal asymmetry index with bilaterally normal (n = 4) or increased (n = 1) thalamic metabolism. No clear association of thalamic metabolic abnormalities was seen with the stage of evolution of CSWS (prodromal, acute, or residual) or with the cortical FDG abnormalities.

SIGNIFICANCE: Functional thalamic abnormalities, both unilateral and bilateral, are frequently seen in patients with CSWS. FDG-PET is a sensitive and quantifiable modality to detect these changes.

Impulsivity is Associated with Increased Metabolism in the Fronto-Insular Network in Parkinson’s Disease.

Tahmasian M, Rochhausen L, Maier F, Williamson KL, Drzezga A, Timmermann L, Van Eimeren T, Eggers C.

Various neuroimaging studies demonstrated that the fronto-insular network is implicated in impulsive behavior. We compared glucose metabolism (as a proxy measure of neural activity) among 24 patients with Parkinson's disease (PD) who presented with low or high levels of impulsivity based on the Barratt Impulsiveness Scale 11 (BIS) scores.

Subjects underwent $^{18}$-fluorodeoxyglucose positron emission tomography (FDG-PET) and the voxel-wise group difference of FDG-metabolism was analyzed in Statistical Parametric Mapping (SPM8). Subsequently, we performed a partial correlation analysis between the FDG-metabolism and BIS scores, controlling for covariates (i.e., age, sex, severity of disease and levodopa equivalent daily doses). Voxel-wise group comparison revealed higher FDG-metabolism in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and right insula in patients with higher impulsivity scores. Moreover, there was a positive correlation between the FDG-metabolism and BIS scores.

Our findings provide evidence that high impulsivity is associated with increased FDG-metabolism within the fronto-insular network in PD.

Metabolic Activity by $^{18}$F-FDG-PET/CT Is Prognostic for Stage I and II Pancreatic Cancer.

**Pimiento JM, Davis-Yadley AH, Kim RD, Chen DT, Eikman EA, Berman CG, Malafa MP.**

Metabolic activity, as defined by F-FDG uptake on PET, is a prognostic marker for multiple malignancies; however, no study has examined the prognostic value of imaging with FDG PET in stage I and II pancreatic cancer. We examined the value of PET FDG uptake in early-stage pancreatic cancer patients.

**METHODS:** We identified patients with early-stage pancreatic cancer (I-II) who had FDG PET scan performed as part of their preoperative evaluation. The patients were divided into either high or low FDG uptake according to the median primary tumor standard uptake value (SUVmax). Our primary end points were overall survival (OS) and recurrence-free survival (RFS). Kaplan-Meier estimate was used for survival analysis. Pathologic data were compared using the Fisher exact and χ² tests.

**RESULTS:** One hundred five patients were identified: 51 patients with low FDG uptake and 54 patients with high FDG uptake. Eighty-five patients (81%) had PET avid tumors, whereas 20 (19%) patients did not. High FDG uptake correlated with pathologic stage ($P = 0.012$). Patients with low FDG uptake had significantly better median OS than patients with high FDG uptake (28 vs. 16 months; $P = 0.036$). Patients with low-FDG uptake had significantly longer median RFS than patients with high FDG uptake (14 vs. 12 months; $P = 0.049$).

**CONCLUSIONS:** Low FDG uptake in PET scans in patients with stage I and II pancreatic cancer correlates with improved OS and RFS. This supports the concept that glucose metabolic pathways are important in pancreatic cancer biology and that PET scan activity can be used as a prognostic biomarker after pancreatectomy.


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A prospective trial of dynamic contrast-enhanced MRI perfusion and fluorine-$^{18}$ FDG PET-CT in differentiating brain tumor progression from radiation injury after cranial irradiation.


The aim of this study was to assess the effectiveness of fluorine-$^{18}$ fluorodeoxyglucose (FDG) PET-CT and dynamic contrast-enhanced (DCE) MRI in differentiating tumor progression and radiation injury in patients with indeterminate enhancing lesions after radiation therapy (RT) for brain malignancies.

**METHODS:** Patients with indeterminate enhancing brain lesions on conventional MRI after RT underwent brain DCE-MRI and PET-CT in a prospective trial. Informed consent was obtained. Lesion outcomes were determined by histopathology and/or clinical and imaging follow-up. Metrics obtained included plasma volume (Vp) and volume transfer coefficient ($K^{\text{trans}}$) from DCE-MRI, and maximum standardized uptake value (SUV$_{\text{max}}$) from PET-CT; lesion-to-normal brain ratios of all metrics were calculated. The Wilcoxon rank sum test and receiver operating characteristic analysis were performed.

**RESULTS:** The study included 53 patients (29 treated for 29 gliomas and 24 treated for 26 brain metastases). Progression was determined in 38/55 (69%) indeterminate lesions and radiation injury in 17 (31%). Vp$_{\text{ratio}}$ ($V_p$ lesion/$V_p$ normal brain, $P < .001$), $K^{\text{trans}}$$_{\text{ratio}}$ ($P = .002$), and SUV$_{\text{ratio}}$ ($P = .002$) correlated significantly with diagnosis of progression versus radiation injury. Progressing
lesions exhibited higher values of all 3 metrics compared with radiation injury. \( Vp_{ratio} \) had the highest accuracy in determining progression (area under the curve = 0.87), with 92% sensitivity and 77% specificity using the optimal, retrospectively determined threshold of 2.1. When \( Vp_{ratio} \) was combined with \( K_{trans}^{ratio} \) (optimal threshold 3.6), accuracy increased to 94%.

**CONCLUSIONS:** \( Vp_{ratio} \) was the most effective metric for distinguishing progression from radiation injury. Adding \( K_{trans}^{ratio} \) to \( Vp_{ratio} \) further improved accuracy. DCE-MRI is an effective imaging technique for evaluating nonspecific enhancing intracranial lesions after RT.


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**18**F-FDG PET/CT to assess response and guide risk-stratified follow-up after chemoradiotherapy for oropharyngeal squamous cell carcinoma.


To evaluate the use of \( 18 \)F-FDG PET/CT as the principal investigation to assess tumour response, to determine the need for further surgery and to guide follow-up following radical chemoradiotherapy for stage III/IV oropharyngeal squamous cell carcinoma (OPSCC).

**METHODS:** A retrospective analysis was undertaken in 146 patients treated at our centre with radical chemoradiotherapy for OPSCC and who had a PET/CT scan to assess response. According to the PET/CT findings, patients were divided into four groups and recommendations: (1) complete metabolic response (enter clinical follow-up); (2) low-level uptake only (follow-up PET/CT scan in 12 weeks); (3) residual uptake suspicious for residual disease (further investigation with or without neck dissection); and (4) new diagnosis of distant metastatic disease (palliative treatment options).

**RESULTS:** The initial PET/CT scan was performed at a median of 12.4 weeks (range 4.3 - 21.7 weeks) following treatment. Overall sensitivity and specificity rates were 92.0 % (74.0 - 99.0 %) and 85 % (77.5 - 90.9 %). Of the 146 patients, 90 (62 %) had a complete response and had estimated 3-year overall and disease-free survival rates of 91.9 % (85.6 - 98.2 %) and 85.6 % (78.0 - 93.2 %), respectively. 17 (12 %) had residual low-level uptake only (with two having confirmed residual disease on subsequent PET/CT, both surgically salvaged), 30 (21 %) had suspicious residual uptake (12 proceeded to neck dissection; true positive rate at surgery 33 %). HPV-positive patients with reassuring PET/CT findings had an estimated 3-year progression-free survival rate of 91.7 % (85.2 - 98.2 %), compared with 66.2 % (41.5 - 90.9 %) of HPV-negative patients.

**CONCLUSION:** A strategy of using PET/CT results alongside clinical examination to help select patients for salvage surgery appears successful. Despite a complete response on the 12-week PET/CT scan, HPV-negative patients have a significant risk of disease relapse in the following 2 years and further studies to assess whether surveillance imaging in this group could improve outcomes are warranted.

A method to improve the semi-quantification of $^{18}$F-fluorodeoxyglucose uptake: reliability of the estimated lean body mass using a limited field of acquisition, low dose CT from PET/CT.

Decazes P, Métivier D, Rouquette A, Talbot JN, Kerrou K.

The Standardized Uptake Lean mass (SUL), calculated using lean body mass (LBM), is essential for the semi-quantification of $^{18}$F-fluorodeoxyglucose (FDG) uptake using Positron Emission Tomography coupled with Computed Tomography (PET/CT) to avoid a bias linked to the adipose mass. It allows evaluating a response to therapy according the PET response criteria in solid tumors (PERCIST) 1.0. The aim of this study was to evaluate the reliability of a method for the estimation of the LBM using the data of the low-dose CT from PET/CT acquired over standard acquisition fields (from skull base to ischia, from vertex to ischia, from skull base to mid-thigh, from vertex to mid-thigh).

METHODS: We wrote an automated program which determined the LBM from a CT with limited fields of acquisition and applied this method in a large (184 patients) and heterogeneous population. Its results were compared with the measurement of LBM from whole body CT (reference standard) and the results of 5 predictive equations described in the literature.

RESULTS: The results of LBM measurement evaluated with this technique were much closer to the reference standard than those obtained by the mathematical formulas. The Intraclass Correlations (ICC) of this technique compared to the reference standard were excellent (the best ICC being obtained for the largest acquisition field, from vertex to mid-thigh: ICC 0.994, IC 95% [0.992-0.995], P < 0.0001), much better than the ICC obtained with the mathematical formulas (the best ICC for a mathematical formula was 0.841, CI 95% [0.714;0.903], P < 0.0001). Moreover, the analysis with the Bland-Altman plots showed that the differences in mean lean masses between the studied technique and the reference standard was the smallest for the proposed technique (for the largest acquisition field, mean difference 0.2 kg with the narrowest 95% CI [-1.8 to 2.2 kg]).

CONCLUSION: This technique could be easily implemented on computers used in practice to allow a more reliable assessment of the SUL in clinical practice notably for the therapeutic evaluations following PERCIST 1.0.

Adaptive neoadjuvant chemotherapy guided by $^{18}$F-FDG-PET in resectable non-small-cell lung cancers: the NEOSCAN trial.

Adaptive neoadjuvant chemotherapy guided by $^{18}$F-FDG-PET in resectable non-small-cell lung cancers: the NEOSCAN trial.

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Adaptive neoadjuvant chemotherapy guided by $^{18}$F-FDG-PET in resectable non-small-cell lung cancers: the NEOSCAN trial.
initial chemotherapy. Individuals with <35% PET response were switched to vinorelbine +
docetaxel. Post operative radiotherapy was recommended to all patients with positive N2 nodes.
A Simon-optimal two stage design was used to evaluate the primary endpoint of a PERCIST-
declared response rate to vinorelbine + docetaxel in previously non-responding patients.

RESULTS: 40 patients were enrolled. 15 patients (38%, 95% CI: 38-53%) had <35% decrease in
SUV\textsubscript{peak} and 13 received vinorelbine + docetaxel. The study met its primary endpoint with 10/15
(67%) PET metabolic responses to alternate therapy. Chemotherapy toxicities never precluded
surgical exploration.

CONCLUSIONS: Utilizing FDG PET/CT to assess response and change preoperative
chemotherapy in non-responding patients can improve radiographic measures of response. This
adaptive approach can also be used to test new drugs, attempting to optimize perioperative
chemotherapy to achieve better long term outcomes.


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Diagnostic accuracy of imaging methods for the diagnosis of skeletal malignancies: A
retrospective analysis against a pathology-proven reference.

Lange MB, Nielsen ML, Andersen JD, Lilholt HJ, Vyberg M, Petersen LJ.

To examine the diagnostic accuracy of imaging modalities in skeletal tumours versus pathology
reports.

MATERIALS AND METHODS: Pathology reports of bone biopsies were compared to diagnostic
imaging with X-ray, computed tomography (CT), magnetic resonance imaging (MRI), bone
scintigraphy (BS), and \textsuperscript{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT)
performed within 6 months of biopsy.

RESULTS: A total of 409 biopsies were included. Sensitivity and specificity were significantly
different among the five modalities (p<0.0001). The sensitivity of MRI and PET/CT was better
than CT, but CT had a better specificity than PET/CT. In general, these methods outperformed
BS and X-ray. The sensitivity for osteolytic lesions varied significantly between modalities
(p<0.0001), with MRI and PET/CT being more sensitive than CT. Differences in sensitivity were
also observed in mixed lesions (p=0.0002) but not in osteosclerotic lesions. In spine lesions, MRI
showed the best sensitivity followed by PET/CT and CT (p<0.0005 vs. MRI). There was no
significant differences among non-spine lesions.

CONCLUSIONS: MRI and FDG-PET/CT showed comparable diagnostic characteristics in
general, in individual tumour types, and in different bone lesions and locations. Nominally, they
outperformed CT in most situations. The diagnostic accuracy of X-ray and BS were notably
inferior to other modalities.

**Increasing feasibility and utility of \(^{18}\)F-FDOPA PET for the management of glioma.**


Despite radical treatment therapies, glioma continues to carry with it a uniformly poor prognosis. Patients diagnosed with WHO Grade IV glioma (glioblastomas; GBM) generally succumb within two years, even those with WHO Grade III anaplastic gliomas and WHO Grade II gliomas carry prognoses of 2-5 and 2 years, respectively. PET imaging with \(^{18}\)F-FDOPA allows in vivo assessment of the metabolism of glioma relative to surrounding tissues. The high sensitivity of \(^{18}\)F-DOPA imaging grants utility for a number of clinical applications.

**METHODS:** A collection of published work about \(^{18}\)F-FDOPA PET was made and a critical review was discussed and written.

**RESULTS:** A number of research papers have been published demonstrating that in conjunction with MRI, \(^{18}\)F-FDOPA PET provides greater sensitivity and specificity than these modalities in detection, grading, prognosis and validation of treatment success in both primary and recurrent gliomas. In further comparisons with \(^{11}\)C-MET, \(^{18}\)F-FLT, \(^{18}\)F-FET and MRI, \(^{18}\)F-FDOPA has shown similar or better efficacy. Recently synthesis cassettes have become available, making \(^{18}\)F-FDOPA more accessible.

**CONCLUSIONS:** According to the available data, \(^{18}\)F-FDOPA PET is a viable radiotracer for imaging and treatment planning of gliomas. ADVANCES IN KNOWLEDGE AND IMPLICATION FOR PATIENT CARE: \(^{18}\)F-FDOPA PET appears to be a viable radiopharmaceutical for the diagnosis and treatment planning of gliomas cases, improving on that of MRI and \(^{18}\)F-FDG PET.


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**MAOA-VNTR polymorphism modulates context-dependent dopamine release and aggressive behavior in males.**


A recent \([-^{(18)}F\)]FDOPA-PET study reports negative correlations between dopamine synthesis rates and aggressive behavior. Since dopamine is among the substrates for monoamine oxidase A (MAOA), this investigation examines whether functional allelic variants of the MAOA tandem repeat (VNTR) promoter polymorphism, which is known to modulate aggressive behavior, influences dopamine release and aggression in response to violent visual stimuli. We selected from a genetic prescreening sample, strictly case-matched groups of 2×12 healthy male subjects with VNTRs predictive of high (MAOA-High) and low (MAOA-Low) MAOA expression.

Subjects underwent pairs of PET sessions (dopamine D2/3 ligand \([-^{(18)}F\)]DMFP) while viewing a movie of neutral content, versus violent content. Directly afterwards, aggressive behavior was assessed by the Point Subtraction Aggression Paradigm (PSAP). Finally, PET data of 23 participants and behavioral data of 22 participants were analyzed due to post hoc exclusion criteria. In the genetic prescreening sample MAOA-Low carriers had significantly increased scores on the Buss-Perry Aggression Questionnaire. In the PET-study-group, aggressive behavior under the emotional neutral condition was significantly higher in the MAOA-Low group. Interestingly, the two MAOA-groups showed inverse dopaminergic and behavioral reactions to
the violent movie: The MAOA-High group showed higher dopamine release and increased aggression after the violent movie; MAOA-Low subjects showed decreases in aggressive behavior and no consistent dopamine release. These results indicate a possible impact of the MAOA-promotor polymorphism on the neurobiological modulation of aggressive behavior. However, the data do not support approaches stating that MAOA-Low fosters aggression by a simple pro-dopaminergic mechanism.


Weak Uptake of 123I-MIBG and 18F-FDOPA Contrasting With High 18F-FDG Uptake in Stage I Neuroblastoma.

Wartski M, Jehanno N, Michon J, de Labriolle-Vaylet C, Montravers F.

Hypertension in a 6-year-old girl was the presenting sign of a stage I neuroblastoma. This tumor corresponded to a left adrenal gland mass. Hypertension resolved immediately after complete surgical resection of the tumor with an uneventful follow-up (24 months at the present time). Preoperative assessment by nuclear medicine techniques showed weak uptake of I-MIBG and F-FDOPA contrasting with high F-FDG uptake by the tumor.


Evaluation of 6-11C-Methyl-m-tyrosine as a PET Probe for Presynaptic Dopaminergic Activity: A Comparison PET Study with β-11-L-DOPA and 18F-FDOPA in Parkinson's Disease Monkeys.

Kanazawa M, Ohba H, Harada N, Kakiuchi T, Muramatsu SI, Tsukada H.

We recently developed a novel PET probe, 6-11C-Methyl-m-tyrosine (11C-6MemTyr), for quantitative imaging of presynaptic dopamine (DA) synthesis in the living brain. In the present study, 11C-6MemTyr was compared with β-11C-L-DOPA and 6-18F-fluoro-L-dopa (18F-FDOPA), in the brains of normal and Parkinson's disease (PD) model monkeys (Macaca fascicularis).

METHODS: PD model monkeys were prepared by MPTP administration, and 11C-β-CFT was applied to assess neuronal damage as DA transporter (DAT) availability. 11C-6MemTyr, β-11C-L-DOPA, or 18F-FDOPA was injected with and without carbidopa, a specific inhibitor of peripheral aromatic L-amino acid decarboxylase (AADC). In normal and PD monkeys, the DA synthesis rates calculated using PET probes were analyzed by the correlation plot with DAT availability in the striatum (Str).

RESULTS: In normal monkeys, whole brain uptakes of β-11C-L-DOPA and 18F-FDOPA were significantly increased by carbidopa at the clinical dose of 5 mg/kg p.o.. In contrast, 11C-6MemTyr was not affected by carbidopa at this dose, and Patlak Ki value of 11C-6MemTyr in Str was significantly higher than those of the other 2 PET probes. Significant reduction of the presynaptic DAT availability in Str was detected in MPTP monkeys, and correlation analyses demonstrated that 11C-6MemTyr could detect DA damage in Str with much more sensitivity than the other PET probes.
CONCLUSION: $^{11}$C-6MemTyr is a potential PET probe for quantitative imaging of presynaptic DA activity in the living brain with PET.

Multicenter study evaluating extraprostatic uptake of 11C-choline, $^{18}$F-methylcholine, and $^{18}$F-ethylcholine in male patients: physiological distribution, statistical differences, imaging pearls, and normal variants.


Abstract

AIM: The aim of the study was to evaluate the visceral localization of the three most commonly used choline-based radiotracers (C-choline, F-methylcholine, and F-ethylcholine) with the aim of analyzing uptake in metabolically and anatomically disease-free patients.

MATERIALS AND METHODS: A total of 1250 standardized uptake values (SUVmax, SUVmean) were analyzed in 45 anatomical regions in 45 patients (15 patients with C-Choline, 15 with F-methylcholine, and 15 with F-ethylcholine). These patients were selected from a cohort of 3721 choline PET/computed tomography studies performed at three teaching hospitals over a period of 10 years. They had no evidence of metabolically active primary disease, metastatic disease, or altered morphology on the computed tomography component of the study or any evidence of disease elsewhere on other imaging modalities. The sites of primary disease (prostate and seminal vesicles) were excluded from evaluation.

RESULTS: No adverse effect was documented when using the three tracers. Visceral localization was the same for all three tracers. Viscera with a statistical difference in intensity of uptake included the choroid plexus ($P=0.0001$), occipital lobe ($P=0.014$), parietal lobe ($P=0.008$), cerebellum ($P=0.003$), parotid gland ($P=0.005$), submandibular gland ($P=0.001$), tonsils ($P=0.001$), thyroid ($P=0.0001$), lungs ($P=0.001$), aorta ($P=0.001$), pulmonary artery ($P=0.0001$), liver segments I ($P=0.005$), III ($P=0.005$), IVB ($P=0.03$), and V ($P=0.01$), spleen [hilum ($P=0.0009$), body ($P=0.0001$)], pancreas [head ($P=0.0001$), body ($P=0.01$), tail ($P=0.002$)], esophagus ($P=0.001$), stomach ($P=0.0001$), duodenum ($P=0.0002$), large intestine ($P=0.008$), and rectum ($P=0.0001$). Elsewhere, no statistical difference was observed. Excreted activity was noted in the kidneys and bladder.

CONCLUSION: This study demonstrates that the visceral localization of C-choline, F-methylcholine, and F-ethylcholine in disease-free patients is similar. Depending on the tracer uptake pattern, the viscera can be divided into two distinct categories: those with a statistically significant difference in uptake and those with no difference in uptake. The study outlines the range of SUVs for various organs for the three tracers and identifies some of the potential pitfalls in the evaluation of 'nonavid' but clinically significant presentation of different disease entities.

Repeatability of quantitative $^{18}$F-fluoromethylcholine PET/CT studies in prostate cancer.


Repeatable quantification is essential when using $^{18}$F-fluoromethylcholine ($^{18}$F-FCH) PET/CT for monitoring treatment response in prostate cancer (PC). It has been shown that standardized uptake value (SUV) normalized to the area under the curve (AUC) of the blood activity concentration (SUVAUC) provides better correlation with full kinetic analysis than standard SUV. However, precision of SUVAUC is not known yet. The purpose of this study was to assess repeatability of various semi-quantitative $^{18}$F-FCH parameters in PC.

METHODS: Twelve patients (64±8 years) with metastasized PC underwent 2 sets of $^{18}$F-FCH PET/CT scans, on consecutive days. Each set consisted of a 30 minutes dynamic PET/CT scan of the chest, after intravenous administration of 200 MBq $^{18}$F-FCH, followed by a whole body PET/CT at 40 minutes. Dynamic scan was used to derive AUC of the blood activity concentration. Lesion uptake was derived from the whole body scan using various types of volumes of interest: maximum, peak and mean. Each of these parameters was normalized to injected activity/weight, blood AUC and blood concentration itself at 40 minutes, resulting in several SUV, SUVAUC and SUVTBR values. Test-retest repeatability of these metrics, metabolic tumor volume (MTV) and total lesion choline uptake (TLCU), respectively, were studied. The level of agreement between test-retest data and reliability was assessed using Bland-Altman plots, repeatability coefficients (RC) and intraclass correlation coefficients.

RESULTS: A total of 67 choline avid metastases were identified, 44 bone and 23 lymph node lesions. In case of SUV$_{\text{max}}$, RC for SUV, SUVAUC and SUVTBR were 26% (ICC=0.95), 31% (ICC=0.95), and 46% (ICC=0.89), respectively. Similar values were obtained for SUVpeak and SUVmean. Repeatability of SUVAUC was comparable with that of SUV, for maximum, peak and mean values. Tissue type and tumor localization did not affect repeatability. MTV $<4.2$ cm$^3$ had larger variability than larger volumes (RC 45% versus 29%, $P = 0.048$). Repeatability did not differ between lesions with SUVpeak above or below the median value of 8.3 (RC 19% versus 28%, $P = 0.264$).

CONCLUSION: The repeatability of SUVAUC was comparable to that of standard SUV. RC of various semi-quantitative $^{18}$F-FCH parameters (SUV, MTV, TLCU) were ~35%. Larger differences are likely to represent treatment effects.

Radiation treatment monitoring using multimodal functional imaging: PET/CT ((\(^{18}\)F-Fluoromisonidazole & \(^{(18)}\)F-Fluorocholine) and DCE-US.

Arteaga-Marrero N, Brekke Rygh C, Mainou-Gomez JF, Adamsen TC, Lutay N, Reed RK, Olsen DR.

This study aims to assess the effect of radiation treatment on the tumour vasculature and its downstream effects on hypoxia and choline metabolism using a multimodal approach in the murine prostate tumour model CWR22. Functional parameters derived from Positron Emission Tomography (PET)/Computer Tomography (CT) with \(^{(18)}\)F-Fluoromisonidazole ((\(^{18}\)F-FMISO) and (\(^{18}\)F-Fluorocholine ((\(^{18}\)F-FCH) as well as Dynamic Contrast-Enhanced Ultrasound (DCE-US) were employed to determine the relationship between metabolic parameters and microvascular parameters that reflect the tumour microenvironment. Immunohistochemical analysis was employed for validation.

METHODS: PET/CT and DCE-US were acquired pre- and post-treatment, at day 0 and day 3, respectively. At day 1, radiation treatment was delivered as a single fraction of 10 Gy. Two experimental groups were tested for treatment response with \(^{(18)}\)F-FMISO and \(^{(18)}\)F-FCH.

RESULTS: The maximum Standardized Uptake Values (SUVmax) and the mean SUV (SUVmean) for the \(^{(18)}\)F-FMISO group were decreased after treatment, and the SUVmean of the tumour-to-muscle ratio was correlated to microvessel density (MVD) at day 3. The kurtosis of the amplitude of the contrast uptake A was significantly decreased for the control tumours in the \(^{(18)}\)F-FCH group. Furthermore, the eliminating rate constant of the contrast agent from the plasma k el derived from DCE-US was negatively correlated to the SUVmean of tumour-to-muscle ratio, necrosis and MVD.

CONCLUSIONS: The present study suggests that the multimodal approach using \(^{(18)}\)F-FMISO PET/CT and DCE-US seems reliable in the assessment of both microvasculature and necrosis as validated by histology. Thus, it has valuable diagnostic and prognostic potential for early non-invasive evaluation of radiotherapy.


Pairwise comparison of \(^{18}\)F-FDG and \(^{18}\)F-FCH PET/CT in prostate cancer patients with rising PSA and known or suspected second malignancy.

How Kit N, Dugué AE, Sevin E, Allouache N, Lesaunier F, Joly F, Aide N.

OBJECTIVE: This study aimed to evaluate the usefulness of combining fluorine-\(^{18}\)choline (F-FCH) and fluorine-\(^{18}\) fluorodeoxyglucose (F-FDG) PET/computed tomography (CT) in patients with rising prostate-specific antigen and known or suspected second malignancy.

MATERIALS AND METHODS: F-FCH and F-FDG PET/CT were performed 15±9 days apart on the same PET/CT system and acquisition and reconstruction parameters. A mean standardized uptake value (SUVmean) was computed for every lesion that could be discriminated with both tracers. PET results were confirmed by histology (eight patients) and clinical and imaging follow-up (mean±SD: 15±9 months).
RESULTS: Of 77 consecutive patients who underwent F-FCH PET/CT scans for suspected prostate cancer recurrence, 10 (13%) were suspected to have a second malignancy because of F-FCH PET pattern inconsistency with that of prostate cancer (n=6), because of a history of a second malignancy with similar metastatic patterns (n=2) or inconsistency between disease burden and prostate-specific antigen value (n=2). Seventy lesions were studied, with a final diagnosis of prostate cancer, other cancers and benign disease in 55, nine and six lesions, respectively. F-FCH SUVmean and F-FCH/F-FDG SUVmean ratios were significantly different between prostate cancer, nonprostate cancer and benign disease (P<0.0001 and P=0.04, respectively). Receiving operating characteristic analysis showed that the F-FCH/F-FDG ratios were not better than F-FCH SUVmean in discriminating prostate cancer from nonprostate cancer and benign diseases (sensitivity, specificity and area under the curve were 69%, 80%, 0.71 and 84%, 80% and 0.89, respectively).

CONCLUSION: We found that F-FCH/F-FDG SUVmean ratios cannot differentiate prostate cancer recurrences from other cancer types when both diagnoses are suspected. Doubtful lesions should be biopsied.

Assessment of Lymph Nodes and Prostate Status Using Early Dynamic Curves with $^{18}$F-Choline PET/CT in Prostate Cancer.


Dynamic image acquisition with $^{18}$F-Choline [fluorocholine (FCH)] PET/CT in prostate cancer is mostly used to overcome the bladder repletion, which could obstruct the loco-regional analysis. The aim of our study was to analyze early dynamic FCH acquisitions to define pelvic lymph node or prostate pathological status.

MATERIAL AND METHODS: Retrospective analysis was performed on 39 patients for initial staging ($n=18$), or after initial treatment ($n=21$). Patients underwent 10-min dynamic acquisitions centered on the pelvis, after injection of 3-4 MBq/kg of FCH. Whole-body images were acquired about 1 h after injection using a PET/CT GE Discovery LS (GE-LS) or Siemens Biograph mCT (mCT). Maximum and mean SUV according to time were measured on nodal and prostatic lesions. SUVmean was corrected for partial volume effect (PVEC) with suitable recovery coefficients. The status of each lesion was based on histological results or patient follow-up (>6 months). A Mann-Whitney test and ANOVA were used to compare mean and receiver operating characteristic (ROC) curve analysis.

RESULTS: The median PSA was 8.46 ng/mL and the median Gleason score was 3+4. Ninety-two lesions (43 lymph nodes and 49 prostate lesions) were analyzed, including 63 malignant lesions. In early dynamic acquisitions, the maximum and mean SUV were significantly higher, respectively, on mCT and GE-LS, in malignant versus benign lesions ($p<0.001$, $p<0.001$). Mean SUV without PVEC, allowed better discrimination of benign from malignant lesions, in comparison with maximum and mean SUV (with PVEC), for both early and late acquisitions. For patients acquired on mCT, area under the ROC curve showed a trend to better sensitivity and specificity for early acquisitions, compared with late acquisitions (SUVmax AUC 0.92 versus 0.85, respectively).

CONCLUSION: Assessment of lymph nodes and prostate pathological status with early dynamic imaging using PET/CT FCH allowed prostate cancer detection in situations where proof of malignancy is difficult to obtain.

Radiation Treatment of Lymph Node Recurrence from Prostate Cancer: Is 11C-Choline PET/CT Predictive of Survival Outcomes?


Abstract

PET/CT is a valuable tool to detect lymph node (LN) metastases in patients with biochemical failure after primary treatment for prostate cancer (PCa). The aim was to assess the predictive role of imaging parameters derived by (11)C-choline PET/CT on survival outcomes-overall survival, locoregional relapse-free survival, clinical relapse-free survival (cRFS), and biochemical relapse-free survival (bRFS)-in patients treated with helical tomotherapy (HTT) for LN recurrence.

METHODS: This retrospective study included 68 patients affected by PCa (mean age, 68 y; age range, 51-81 y) with biochemical recurrence after primary treatment (median prostate-specific antigen values obtained at the time of PET/CT scan, 2.42 ng/mL; range, 0.61-27.56 ng/mL) who underwent (11)C-choline PET/CT from January 2005 to January 2013 and were treated with HTT in correspondence of the pathologic choline LN uptake. PET-derived parameters, including maximum/mean standardized uptake value (SUVmax and SUVmean, respectively) and metabolic tumor volume (MTV) with a threshold of 40%, 50%, and 60% were calculated. The best cutoff values of PET-derived parameters discriminating between patients with and without relapse, after treatment guided by PET, were assessed by receiver-operating-characteristic (ROC) curve analysis. Univariate and multivariate Cox regression analysis including the most predictive PET-derived parameters and survival outcomes were performed.

RESULTS: The median follow-up was 20 mo (mean, 26 mo; range, 3-97 mo). (11)C-choline PET/CT showed pathologic LN uptake in 4 patients at the pelvic level, in 5 at the abdominal level, in 13 at both the pelvic and the abdominal level, and in 46 at the abdominal or pelvic or other sites. The 2-y overall survival, locoregional relapse-free survival, cRFS, and bRFS were 87%, 91%, 51%, and 40%, respectively. On the basis of ROC curves, the most discriminative cutoff value for MTV values was an MTV threshold of 60% (MTV60) of greater than 0.64 cm$^3$. No significant cutoff values were found for SUVmax or SUVmean at univariate analysis, whereas MTV60 was confirmed as an independent predictor in multivariate analysis and significantly correlated with bRFS and cRFS. MTV60 and extrapelvic disease well predict the risk of cRFS.

CONCLUSION: (11)C-choline PET/CT performed as a guide for HTT on LN recurrence is predictive of survival. In particular, MTV60 and extrapelvic disease were the best predictors of tumor response for bRFS and cRFS in PCa patients with LN recurrence after primary treatment. This information may be useful in emerging treatment strategies.


Prognostic value of metabolic parameters and clinical impact of $^{18}$F-fluorocholine PET/CT in biochemical recurrent prostate cancer.


PURPOSE: To evaluate the therapeutic impact of ($^{18}$F-fluorocholine (FCH) PET/CT in biochemical recurrent prostate cancer (PC) and to investigate the value of quantitative FCH PET/CT parameters in predicting progression-free survival (PFS).

METHODS: This retrospective study included 172 consecutive patients with PC who underwent FCH PET/CT for biochemical recurrence. Mean rising PSA was 10.7 ± 35.0 ng/ml. Patients with positive FCH PET were classified into three groups: those with uptake only in the prostatic bed, those with locoregional disease, and those with distant metastases. Referring physicians were asked to indicate the hypothetical therapeutic strategy with and without the FCH PET/CT results. Clinical variables and PET parameters including SUV max, SUVpeak, SUVmean, total lesion choline kinase activity (TLCKA) and standardized added metabolic activity (SAM) were recorded and a multivariate analysis was performed to determine the factors independently predicting PFS.

RESULTS: In 137 of the 172 patients, the FCH PET/CT scan was positive, and of these, 29.9 % (41/137) had prostatic recurrence, 42.3 % (58/137) had pelvic lymph node recurrence with or without prostatic recurrence, and 27.7 % (38/137) had distant metastases. The FCH PET/CT result led to a change in treatment plan in 43.6 % (75/172) of the 172 patients. Treatment was changed in 49.6 % (68/137) of those with a positive FCH PET/CT scan and in 20 % (7/35) of those with a negative FCH PET/CT scan. After a median follow-up of 29.3 months (95 % CI 18.9 - 45.9 months), according to multivariate analysis age <70 years, SAM $\geq$ 23 and SUVmean $\geq$ 3 were parameters independently predicting PFS. A nomogram constructed using the three parameters showed 49 months of PFS in patients with the best scores (0 or 1) and only 11 months in patients with a poor score (score 3).

CONCLUSION: This study indicates that a positive FCH PET result in PC patients with biochemical recurrence predicts a shorter PFS and confirms the major impact of the FCH PET result on the management of biochemical recurrent PC.

Correlation of \(^{18}\)F-fluoroethyl tyrosine positron-emission tomography uptake values and histomorphological findings by stereotactic serial biopsy in newly diagnosed brain tumors using a refined software tool.


Magnetic resonance imaging (MRI) is the standard neuroimaging method to diagnose neoplastic brain lesions, as well as to perform stereotactic biopsy surgical planning. MRI has the advantage of providing structural anatomical details with high sensitivity, though histological specificity is limited. Although combining MRI with other imaging modalities, such as positron-emission tomography (PET), has proven to increment specificity, exact correlation between PET threshold uptake ratios (URs) and histological diagnosis and grading has not yet been described.

OBJECTIVES: The aim of this study was to correlate exactly the histopathological criteria of the biopsy site to its PET uptake value with high spatial resolution (mm\(^3\)), and to analyze the diagnostic value of PET using the amino acid O-(2-\(^{18}\)F]fluoroethyl)-l-tyrosine (\(^{18}\)F-FET) PET in patients with newly diagnosed brain lesions in comparison to histological findings obtained from stereotactic serial biopsy.

PATIENTS AND METHODS: A total of 23 adult patients with newly diagnosed brain tumors on MRI were enrolled in this study. Subsequently to diagnoses, all patients underwent a \(^{18}\)F-FET PET-guided stereotactic biopsy, using an original newly developed software module, which is presented here. Conventional MRI, stereotactic computed tomography series, and \(^{18}\)F-FET PET images were semiautomatically fused, and hot-spot detection was performed for target planning. UR was determined using the uptake value from the biopsy sites in relation to the contralateral frontal white matter. UR values \(\geq 1.6\) were considered positive for glioma. High-grade glioma (HGG) was suspected with URs \(\geq 3.0\), while low-grade glioma (LGG) was suspected with URs between 1.6 and 3.0. Stereotactic serial biopsies along the trajectory at multiple sites were performed in millimeter steps, and the FET URs for each site were correlated exactly with a panel of 27 different histopathological markers. Comparisons between FET URs along the biopsy trajectories and the histological diagnoses were made with Pearson product-moment correlation coefficients. Analysis of variance was performed to test for significant differences in maximum UR between different tumor grades.

RESULTS: A total of 363 biopsy specimens were taken from 23 patients by stereotactic serial biopsies. Histological examination revealed eight patients (35%) with an LGG: one with a World Health Organization (WHO)-I lesion and seven with a WHO-II lesion. Thirteen (57%) patients revealed an HGG (two with a WHO-III and three with a WHO-IV tumor), and two patients (9%) showed a process that was neither HGG nor LGG (group X or no-grade group). The correlation matrix between histological findings and the UR revealed five strong correlations. Low cell density in tissue samples was found to have a significant negative correlation with the measured cortical uptake rate (\(r=-0.43, P=0.02\)), as well as moderate cell density (\(r=-0.48, P=0.02\)). Pathological patterns of proliferation (\(r=0.37, P=0.04\)), GFAP (\(r=0.37, P=0.04\)), and Olig2 (\(r=0.36, P=0.05\)) showed a significant positive correlation with cortical URs. Analysis of variance tests showed a significant difference between the LGG and the HGG groups (\(F=8.27, P<0.002\)), but no significant differences when differentiating between the X group and the HGG (\(P=0.2\))/LGG (\(P=0.8\)) groups, nor between the no-grade group and the WHO-I group.

CONCLUSION: \(^{18}\)F-FET PET is a valuable tool, as it allows the differentiation of HGGs from LGGs. Its use is not limited to preoperative evaluation; it may also refine biopsy targeting and improve tumor delimitation for radiotherapy. Histology is still necessary, and remains the gold standard for definitive diagnosis of brain lesions.

Late pseudoprogression in glioblastoma: diagnostic value of dynamic O-(2-[\(^{18}\)F]fluoroethyl)-L-tyrosine PET.


Pseudoprogression (PsP) is characterized by therapy-associated but not tumor growth-associated increases of contrast-enhancing glioblastoma lesions on MRI. Although typically occurring during the first 3 months after radiochemotherapy (RCX), PsP may occur later in the course of the disease and may then be particularly difficult to distinguish from true tumor progression. We explored PET using O-(2-[\(^{18}\)F]fluoroethyl)-L-tyrosine (\(^{18}\)F-FET-PET) to approach the diagnostic dilemma.

EXPERIMENTAL DESIGN: Twenty-six patients with glioblastoma that presented with increasing contrast-enhancing lesions later than 3 months after completion of RCX underwent \(^{18}\)F-FET-PET. Maximum and mean tumor/brain ratios (TBRmax, TBRmean) of \(^{18}\)F-FET uptake as well as time-to-peak (TTP) and patterns of the time-activity curves were determined. The final diagnosis of true progression vs. latePsP was based on follow-up MRI using RANO criteria.

RESULTS: LatePsP occurred in seven patients with a median time from RCX completion of 24 weeks while the remaining patients showed true tumor progression. TBRmax and TBRmean were significantly higher in patients with true progression than in patients with latePsP (TBRmax 2.4±0.1 vs. 1.5±0.2, p=0.003; TBRmean 2.1±0.1 vs. 1.5±0.2, p=0.012) while TTP was significantly shorter (mean TTP 25±2 vs. 40±2 min, p<0.001). ROC analysis yielded an optimal cut-off of 1.9 for TBRmax to differentiate between true progression and latePsP (sensitivity 84%, specificity 86%, accuracy 85%, p=0.015).

CONCLUSIONS: O-(2-[\(^{18}\)F]fluoroethyl)-L-tyrosine PET provides valuable information in assessing the elusive phenomenon of late pseudoprogression.


Early static \(^{18}\)F-FET-PET scans have a higher accuracy for glioma grading than the standard 20-40 min scans.


Author information

Current guidelines for glioma imaging by positron emission tomography (PET) using the amino acid analogue O-(2-[\(^{18}\)F]fluoroethyl)-L-tyrosine (\(^{18}\)F-FET) recommend image acquisition from 20-40 min post injection (p.i.). The maximal tumour-to-background evaluation (TBR\(_{\text{max}}\)) obtained in these summation images does not enable reliable differentiation between low and high grade glioma (LGG and HGG), which, however, can be achieved by dynamic \(^{18}\)F-FET-PET. We investigated the accuracy of tumour grading using TBR\(_{\text{max}}\) values at different earlier time points after tracer injection.

METHODS: Three hundred and fourteen patients with histologically proven primary diagnosis of glioma (131 LGG, 183 HGG) who had undergone 40-min dynamic \(^{18}\)F-FET-PET scans were retrospectively evaluated. TBR\(_{\text{max}}\) was assessed in the standard 20-40 min summation images,
as well as in summation images from 0-10 min, 5-15 min, 5-20 min, and 15-30 min p.i., and kinetic analysis was performed. TBR\textsubscript{max} values and kinetic analysis were correlated with histological classification. ROC analyses were performed for each time frame and sensitivity, specificity, and accuracy were assessed.

**RESULTS:** TBR\textsubscript{max} values in the earlier summation images were significantly better for tumour grading (P < 0.001) when compared to standard 20-40 min scans, with best results for the early 5-15 min scan. This was due to higher TBR\textsubscript{max} in the HGG (3.9 vs. 3.3; p < 0.001), while TBR\textsubscript{max} remained nearly stable in the LGG (2.2 vs. 2.1). Overall, accuracy increased from 70 % in the 20-40 min analysis to 77 % in the 5-15 min images, but did not reach the accuracy of dynamic analysis (80 %).

**CONCLUSIONS:** Early TBR\textsubscript{max} assessment (5-15 min p.i.) is more accurate for the differentiation between LGG and HGG than the standard static scan (20-40 min p.i.) mainly caused by the characteristic high \(^{18}\text{F}-\text{FET}\) uptake of HGG in the initial phase. Therefore, when dynamic \(^{18}\text{F}-\text{FET}\)-PET cannot be performed, early TBR\textsubscript{max} assessment can be considered as an alternative for tumour grading.


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The Sum of Tumour-to-Brain Ratios Improves the Accuracy of Diagnosing Gliomas Using \(^{18}\text{F}-\text{FET}\) PET.


Gliomas are common brain tumours, but obtaining tissue for definitive diagnosis can be difficult. There is, therefore, interest in the use of non-invasive methods to diagnose and grade the disease. Although positron emission tomography (PET) with \(^{18}\text{F}\)-fluorethyltyrosine (\(^{18}\text{F}-\text{FET}\)) can be used to differentiate between low-grade (LGG) and high-grade (HGG) gliomas, the optimal parameters to measure and their cut-points have yet to be established.

We therefore assessed the value of single and dual time-point acquisition of \(^{18}\text{F}-\text{FET}\) PET parameters to differentiate between primary LGGs (n = 22) and HGGs (n = 24). PET examination was considered positive for glioma if the metabolic activity was 1.6-times higher than that of background (contralateral) brain, and maximum tissue-brain ratios (TBR\text{max}) were calculated 10 and 60 min after isotope administration with their sums and differences calculated from individual time-point values. Using a threshold-based method, the overall sensitivity of PET was 97%. Several analysed parameters were significantly different between LGGs and HGGs. However, in a receiver operating characteristics analysis, TBR sum had the best diagnostic accuracy of 87% and sensitivity, specificity, and positive and negative predictive values of 100%, 72.7%, 80%, and 100%, respectively. \(^{18}\text{F}-\text{FET}\) PET is valuable for the non-invasive determination of glioma grade, especially when dual time-point metrics are used. TBR sum shows the greatest accuracy, sensitivity, and negative predictive value for tumour grade differentiation and is a simple method to implement. However, the cut-off may differ between institutions and calibration strategies would be useful.

Reproducibility of O-(2-^{18}F-fluoroethyl)-L-tyrosine uptake kinetics in brain tumors and influence of corticoid therapy: an experimental study in rat gliomas.


PURPOSE: Positron emission tomography (PET) using O-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) is a well-established method for the diagnostics of brain tumors. This study investigates reproducibility of ^{18}F-FET uptake kinetics in rat gliomas and the influence of the frequently used dexamethasone (Dex) therapy.

METHODS: F98 glioma or 9L gliosarcoma cells were implanted into the striatum of 31 Fischer rats. After 10-11 days of tumor growth, the animals underwent dynamic PET after injection of ^{18}F-FET (baseline). Thereafter, animals were divided into a control group and a group receiving Dex injections, and all animals were reinvestigated 2 days later. Tumor-to-brain ratios (TBR) of ^{18}F-FET uptake (18-61 min p.i.) and the slope of the time-activity-curves (TAC) (18-61 min p.i.) were evaluated using a Volume-of-Interest (VOI) analysis. Data were analyzed by two-way repeated measures ANOVA and reproducibility by the intraclass correlation coefficient (ICC).

RESULTS: The slope of the tumor TACs showed high reproducibility with an ICC of 0.93. A systematic increase of the TBR in the repeated scans was noted (3.7 ± 2.8 %; p < 0.01), and appeared to be related to tumor growth as indicated by a significant correlation of TBR and tumor volume (r = 0.77; p < 0.0001). After correction for tumor growth TBR showed high longitudinal stability with an ICC of 0.84. Dex treatment induced a significant decrease of the TBR (-8.2 ± 6.1 %; p < 0.03), but did not influence the slope of the tumor TAC.

CONCLUSION: TBR of ^{18}F-FET uptake and tracer kinetics in brain tumors showed high longitudinal stability. Dex therapy may induce a minor decrease of the TBR; this needs further investigation.

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, Glaudemans AW, de Vries EF, Schröder CP, de Vries EG, Hospers GA.

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 16α-[(18)F]fluoro-17β-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 ≥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 (SUVmax). CT-scan was repeated every 3 months to evaluate treatment response. Clinical benefit was defined as time to radiologic or clinical progression ≥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 SUVmax >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.


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 16α-[18F]fluoro-17β-oestradiol (FES) or 2-[18F]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.


PET Imaging of Breast Cancer: Role in Patient Management.

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Breast cancer is the most common malignancy in females. Imaging plays a critical role in diagnosis, staging and surveillance, and management of disease. Fluorodeoxyglucose (FDG) PET the imaging is indicated in specific clinical setting. Sensitivity of detection depends on tumor histology and size. Whole body FDG PET can change staging and management. In recurrent disease, distant metastasis can be detected. FDG PET imaging has prognostic and predictive value. PET/MR is evolving rapidly and may play a role management, assessment of metastatic lesions, and treatment monitoring. This review discusses current PET modalities, focusing on of FDG PET imaging and novel tracers.

ALTERATIONS IN ANDROGEN DEPRIVATION ENHANCED PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) EXPRESSION IN PROSTATE CANCER CELLS AS A TARGET FOR DIAGNOSTICS AND THERAPY.


BACKGROUND: Prostate-specific membrane antigen (PSMA) is a promising target for diagnostics and therapy of prostate carcinoma (PCa). Based on the hypothesis that PSMA expression can be modulated by variations in androgen deprivation therapy (ADT), we investigated the binding of a PSMA-directed radiopharmaceutical in vitro in order to get an insight of the interactions between altered premedication and PSMA expression before repetitive PSMA-directed PET/CT for therapy response and targeted therapy implementation.

METHODS: The human castration-resistant PCa cell line VCaP (CRPC) was treated with either 1 nmol/L testosterone (T) over 20 passages yielding the androgen-sensitive cell line (revCRPC) or with 5 μmol/L abiraterone acetate (AA) generating the abiraterone-tolerant subtype CRPCAA. In these cell lines, T and AA were varied by either supply or withdrawal of T and AA. PSMA expression of the three cell culture models was detected by Western blot and immunohistochemical staining. For quantitative measurement of tracer uptake, 0.3 nmol/L (68)Ga-labelled PSMA-HBED-CC peptide (100-300 kBq/ml) was added to different treated parallel cultures (n=9 each). Time-dependent uptake per 10(6) cells of each culture was calculated and evaluated. PSMA mRNA expression was investigated by qPCR.

RESULTS: PSMA expression increased dependently on intensified ADT in all three basic cell lines. (68)Ga-PSMA-HBED-CC uptake almost doubled during 3 h in all cell lines (p<0.01). Compared to the basic cells, pre-incubation with abiraterone for 48 h resulted in a significant increased uptake in CRPC (p<0.001). In revCRPC, 48-h AA pre-incubation resulted in an eightfold higher uptake after 3 h (p<0.001). Additional withdrawal of external testosterone increased the uptake up to tenfold (p<0.01). The increase of PSMA expression upon ADT and AA treatments was confirmed by qPCR and Western blot data. Furthermore, in CRPCAA, 48-h AA withdrawal increased the uptake up to fivefold (p<0.01).

CONCLUSIONS: The investigated three PCa cell culture subtypes represent a serial preclinical model of androgen deprivation therapy as a proxy for clinical situations with differing basal PSMA expression. The uptake of PSMA-binding tracers could be stimulated by therapeutic effective short-term variation in premedication in all stages of ADT response. These complex interactions have to be considered in the interpretation of diagnostic imaging using PSMA ligands as well as in the optimal timing of PSMA-based therapies.


Pyka T, Weirich G, Einspieler I, Maurer T, Theisen J, Hatzichristodoulou G, Schwamborn K, Schwaiger M, Eiber M.

RATIONALE: In prostate cancer (PC) patients, differentiation between lung metastases and lesions of different origin, e.g. primary lung cancer, is a common clinical question. Herein we investigate the use of 68Ga-PSMA-HBED-CC for this purpose.
METHODS: 1889 PC patients receiving $^{68}$Ga-PSMA PET/CT or PET/MR scans were evaluated retrospectively for suspicious lung lesions. For up to 5 lesions per patient, location, CT diameter, CT morphology and SUV$_{\text{max}}$ values were determined. Standard for classification was either histopathologic evaluation or, in case of PC metastases, responsivity to anti-hormone therapy. Comparison of the different classes was executed by Student's $t$ test. PSA and PSMA immunohistochemistry were performed if histologic samples were available; $^{68}$Ga-PSMA autoradiography was performed on an exemplary case of PET positive lung cancer.

RESULTS: 89 lesions in 45 patients were identified, of which 76 were classified as PC (39 proven, 37 highly probable), 7 as primary lung cancer and 2 as activated tuberculosis; 4 lesions remained unclear. The mean SUV$_{\text{max}}$ was 4.4±3.9 for PC metastases and 5.6±1.6 for primary lung cancer ($P = 0.408$). Additionally, substantial differences in SUV$_{\text{max}}$ values intra-individually were detected. The two tuberculous lesions showed an SUV$_{\text{max}}$ of 7.8 and 2.5, respectively. Using immunohistochemistry, we could demonstrate PSMA expression in the neo-vasculature of several PSMA PET positive lung cancers, as well as in tuberculous lesions from our histologic database.

CONCLUSION: Quantitative (SUV) analysis of $^{68}$Ga-PSMA PET was not able to discriminate reliably between pulmonary metastases and primary lung cancer in PC patients. The reason for the unexpectedly high tracer uptake in non-PC lesions is not completely clear. PSMA expression in neo-vasculature provides a possible explanation for this finding; however, other contributing factors, such as tracer binding to proteins other than PSMA, cannot be excluded at present.


MRI versus $^{68}$Ga-PSMA PET/CT for gross tumour volume delineation in radiation treatment planning of primary prostate cancer.


PURPOSE: Multiparametric magnetic resonance imaging (mpMRI) is widely used in radiation treatment planning of primary prostate cancer (PCA). Focal dose escalation to the dominant intraprostatic lesions (DIPL) may lead to improved PCA control. Prostate-specific membrane antigen (PSMA) is overexpressed in most PCAs. $^{68}$Ga-labelled PSMA inhibitors have demonstrated promising results in detection of PCA with PET/CT. The aim of this study was to compare $^{68}$Ga-PSMA PET/CT with MRI for gross tumour volume (GTV) definition in primary PCA.

METHODS: This retrospective study included 22 patients with primary PCA analysed after $^{68}$Ga-PSMA PET/CT and mpMRI. GTVs were delineated on MR images by two radiologists (GTV-MRIrad) and two radiation oncologists separately. Both volumes were merged leading to GTV-MRIint. GTVs based on PET/CT were delineated by two nuclear medicine physicians in consensus (GTV-PET). Laterality (left, right, and left and right prostate lobes) on mpMRI, PET/CT and pathological analysis after biopsy were assessed.

RESULTS: Mean GTV-MRIrad, GTV-MRIint and GTV-PET were 5.92, 3.83 and 11.41 cm$^3$, respectively. GTV-PET was significant larger then GTV-MRIint ($p = 0.003$). The MRI GTVs GTV-MRIrad and GTV-MRIint showed, respectively, 40 % and 57 % overlap with GTV-PET. GTV-MRIrad and GTV-MRIint included the SUV$_{\text{max}}$ of GTV-PET in 12 and 11 patients (54.6 % and 50 %), respectively. In nine patients (47 %), laterality on mpMRI, PET/CT and histopathology after biopsy was similar.
CONCLUSION: Ga-PSMA PET/CT and mpMRI provided concordant results for delineation of the DIPL in 47% of patients (40% - 54% of lesions). GTV-PET was significantly larger than GTV-MRlint. 68Ga-PSMA PET/CT may have a role in radiation treatment planning for focal radiation to the DIPL. Exact correlation of PET and MRI images with histopathology is needed.


Follicular Thyroid Adenoma Showing Avid Uptake on 68Ga PSMA-HBED-CC PET/CT.

Kanthan GL, Drummond J, Schembri GP, Izard MA, Hsiao E.

Ga-prostate-specific membrane antigen (PSMA) PET/CT imaging is a relatively new imaging technique used to evaluate the extent of disease in prostate carcinoma. Various other neoplasms may also express PSMA and show uptake on PSMA PET/CT scan. We report a case of a 62-year-old man who had a PSMA PET/CT scan for restaging of prostate carcinoma. A PSMA-avid thyroid lesion was identified, and subsequent tissue sampling confirmed the diagnosis of follicular thyroid adenoma. It is important to be aware of this possibility to avoid scan misinterpretation. Tissue biopsy of PSMA-avid thyroid lesions should be considered to exclude a primary thyroid neoplasm.


Pilot Comparison of 68Ga-RM2 PET and 68Ga-PSMA PET in Patients with Biochemically Recurrent Prostate Cancer.


OBJECTIVES: Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] ([68Ga-PSMA]) is a positron emission tomography (PET) tracer that can detect prostate cancer relapses and metastases by binding to the extracellular domain of PSMA. 68Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 ([68Ga-RM2]) is a synthetic bombesin receptor antagonist that targets gastrin-releasing peptide receptors (GRPr). We present pilot data on the biodistribution of these PET tracers in a small cohort of patients with biochemically recurrent prostate cancer (BCRPC).

METHODS: Seven men (mean age ± SD: 74.3±5.9 year-old) with BCRPC had both 68Ga-PSMA PET/CT and 68Ga-RM2 PET/MRI scans. The maximum standardized uptake value (SUVmax) and mean SUV (SUVmean) measurements were recorded in normal tissues and areas of uptake outside the expected physiologic biodistribution.

RESULTS: All patients had rising prostate-specific antigen (PSA) (mean±SD: 13.5±11.5) and non-contributory conventional imaging. 68Ga-PSMA had the highest physiologic uptake in the salivary glands and small bowel, with hepatobiliary and renal clearance noted, while 68Ga-RM2 had the highest physiologic uptake in the pancreas, with renal clearance noted. Uptake values uptake outside the expected physiologic biodistribution were not statistically different between 68Ga-PSMA and 68Ga-RM2; however, 68Ga-PSMA localized in a lymph node and seminal vesicle.
in a patient with no abnormal $^{68}$Ga-RM2 uptake. Abdominal periaortic lymph nodes were more easily visualized by $^{68}$Ga-RM2 in two patients due to lack of interference by radioactivity accumulation in the small intestine.

**CONCLUSION:** $^{68}$Ga-PSMA and $^{68}$Ga-RM2 have distinct biodistribution in this small cohort of patients with BCRPC. The findings here indicate that additional work is needed to understand the expression of PSMA and GRPr in different types of prostate cancer.


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**PSMA Ligands for Radionuclide Imaging and Therapy of Prostate Cancer: Clinical Status.**


Prostate cancer (PCa) is the most common malignancy in men worldwide, leading to substantial morbidity and mortality. At present, imaging of PCa has become increasingly important for staging, restaging, and treatment selection. Until recently, choline-based positron emission tomography/computed tomography (PET/CT) represented the state-of-the-art radionuclide imaging technique for these purposes. However, its application is limited to patients with high PSA levels and Gleason scores. Prostate-specific membrane antigen (PSMA) is a promising new target for specific imaging of PCa, because it is upregulated in the majority of PCa. Moreover, PSMA can serve as a target for therapeutic applications. Currently, several small-molecule PSMA ligands with excellent in vivo tumor targeting characteristics are being investigated for their potential in theranostic applications in PCa. Here, a review of the recent developments in PSMA-based diagnostic imaging and therapy in patients with PCa with radiolabeled PSMA ligands is provided.


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**Diagnostic Efficacy of $^{68}$Gallium-PSMA-PET compared to Conventional Imaging in Lymph Node Staging of of 130 consecutive Patients with Intermediate to High-Risk Prostate Cancer.**


**PURPOSE:** Current standard imaging techniques are insufficient to reliably detect lymph node (LN) metastases in prostate cancer (PCa). Recently, ligands of the prostate-specific membrane antigen (PSMA) have been introduced in PET imaging of PCa. Thus, the aim of this retrospective analysis was to investigate the diagnostic efficacy of $^{68}$Ga-PSMA-PET imaging for LN staging of patients with PCa scheduled for radical prostatectomy (RPX) and to compare it with morphological imaging (CT, MR) with histopathological evaluation as standard of reference.

**MATERIALS AND METHODS:** From 12/2012 to 11/2014, 130 patients with intermediate to high-risk PCa were staged with $^{68}$Ga-PSMA-PET/MR or PET/CT before RPX and template pelvic LN
dissection. Histopathological findings of resected tissue were statistically correlated with the results of $^{68}$Ga-PSMA-PET and morphological imaging in a patient- and template-based manner.

RESULTS: LN metastases were found in 41/130 (31.5%) patients. On patient-based analysis sensitivity, specificity and accuracy for $^{68}$Ga-PSMA-PET were calculated as 65.9%, 98.9% and 88.5% and 43.9%, 85.4% and 72.3% for morphological imaging, respectively. 117/734 (15.9%) of dissected LN templates showed metastases. On template-based analysis sensitivity, specificity and accuracy for $^{68}$Ga-PSMA-PET were 68.3%, 99.1% and 95.2% while for morphological imaging 27.3%, 97.1% and 87.6% were calculated. On ROC-analysis $^{68}$Ga-PSMA-PET performed significantly superior to morphological imaging alone on a patient- (p=0.002) and template-based analysis (p<0.001).

CONCLUSIONS: In patients with intermediate to high-risk PCa preoperative LN staging with $^{68}$Ga-PSMA-PET proved to be superior to standard routine imaging and thus has the potential to replace current standard imaging for this indication if confirmed by prospective studies.


$^{68}$Ga-PSMA has high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment.


OBJECTIVES: To examine the detection rates of $^{68}$Ga-PSMA-PET/CT in patients with biochemical recurrence (BCR) after radical prostatectomy (RP), and also the impact on their management.

MATERIALS AND METHODS: 300 consecutive PC patients who underwent $^{68}$Ga-PSMA-PET/CT between February and July 2015 were prospectively included in the ProCan-I Database. For this analysis, men were included with BCR (PSA $\geq$0.05ng/ml) after RP, PSA <1.0ng/ml, being considered for salvage radiation treatment (RT) according to FROGG guidelines. Two readers assessed each $^{68}$Ga-PSMA-PET/CT, and all positive lesions were assigned to an anatomical location. For each patient, the clinical and pathological features were recorded, their association with pathological $^{68}$Ga-PSMA uptake was investigated, and detection rates were determined according to PSA level.

RESULTS: 70 patients were included, 53 positive $^{68}$Ga-PSMA lesions were detected in 38 (54%) positive patients. For PSA (ng/ml) 0.05-0.09, 8% were definitely positive; for 0.1-0.19, 23%; for 0.2-0.29, 58%; for 0.3-0.49, 36%; and for 0.5-0.99, 57%, respectively. Eighteen of 70 patients (27%) had pathological $^{68}$Ga-PSMA uptake in the prostatic fossa, 11 (14.3%) in the pelvic nodes, and 5 (4.3%) in both the fossa and pelvic lymph nodes. Finally, there was uptake outside the pelvis with or without a lesion in the fossa or pelvic lymph nodes in 4 cases (8.6%). There was a major management impact in 20 (28.6%) men, all were attributable to the $^{68}$Ga-PSMA findings.

CONCLUSION: $^{68}$Ga-PSMA appears useful for re-staging of PC in patients with rising PSA being considered for salvage RT even at PSA levels below 0.5 ng/ml. These results underline the need for further prospective trials to evaluate the changes in RT volume or management attributable to $^{68}$Ga-PSMA findings.

Cardiac amyloidosis (CA) is recognized as a common cause of restrictive cardiomyopathy and heart failure due to the deposition of insoluble proteins in the myocardial interstitium. We emphasize the role of $^{18}$F-sodium fluoride (NaF) PET/CT as a potential noninvasive tool to identify and differentiate the transthyretin-related cardiac amyloidosis from the light-chain cardiac amyloidosis. We report cases of a 73-year-old man and a 75-year-old woman followed in our center for congestive heart failure with marked alteration of the left ventricular ejection fraction due to familial transthyretin Val122Ile cardiac amyloidosis and light-chain cardiac amyloidosis, respectively, confirmed on endomyocardial biopsy.


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We prospectively evaluated the use of combined ($^{18}$)F-NaF/(18)F-FDG PET/CT in patients with breast and prostate cancer and compared the results with those for (99m)Tc-MDP bone scintigraphy and whole-body MRI.

**METHODS:** Thirty patients (15 women with breast cancer and 15 men with prostate cancer) referred for standard-of-care bone scintigraphy were prospectively enrolled in this study. ($^{18}$)F-NaF/(18)F-FDG PET/CT and whole-body MRI were performed after bone scintigraphy. The whole-body MRI protocol consisted of both unenhanced and contrast-enhanced sequences. Lesions detected with each test were tabulated, and the results were compared.

**RESULTS:** For extraskeletal lesions, ($^{18}$)F-NaF/(18)F-FDG PET/CT and whole-body MRI had no statistically significant differences in sensitivity (92.9% vs. 92.9%, P = 1.00), positive predictive value (81.3% vs. 86.7%, P = 0.68), or accuracy (76.5% vs. 82.4%, P = 0.56). However, (18)F-NaF/(18)F-FDG PET/CT showed significantly higher sensitivity and accuracy than whole-body MRI (96.2% vs. 81.4%, P < 0.001, 89.8% vs. 74.7%, P = 0.01) and bone scintigraphy (96.2% vs. 64.6%, P < 0.001, 89.8% vs. 65.9%, P < 0.001) for the detection of skeletal lesions. Overall, (18)F-NaF/(18)F-FDG PET/CT showed higher sensitivity and accuracy than whole-body MRI (95.7% vs. 83.3%, P < 0.002, 87.6% vs. 76.0%, P < 0.02) but not statistically significantly so when compared with a combination of whole-body MRI and bone scintigraphy (95.7% vs. 91.6%, P = 0.17, 87.6% vs. 83.0%, P = 0.53). (18)F-NaF/(18)F-FDG PET/CT showed no significant difference from a combination of (18)F-NaF/(18)F-FDG PET/CT and whole-body MRI. No statistically significant differences in positive predictive value were noted among the 3 examinations.

**CONCLUSION:** ($^{18}$)F-NaF/(18)F-FDG PET/CT is superior to whole-body MRI and (99m)Tc-MDP scintigraphy for evaluation of skeletal disease extent. Further, ($^{18}$)F-NaF/(18)F-FDG PET/CT and whole-body MRI detected extraskeletal disease that may change the management of these patients. ($^{18}$)F-NaF/(18)F-FDG PET/CT provides diagnostic ability similar to that of a combination of whole-body MRI and bone scintigraphy in patients with breast and prostate cancer. Larger
cohorts are needed to confirm these preliminary findings, ideally using the newly introduced simultaneous PET/MRI scanners.


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Motion correction of \( ^{18} \text{F} \)-sodium fluoride PET for imaging coronary atherosclerotic plaques.


Ruptured coronary atherosclerotic plaques commonly cause acute myocardial infarction. It has been recently shown that active microcalcification in the coronary arteries, one of the features that characterizes vulnerable plaques at risk of rupture, can be imaged using \( ^{18} \text{F} \)-sodium fluoride (\( ^{18} \text{F-NaF} \)) PET. We aimed to determine whether a motion correction technique applied to gated \( ^{18} \text{F-NaF} \) PET images could enhance image quality and improve uptake estimates.

METHODS: Seventeen patients with myocardial infarction (n = 7) and stable angina (n = 10) underwent \( ^{18} \text{F-NaF} \) PET and prospective coronary CT angiography (CCTA). PET data were reconstructed in 4 different ways: (i) one gated bin (end-diastolic phase with 25% of the counts), (ii) 4 gated bins (consecutive 25% segments), (iii) 10 gated bins (consecutive 10% segments), and (iv) ungated. Subsequently, gated PET images were registered using a local and non-linear motion correction method guided by the extracted coronary arteries from CT angiography using either 4 or 10 bins. Global noise levels and target-to-background ratios (TBR) defined on manually delineated coronary plaque lesions were compared to assess image quality and uptake estimates.

RESULTS: Compared to the reference standard of using only one bin of PET data, motion correction using the 10 bins of PET data reduced image noise (-46%, p<0.0001). TBR in positive lesions was 11% higher using 10-bin motion corrected data, compared to one-bin data (1.98 [IQR 1.70-2.37] vs 1.78 [IQR 1.58-2.16], P = 0.0027), and 33% higher compared to ungated data (1.98 [IQR 1.70-2.37] vs 1.48 [IQR 1.39-1.88], p<0.0001).

CONCLUSION: Motion correction of gated \( ^{18} \text{F-NaF} \) PET/CCTA is feasible, reduces image noise and increases TBR. This improvement may allow more reliable identification of vulnerable coronary artery plaques using \( ^{18} \text{F-NaF} \) PET.

Bone marrow abnormalities and early bone lesions in multiple myeloma and its precursor disease: A prospective study using functional and morphologic imaging.


The incidence and importance of bone marrow involvement and/or early bone lesions in multiple myeloma (MM) precursor diseases is largely unknown. We prospectively compared the sensitivity of several imaging modalities in monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM) and MM. Thirty patients (10 each with MGUS, SMM and MM) were evaluated with skeletal survey, $^{[18]}$F-FDG-PET/CT, $^{[18]}$F-NaF-PET/CT, and morphologic dynamic contrast enhanced (DCE)-MRI. Additional 16 SMM patients had skeletal surveys and FDG-PET/CT. Among MGUS patients, DCE-MRI found only one focal marrow abnormality; other evaluations were negative. Among 26 SMM patients, (19%) were re-classified as MM based on lytic bone lesions on CT, and 6 had unifocal or diffuse marrow abnormality. Among MM, marrow abnormalities were observed on FDG-PET/CT in 8/10 patients, and on DCE-MRI in 9 evaluable patients. Abnormal NaF uptake was observed only in MM patients with lytic lesions on CT, providing no additional clinical information.

Striatal Dopamine D2/D3 Receptor Availability Is Associated with Executive Function in Healthy Controls but Not Methamphetamine Users.

Ballard ME, Dean AC, Mandelkern MA, London ED.

Dopamine D2/D3 receptor availability in the striatum has been linked with executive function in healthy individuals, and is below control levels among drug addicts, possibly contributing to diminished executive function in the latter group. This study tested for an association of striatal D2/D3 receptor availability with a measure of executive function among research participants who met DSM-IV criteria for methamphetamine dependence. Methamphetamine users and non-user controls (n = 18 per group) completed the Wisconsin Card Sorting Test and positron emission tomography with \([^{18}\text{F}]\)fallypride. The methamphetamine users displayed significantly lower striatal D2/D3 receptor availability on average than controls after controlling for age and education (p = 0.008), but they did not register greater proportions of either perseverative or non-perseverative errors when controlling for education (both ps ≥ 0.622). The proportion of non-perseverative, but not perseverative, errors was negatively correlated with striatal D2/D3 receptor availability among controls (r = -0.588, p = 0.010), but not methamphetamine users (r = 0.281, p = 0.258), and the group-wise interaction was significant (p = 0.030). These results suggest that cognitive flexibility, as measured by perseverative errors on the Wisconsin Card Sorting Test, is not determined by signaling through striatal D2/D3 receptors in healthy controls, and that in stimulant abusers, who have lower D2/D3 receptor availability, compensation can effectively maintain other executive functions, which are associated with D2/D3 receptor signaling in controls.


Relationship of Alexithymia Ratings to Dopamine D2-type Receptors in Anterior Cingulate and Insula of Healthy Control Subjects but not Methamphetamine-Dependent Individuals.

Okita K, Ghahremani DG, Payer DE, Robertson CL, Mandelkern MA, London ED.

Individuals with substance-use disorders exhibit emotional problems, including deficits in emotion recognition and processing, and this class of disorders also has been linked to deficits in dopaminergic markers in the brain. Because associations between these phenomena have not been explored, we compared a group of recently abstinent methamphetamine-dependent individuals (n = 23) with a healthy-control group (n = 17) on dopamine D2-type receptor availability, measured using positron emission tomography with \([^{18}\text{F}]\)fallypride. The anterior cingulate and anterior insular cortices were selected as the brain regions of interest because they receive dopaminergic innervation and are thought to be involved in emotion awareness and processing.

The Toronto Alexithymia Scale, which includes items that assess difficulty in identifying and describing feelings as well as externally-oriented thinking, was administered, and the scores were tested for association with D2-type receptor availability. Relative to controls, methamphetamine-dependent individuals showed higher alexithymia scores, reporting difficulty in identifying feelings. The groups did not differ in D2-type receptor availability in the anterior cingulate or anterior insular cortices, but a significant interaction between group and D2-type receptor availability in both regions, on self-report score, reflected significant positive correlations in the control group (higher receptor availability linked to higher alexithymia) but non-significant, negative correlations (lower receptor availability linked to higher alexithymia) in methamphetamine-dependent subjects. The results suggest that neurotransmission through D2-type receptors in the anterior
cingulate and anterior insular cortices influences capacity of emotion processing in healthy people, but that this association is absent in individuals with methamphetamine dependence.


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Reduced D2/D3 Receptor Binding of Extrastriatal and Striatal Regions in Temporal Lobe Epilepsy.

Bernedo Paredes VE, Buchholz HG, Gartenschläger M, Breimhorst M, Schreckenberger M, Werhahn KJ.

OBJECTIVE: Dopamine is an endogenous neuromodulator in cortical circuits and the basal ganglia. In animal models of temporal lobe epilepsy (TLE), seizure threshold is modulated to some extent by dopamine, with D1-receptors having a pro- and D2-receptors an anticonvulsant effect. We aimed to extend our previously reported results on decreased D2/D3 receptor binding in the lateral epileptogenic temporal lobe and to correlate them with demographic and seizure variables to gain a more comprehensive understanding of the underlying involvement of the dopaminergic system in the epileptogenesis of TLE.

METHODS: To quantify D2/D3 receptor binding, we studied 21 patients with TLE and hippocampal sclerosis (13 left- and eight right-sided) and 18 controls using PET with the high-affinity dopamine D2/D3-receptor ligand 18F-Fallypride to image striatal and extrastriatal binding. TLE was defined by interictal and ictal video-EEG, MRI and 18F-Fluorodeoxyglucose PET. Voxel-based statistical and regions-of-interest analyses were performed.

RESULTS: 18F-Fallypride binding potential was significantly reduced in the affected temporal lobe and bilateral putamen. A positive correlation between age at onset of epilepsy and [18F]FP BPnD (binding potential non-displaceable) in temporal regions on the epileptogenic side was found, as well as a negative correlation between epilepsy duration and [18F]FP BPnD in the temporal pole on the epileptogenic side and a positive correlation between the estimated number of lifetime GTCS and [18F]FP BPnD in the hippocampus on the epileptogenic side.

SIGNIFICANCE: The areas of reduced D2/D3 receptor availability correspond to "the irritative zone" surrounding the epileptogenic area. Moreover, reduced D2/D3 receptor availability was detectable in the basal ganglia, which are suspected to be involved in a control circuit for epileptic seizures. The correlational analysis additionally suggests that increased epilepsy duration leads to increasing impairment of the dopaminergic system.


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Effect of Exercise Training on Striatal Dopamine D2/D3 Receptors in Methamphetamine Users during Behavioral Treatment.


Abstract

Methamphetamine use disorder is associated with striatal dopaminergic deficits that have been linked to poor treatment outcomes, identifying these deficits as an important therapeutic target. Exercise attenuates methamphetamine-induced neurochemical damage in the rat brain, and a preliminary observation suggests that exercise increases striatal D2/D3 receptor availability (measured as nondisplaceable binding potential (BPND)) in patients with Parkinson's disease. The goal of this study was to evaluate whether adding an exercise training program to an inpatient behavioral intervention for methamphetamine use disorder reverses deficits in striatal D2/D3 receptors. Participants were adult men and women who met DSM-IV criteria for methamphetamine dependence and were enrolled in a residential facility, where they maintained abstinence from illicit drugs of abuse and received behavioral therapy for their addiction. They were randomized to a group that received 1 h supervised exercise training (n=10) or one that received equal-time health education training (n=9), 3 days/week for 8 weeks. They came to an academic research center for positron emission tomography (PET) using [18F]fallypride to determine the effects of the 8-week interventions on striatal D2/D3 receptor BPND. At baseline, striatal D2/D3 BPND did not differ between groups. However, after 8 weeks, participants in the exercise group displayed a significant increase in striatal D2/D3 BPND, whereas those in the education group did not. There were no changes in D2/D3 BPND in extrastriatal regions in either group. These findings suggest that structured exercise training can ameliorate striatal D2/D3 receptor deficits in methamphetamine users, and warrants further evaluation as an adjunctive treatment for stimulant dependence.


Differential dopamine function in fibromyalgia.

Albrecht DS, MacKie PJ, Kareken DA, Hutchins GD, Chumin EJ, Christian BT, Yoder KK.

Approximately 30 % of Americans suffer from chronic pain disorders, such as fibromyalgia (FM), which can cause debilitating pain. Many pain-killing drugs prescribed for chronic pain disorders are highly addictive, have limited clinical efficacy, and do not treat the cognitive symptoms reported by many patients. The neurobiological substrates of chronic pain are largely unknown, but evidence points to altered dopaminergic transmission in aberrant pain perception. We sought to characterize the dopamine (DA) system in individuals with FM. Positron emission tomography (PET) with [18F]fallypride (FAL) was used to assess changes in DA during a working memory challenge relative to a baseline task, and to test for associations between baseline D2/D3 availability and experimental pain measures. Twelve female subjects with FM and 11 female controls completed study procedures. Subjects received one FAL PET scan while performing a "2-back" task, and one while performing a "0-back" (attentional control, "baseline") task. FM subjects had lower baseline FAL binding potential (BP) in several cortical regions relative to controls, including anterior cingulate cortex. In FM subjects, self-reported spontaneous pain negatively correlated with FAL BP in the left orbitofrontal cortex and parahippocampal gyrus. Baseline BP was significantly negatively correlated with experimental pain sensitivity and tolerance in both FM and CON subjects, although spatial patterns of these associations differed between groups. The data suggest that abnormal DA function may be associated with differential...
processing of pain perception in FM. Further studies are needed to explore the functional significance of DA in nociception and cognitive processing in chronic pain.


**Dopamine D3 receptor binding of (18) F-fallypride: Evaluation using in vitro and in vivo PET imaging studies.**

*Mukherjee J, Constantinescu CC, Hoang AT, Jerjian T, Majji D, Pan ML.*

Identification of dopamine D3 receptors (D3R) in vivo is important to understand several brain functions related to addiction. The goal of this work was to identify D3R binding of the dopamine D2 receptor (D2R)/D3R imaging agent, (18) F-fallypride. Brain slices from male Sprague-Dawley rats (n = 6) and New Zealand White rabbits (n = 6) were incubated with (18) F-fallypride and D3R selective agonist (R)-7-OH-DPAT (98-fold D3R selective). Rat slices were also treated with BP 897 (68-fold D3R selective partial agonist) and NGB 2904 (56-fold D3R selective antagonist). In vivo rat studies (n = 6) were done on Inveon PET using 18-37 MBq (18) F-fallypride and drug-induced displacement by (R)-7-OH-DPAT, BP 897 and NGB 2904. PET/CT imaging of wild type (WT, n = 2) and D2R knock-out (KO, n = 2) mice were carried out with (18) F-fallypride. (R)-7-OH-DPAT displaced binding of (18) F-fallypride, both in vitro and in vivo. In vitro, at 10 nM (R)-7-OH-DPAT, (18) F-fallypride binding in the rat ventral striatum (VST) and dorsal striatum (DST) and rabbit nucleus accumbens were reduced by ~10-15%. At 10 μM (R)-7-OH-DPAT all regions in rat and rabbit were reduced by ≥85%. In vivo reductions for DST and VST before and after (R)-7-OH-DPAT were: low-dose (0.015 mg kg(-1) ) DST -22%, VST -29%; high-dose (1.88 mg kg(-1) ) DST -58%, VST -77%, suggesting D3 R/D2 R displacement. BP 897 and NGB 2904 competed with (18) F-fallypride in vitro, but unlike BP 897, NGB 2904 did not displace (18) F-fallypride in vivo. The D2R KO mice lacked (18) F-fallypride binding in the DST. In summary, our findings suggest that up to 20% of (18) F-fallypride may be bound to D3R sites in vivo.

A Phase II Study of 3'-Deoxy-3'-[18]F-Fluorothymidine PET in the Assessment of Early Response of Breast Cancer to Neoadjuvant Chemotherapy: Results from ACRIN 6688.


Our objective was to determine whether early change in standardized uptake values (SUVs) of 3'deoxy-3'-(18)F-fluorothymidine ((18)F-FLT) using PET with CT could predict pathologic complete response (pCR) of primary breast cancer to neoadjuvant chemotherapy (NAC). The key secondary objective was to correlate SUV with the proliferation marker Ki-67 at baseline and after NAC.

METHODS: This prospective, multicenter phase II study did not specify the therapeutic regimen, thus, NAC varied among centers. All evaluable patients underwent (18)F-FLT PET/CT at baseline (FLT1) and after 1 cycle of NAC (FLT2); 43 patients were imaged at FLT1, FLT2, and after NAC completion (FLT3). The percentage change in maximum SUV (%ΔSUVmax) between FLT1 and FLT2 and FLT3 was calculated for the primary tumors. The predictive value of ΔSUVmax for pCR was determined using receiver-operating-characteristic curve analysis. The correlation between SUVmax and Ki-67 was also assessed.

RESULTS: Fifty-one of 90 recruited patients (median age, 54 y; stage IIA-IIIC) met the eligibility criteria for the primary objective analysis, with an additional 22 patients totaling 73 patients for secondary analyses. A pCR in the primary breast cancer was achieved in 9 of 51 patients. NAC resulted in a significant reduction in %SUVmax (mean Δ, 39%; 95% confidence interval, 31-46). There was a marginal difference in %ΔSUVmax_FLT1-FLT2 between pCR and no-pCR patient groups (Wilcoxon 1-sided P = 0.050). The area under the curve for ΔSUVmax in the prediction of pCR was 0.68 (90% confidence interval, 0.50-0.83; Delong 1-sided P = 0.05), with slightly better predictive value for percentage mean SUV (P = 0.02) and similar prediction for peak SUV (P = 0.04). There was a weak correlation with pretherapy SUVmax and Ki-67 (r = 0.29, P = 0.04), but the correlation between SUVmax and Ki-67 after completion of NAC was stronger (r = 0.68, P < 0.0001).

CONCLUSION: (18)F-FLT PET imaging of breast cancer after 1 cycle of NAC weakly predicted pCR in the setting of variable NAC regimens. Posttherapy (18)F-FLT uptake correlated with Ki-67 on surgical specimens. These results suggest some efficacy of (18)F-FLT as an indicator of early therapeutic response of breast cancer to NAC and support future multicenter studies to test (18)F-FLT PET in a more uniformly treated patient population.


18F-FLT PET/CT in the Evaluation of Pheochromocytomas and Paragangliomas: A Pilot Study.


(18)F-FDG PET/CT has been proven to be a highly sensitive method for pheochromocytomas/paragangliomas (PHEOs/PGLs) associated with succinate dehydrogenase (SDH) mutations. This finding has been attributed to altered tumor cell metabolism resulting from these mutations and does not provide additional prognostic information to genotype. Therefore, identification of new biomarkers for aggressiveness is needed. A high Ki-67 index was proposed to be an additional prognostic factor. This pilot study aimed to evaluate 3'-deoxy-3'-(18)F-
fluorothymidine ($^{18}$F-FLT) PET/CT, a PET proliferation tracer, as a potential imaging agent in a series of 12 PHEO/PGL patients with different genetic backgrounds, to compare ($^{18}$)F-FLT uptake with ($^{18}$)F-FDG PET/CT, and to evaluate classic factors of aggressiveness.

**METHODS:** Twelve patients (7 metastatic and 5 nonmetastatic) were prospectively evaluated with ($^{18}$)F-FDG and ($^{18}$)F-FLT and followed for at least 2 y after the initial imaging work-up. Uptake was assessed at a lesion level, visually and quantitatively by maximum standardized uptake values (SUVmax) for both tracers. ($^{18}$)F-FLT uptake was compared with risk factors known to be linked with a poor prognosis in PGLs (SDHB-mutated status, lesion size, dopaminergic phenotype) and with ($^{18}$)F-FDG uptake.

**RESULTS:** In 12 patients, 77 lesions were assessed. All lesions had low ($^{18}$)F-FLT uptake (median SUVmax, 2.25; range, 0.7-4.5). There was no apparent superiority of ($^{18}$)F-FLT uptake in progressive lesions, and most of the lesions showed a mismatch, with high ($^{18}$)F-FDG uptake (median SUVmax, 10.8; range, 1.1-79.0) contrasting with low ($^{18}$)F-FLT uptake.

**CONCLUSION:** This study suggests that PHEOs/PGLs—even those that progress—do not exhibit intense ($^{18}$)F-FLT uptake. It provides the first in vivo demonstration that proliferation may not be a major determinant of ($^{18}$)F-FDG uptake in these tumors. These findings provide new insight into the biologic behavior of PGL and suggest that antiproliferative agents may be suboptimal for treatment of these tumors.

Multimodal imaging based on MRI and PET reveals $[^{18}\text{F}]$FLT PET as a specific and early indicator of treatment efficacy in a preclinical model of recurrent glioblastoma.


PURPOSE: The primary objective of this study was to compare the ability of PET and MRI biomarkers to predict treatment efficacy in a preclinical model of recurrent glioblastoma multiforme.

METHODS: MRI (anatomical, diffusion, vasculature and oxygenation) and PET ($[^{18}\text{F}]$FDG and $[^{18}\text{F}]$FLT) parameters were obtained 3 days after the end of treatment and compared with late tumour growth and survival.

RESULTS: Early after tumour recurrence, no effect of treatment with temozolomide combined with bevacizumab was observed on tumour volume as assessed by T2-W MRI. At later times, the treatment decreased tumour volume and increased survival. Interestingly, at the earlier time, temozolomide + bevacizumab decreased $[^{18}\text{F}]$FLT uptake, cerebral blood volume and oedema. $[^{18}\text{F}]$FLT uptake, oedema and cerebral blood volume were correlated with overall survival but $[^{18}\text{F}]$FLT uptake had the highest specificity and sensitivity for the early prediction of treatment efficacy.

CONCLUSION: The present investigation in a preclinical model of glioblastoma recurrence underscores the importance of multimodal imaging in the assessment of oedema, tumour vascular status and cell proliferation. Finally, $[^{18}\text{F}]$FLT holds the greatest promise for the early assessment of treatment efficacy. These findings may translate clinically in that individualized treatment for recurrent glioma could be prescribed for patients selected after PET/MRI examinations.

Multimodal In Vivo Imaging of Tumorigenesis and Response to Chemotherapy in a Transgenic Mouse Model of Mammary Cancer.


PURPOSE: Transgenic mice expressing the polyoma middle T oncprotein (PyMT) in the mammary epithelium were explored by multimodal imaging to monitor longitudinally spontaneous tumor growth and response to chemotherapy.

PROCEDURES: Positron emission tomography (PET) with 2-deoxy-2-\([^{18}\text{F}]\)fluoro-D-glucose (\([^{18}\text{F}]\)FDG) and 3'-deoxy-3'-\([^{18}\text{F}]\)fluorothymidine (\([^{18}\text{F}]\)FLT), single photon emission tomography (SPECT) with [99mTc]TcO4 ([99mTc]TEC), X-ray computed tomography, and fluorescent confocal endomicroscopy (FCE) images were acquired during tumor progression in female PyMT mice. Imaging with \([^{18}\text{F}]\)FDG and [99mTc]TEC was also performed in untreated, doxorubicin-treated, and docetaxel-treated PyMT mice. Total tumor volumes were quantified. Tumors were collected and macroscopic and histological examinations were performed.

RESULTS: All PyMT mice developed multifocal tumors of the mammary epithelium that became palpable at 8 weeks of age (W8). Computed tomography (CT) detected tumors at W14, while a clear tumoral uptake of [99mTc]TEC and \([^{18}\text{F}]\)FDG was present as early as W6 and W8, re. No contrast between mammary tumors and surrounding tissue was observed at any stage with \([^{18}\text{F}]\)FLT. FCE detected an angiogenic switch at W10. Lung metastases were not clearly evidenced by imaging. Doxorubicin and docetaxel treatments delayed tumor growth, as shown by \([^{18}\text{F}]\)FDG and [99mTc]TEC, but tumor growth resumed upon treatment discontinuation. Tumor growth fitted an exponential model with time constant rates of 0.315, 0.145, and 0.212 week-1 in untreated, doxorubicin, and docetaxel groups, respectively.

CONCLUSIONS: Molecular imaging of mammary tumors in PyMT is precocious, precise, and predictive. \([^{18}\text{F}]\)FDG-PET and [99mTc]TEC SPECT monitor tumor response to chemotherapy.

Fluorine-$^{18}$-Labeled Thymidine Positron Emission Tomography (FLT-PET) as an Index of Cell Proliferation after Pharmacological Ascorbate-Based Therapy.

Cieslak JA, Sibenaller ZA, Walsh SA, Ponto LL, Du J, Sunderland JJ, Cullen JJ.

Pharmacological ascorbate (AscH$^-$) induces cytotoxicity and oxidative stress selectively in pancreatic cancer cells compared with normal cells. Positron emission tomography (PET) with the thymidine analog 3′-deoxy-3′-(18F) fluorothymidine (FLT) enables noninvasive imaging and quantification of the proliferation fraction of tumors. We hypothesized that the rate of tumor proliferation determined by FLT-PET imaging, would be inversely proportional to tumor susceptibility to pharmacological AscH$^-$-based treatments.

Indeed, there was decreased FLT uptake in human pancreatic cancer cells treated with AscH$^-$ in vitro, and this effect was abrogated by co-treatment with catalase. In separate experiments, cells were treated with AscH$^-$, ionizing radiation or a combination of both. These studies demonstrated that combined AscH$^-$ and radiation treatment resulted in a significant decrease in FLT uptake that directly correlated with decreased clonogenic survival. MicroPET $^{18}$F-FLT scans of mice with pre-established tumors demonstrated that AscH$^-$ treatment induced radiosensitization compared to radiation treatment alone. These data support testing of pharmacological ascorbate as a radiosensitizer in pancreatic cancer as well as the use of FLT-PET to monitor response to therapy.

Feasibility of $^{18}$F-fluoromisonidazole kinetic modeling in head and neck cancer using shortened acquisition times.


Abstract

$^{18}$F-fluoromisonidazole dynamic positron emission tomography (dPET) is used to identify tumor hypoxia non-invasively. Its routine clinical implementation, however, has been hampered by the long acquisition times required. We investigated the feasibility of kinetic modeling using shortened acquisition times in $^{18}$F-fluoromisonidazole dPET, with the goal of expediting the clinical implementation of $^{18}$F-fluoromisonidazole dPET protocols.

METHODS: Six patients with squamous cell carcinoma of the head and neck and ten HT29 colorectal carcinoma-bearing nude rats were studied. In addition to an 18F-fluorodeoxyglucose PET scan, each patient underwent a 45-min 18F-fluoromisonidazole dPET scan, followed by 10 min acquisitions at 96±4 and 163±17 min post-injection. Ninety-minute 18F-fluoromisonidazole dPET acquisitions were performed in animals. Intra-tumor voxels were classified into 4 clusters based on their kinetic behavior using k-means clustering. Kinetic modeling was carried out using the foregoing full datasets (FD) and repeated for each of two shortened datasets corresponding to the first ~100 min (SD1; patients only) or the first 45 min (SD2) of dPET data. The kinetic rate constants (KRCs) as calculated with a 2-compartment model for both SD1 and SD2 were compared to those derived from FD by correlation (Pearson), regression (Passing-Bablok), deviation (Bland-Altman) and classification (area under receiver operating characteristic curve; AUC) analyses. Simulations were performed to assess uncertainties due to statistical noise.

RESULTS: Strong correlation ($r\geq0.75$, $p<0.001$) existed between all KRCs deduced from both SD1 and SD2, and from FD. Significant differences between KRCs were only found for FD-SD2 correlations in patient studies. $K_1$ and $k_3$ were reproducible to within ~6% and ~30% (FD-SD1; patients) and ~4% and ~75% (FD-SD2; animals). AUC values for classification of patient clusters as hypoxic, using a tumor-to-blood ratio>1.2, were 0.91 (SD1) and 0.86 (SD2). The percentage standard deviation in estimating $K_1$ and $k_3$ from 45-min shortened datasets due to noise was <1% and between 2-12% respectively.

CONCLUSION: Using single-session 45-min shortened 18F-fluoromisonidazole dynamic PET datasets appears to be adequate for the identification of intra-tumor regions of hypoxia. However, $k_3$ was significantly overestimated in the clinical cohort. Further studies are necessary to evaluate the clinical significance of differences between the results as calculated from full and shortened datasets.

Comparison of $^{[18}\text{F}]$-FMISO, $^{[18}\text{F}]$-FAZA and $^{[18}\text{F}]$-HX4 for PET imaging of hypoxia - a simulation study.

**Wack LJ, Mönnich D, van Elmpt W, Zegers CM, Troost EG, Zips D, Thorwarth D.**

**OBJECTIVE:** To investigate the effect of hypoxia tracer properties on positron emission tomography (PET) image quality for three tracers $^{[18}\text{F}]$-fluoromisonidazole (FMISO), $^{[18}\text{F}]$-fluoroazomycinarabinoside (FAZA) and $^{[18}\text{F}]$-flortanidazole (HX4), using mathematical simulations based on microscopic tumor tissue sections.

**MATERIAL AND METHODS:** Oxygen distribution and tracer binding was mathematically simulated on immunohistochemically stained cross-sections of tumor xenografts. Tracer diffusion properties were determined based on available literature. Blood activity and clearance over a four-hour period post-injection (p.i.) were derived from clinical dynamic PET scans of patients suffering from head and neck or bronchial cancer. Simulations were performed both for average patient blood activities and for individual patients, and image contrast between normoxic and hypoxic tissue areas was determined over this four-hour period p.i.

**RESULTS:** On average, HX4 showed a six-fold higher clearance than FMISO and an almost three-fold higher clearance than FAZA based on the clinical PET data. The absolute variation in clearance was significantly higher for HX4 than for FMISO (standard deviations of $5.75 \times 10^{-5}$ s$^{-1}$ vs. $1.55 \times 10^{-5}$ s$^{-1}$). The absolute tracer activity in these scans at four hours p.i. was highest for FMISO and lowest for HX4. Simulated contrast at four hours p.i. was highest for HX4 (2.39), while FMISO and FAZA were comparable (1.67 and 1.75, respectively). Variations in contrast of 7-11% were observed for each tracer depending on the vascularization patterns of the chosen tissue. Higher variations in clearance for HX4 resulted in an increased inter-patient variance in simulated contrast at four hours p.i.

**CONCLUSIONS:** In line with recent experimental and clinical data, the results suggest that HX4 is a promising new tracer that provides high image contrast four hours p.i., though inter-patient variance can be very high. Nevertheless, the widely used tracer FMISO provides a robust and reproducible signal four hours p.i., but with a lower contrast. The simulations revealed tracer clearance to be the key factor in determining image contrast.


Radiation treatment monitoring using multimodal functional imaging: PET/CT (($^{18}\text{F}$)Fluoromisonidazole & ($^{18}\text{F}$)Fluorocholine) and DCE-US.

**Arteaga-Marrero N, Brekke Rygh C, Mainou-Gomez JF, Adamsen TC, Lutay N, Reed RK, Olsen DR.**

This study aims to assess the effect of radiation treatment on the tumour vasculature and its downstream effects on hypoxia and choline metabolism using a multimodal approach in the murine prostate tumour model CWR22. Functional parameters derived from Positron Emission Tomography (PET)/Computer Tomography (CT) with ($^{18}\text{F}$)Fluoromisonidazole ($^{[18}\text{F}]$-FMISO) and ($^{18}\text{F}$)Fluorocholine ($^{[18}\text{F}]$-FCH) as well as Dynamic Contrast-Enhanced Ultrasound (DCE-US) were employed to determine the relationship between metabolic parameters and microvascular parameters that reflect the tumour microenvironment. Immunohistochemical analysis was employed for validation.
METHODS: PET/CT and DCE-US were acquired pre- and post-treatment, at day 0 and day 3, respectively. At day 1, radiation treatment was delivered as a single fraction of 10 Gy. Two experimental groups were tested for treatment response with $^{18}$F-FMISO and $^{18}$F-FCH.

RESULTS: The maximum Standardized Uptake Values (SUVmax) and the mean SUV (SUVmean) for the $^{18}$F-FMISO group were decreased after treatment, and the SUVmean of the tumour-to-muscle ratio was correlated to microvessel density (MVD) at day 3. The kurtosis of the amplitude of the contrast uptake A was significantly decreased for the control tumours in the $^{18}$F-FCH group. Furthermore, the eliminating rate constant of the contrast agent from the plasma derived from DCE-US was negatively correlated to the SUVmean of tumour-to-muscle ratio, necrosis and MVD.

CONCLUSIONS: The present study suggests that the multimodal approach using $^{18}$F-FMISO PET/CT and DCE-US seems reliable in the assessment of both microvasculature and necrosis as validated by histology. Thus, it has valuable diagnostic and prognostic potential for early non-invasive evaluation of radiotherapy.

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


Depression frequently accompanies in Parkinson's disease (PD). Previous research suggested that dopamine (DA) 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: [(18)F]FP-CIT for DA transporters and [(18)F]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 DA system and hippocampus and cerebellum for the 5-HT system. The cerebellum was chosen as a reference region. Nondisplaceable binding potential in the striatum and hippocampus were compared between 6-OHDA and sham groups. As a result, the degree of DA 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. The degree of dopaminergic dysfunction was positively correlated with the impairment of the serotonin system. Severity of motor symptoms was also closely related to depressive behavior.


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**Comparative assessment of $^{18}$F-Mefway as a serotonin 5-HT1A receptor PET imaging agent across species- rodents, nonhuman primates, and humans\%**

Mukherjee J, Bajwa AK, Wooten DW, Hillmer AT, Pan ML, Pandey SK, Saigal N, Christian BT.

We have developed $^{18}$F-trans-Mefway ($^{18}$F-Mefway) for PET imaging studies of serotonin 5-HT$_{1A}$ receptors which are implicated in various brain functions. Translation of imaging the 5-HT$_{1A}$ receptor in animal models to humans will facilitate an understanding of the role of the receptor in human brain disorders. We report comparative brain distribution of $^{18}$F-Mefway in normal mice, rats, monkeys and healthy human volunteers.

Mefway was found to be very selective with subnanomolar affinity for the serotonin 5-HT$_{1A}$ receptor. Affinities of >55 nM were found for all other human-cloned receptor subtypes tested. Mefway was found to be a poor substrate (>30 μM) for the multidrug resistance 1 protein, suggesting low likelihood of brain uptake being affected by P-glycoprotein. Cerebellum was used as a reference region in all imaging studies across all species due to the low levels of $^{18}$F-Mefway binding. Consistent binding of $^{18}$F-Mefway in cortical regions, hippocampus and raphe was observed across all species. $^{18}$F-Mefway in the human brain regions correlated with the known postmortem distribution of 5-HT$_{1A}$ receptors. Quantitation of raphe was affected by the resolution of the PET scanners in the rodents, while monkeys and humans showed a raphe to cerebellum ratio approximately 3. $^{18}$F-Mefway appears to be an effective serotonin 5-HT$_{1A}$ receptor imaging agent in all models including humans. $^{18}$F-Mefway therefore may be used to
quantify serotonin 5-HT$_{1A}$ receptor distribution in brain regions for the study of various CNS disorders.


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**Optimal timing of [(18)F]Mefway PET for imaging the serotonin 1A receptor in healthy male subjects.**

Lee JH, Ryu YH, Lyoo CH, Choi SH, Kim JJ, Choi JY.

To determine the optimal acquisition time of [(18)F]Mefway PET, we examined the regional specific-to-nonspecific binding ratios and evaluated the relationship between distribution volume ratios (DVRs) and standardized uptake value ratios (SUVRs) in various time windows. The specific-to-nonspecific binding ratios peaked after 40min and there was a strong correlation between DVR and SUVR in the 60-80min. Therefore, we recommend the use of a single time point between 60 and 80min for [(18)F]Mefway static PET.

Somatostatin receptor PET/CT in restaging of typical and atypical lung carcinoids.


To assess the role of somatostatin receptor (SR) PET/CT using Ga-\(^{68}\) DOTATOC or DOTATATE in staging and restaging of typical (TC) and atypical (AC) lung carcinoids.

METHODS: Clinical and PET/CT data were retrospectively analyzed in 27 patients referred for staging (N = 5; TC, N = 4; AC, N = 1) or restaging (N = 22; TC, N = 8; AC, N = 14). Maximum standardized uptake value (SUVmax) of SR-positive lesions was normalized to the SUVmax of the liver to generate SUVratio; SR PET was compared to contrast-enhanced (ce) CT. The classification system proposed by Rindi et al. (Endocr Relat Cancer. 2014;21(1):1-16, 2014) was used for classification of patients in TC and AC groups.

RESULTS: Only 18/27 patients were found to have metastases on PET/CT. Of the 186 lesions, 101 (54.3%) were depicted on both PET and CT, 53 (28.5%) lesions only on CT, and 32 (17.2%) only on PET. SUVratio of lesions was significantly higher in AC as compared to TC (p < 0.001). In patients referred for restaging, additional findings on PET lead to upstaging with change in management strategy in 5/22 (22.7%) patients (AC, N = 5; TC, N = 1). In four patients (all AC) referred for restaging and in one patient (TC) referred for staging, additional findings on CT missed on PET lead to correct staging.

CONCLUSIONS: Typical and atypical carcinoid patients have complex patterns of metastases which make it necessary to combine functional SR PET and contrast-enhanced CT for appropriate restaging. In patients referred for restaging SR, PET may have a relevant impact on treatment strategy in up to 22.7% of patients with typical and atypical lung carcinoids.


Comparison of Diagnostic Sensitivity and Quantitative Indices Between \(^{68}\)Ga-DOTATOC PET/CT and \(^{111}\)In-Pentetreotide SPECT/CT in Neuroendocrine Tumors: a Preliminary Report.


In-pentetreotide has been used for neuroendocrine tumors expressing somatostatin receptors. Recently, \(^{68}\)Ga-DOTATOC PET has been used with the advantage of high image quality. In this study, we compared quantitative indices between \(^{111}\)In-pentetreotide SPECT/CT and \(^{68}\)Ga-DOTATOC PET/CT.

METHODS: Thirteen patients diagnosed with neuroendocrine tumors were prospectively recruited. Patients underwent \(^{111}\)In-pentetreotide scans with SPECT/CT and \(^{68}\)Ga-DOTATOC PET/CT before treatment. The number and location of lesions were analyzed on both imaging techniques to compare lesion detectability. Additionally, the maximal uptake count of each lesion and mean uptake count of the lungs were measured on both imagings, and target-to-normal lung ratios (TNR) were calculated as quantitative indices.

RESULTS: Among 13 patients, 10 exhibited lesions with increased uptake on \(^{111}\)In-pentetreotide SPECT/CT and/or \(^{68}\)Ga-DOTATOC PET/CT. Scans with SPECT/CT detected 19 lesions, all of which were also detected on PET/CT. Moreover, 16 additional lesions were
detected on PET/CT (6 in the liver, 9 in the pancreas and 1 in the spleen). PET/CT exhibited a significantly higher sensitivity than SPECT/CT (100 % vs. 54 %, P < 0.001). TNR was significantly higher on PET/CT than on SPECT/CT (99.9 ± 84.3 vs. 71.1 ± 114.9, P < 0.001) in spite of a significant correlation (r = 0.692, P = 0.01).

CONCLUSION: Ga-DOTATOC PET/CT has a higher diagnostic sensitivity than (111)In-pentetreotide scans with SPECT/CT. The TNR on PET/CT is higher than that of SPECT/CT, which also suggests the higher sensitivity of PET/CT. (111)In-pentetreotide SPECT/CT should be used carefully if it is used instead of (68)Ga-DOTATOC PET/CT.


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Prospective comparison of 68Ga-DOTATATE and 18F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with emphasis on sporadic cases.


Pheochromocytomas/paragangliomas (PHEOs/PGLs) overexpress somatostatin receptors and recent studies have already shown excellent results in the localization of these tumors using 68Ga-labeled somatostatin analogs (68Ga-DOTA-SSA), especially in patients with germline succinate dehydrogenase subunit B gene (SDHB) mutations and head and neck PGLs (HNPGLs). The value of 68Ga-DOTA-SSA has to be established in sporadic cases, including PHEOs. Thus, the aim of this study was to compare 68Ga-DOTATATE PET/CT, 18F-FDOPA PET/CT, and conventional imaging in patients with various PHEOs/PGLs with a special emphasis on sporadic cases, including those located in the adrenal gland. DESIGN: 68Ga-DOTATATE, 18F-FDOPA PET/CT, and conventional imaging (contrast-enhanced CT and MRI with MR angiography sequences) were prospectively performed in 30 patients (8 with SDHD mutations, 1 with a MAX mutation and 21 sporadic cases) with PHEO/PGL at initial diagnosis or relapse.

RESULTS: The patient-based sensitivities were 93 % (28/30), 97 % (29/30), and 93 % (28/30) for 68Ga-DOTATATE PET/CT, 18F-FDOPA PET/CT, and conventional imaging, respectively. The lesion-based sensitivities were 93 % (43/46), 89 % (41/46), and 76 % (35/46) for 68Ga-DOTATATE PET/CT, 18F-FDOPA PET/CT, and conventional imaging respectively (p = 0.042). 68Ga-DOTATATE PET/CT detected a higher number of HNPGLs (30/30) than 18F-FDOPA PET/CT (26/30: p = 0.112) and conventional imaging (24/30: p = 0.024). 68Ga-DOTATATE PET/CT missed two PHEOs of a few millimeters in size and a large recurrent PHEO. One lesion was considered false-positive on 68Ga-DOTATATE PET/CT and corresponded to a typical focal lesion of fibrous dysplasia on MRI. Among the 11 lesions missed by conventional imaging, 7 were detected by conventional imaging with knowledge of the PET results (4 HNPGLs, 2 LNs, and 1 recurrent PHEO).

CONCLUSION: 68Ga-DOTATATE PET/CT is the most sensitive tool in the detection of HNPGLs, especially SDHD-related tumors, which may be very small and fail to concentrate sufficient 18F-FDOPA. The present study further expands the use of 68Ga-DOTATATE for all patients with HNPGLs, regardless of their genotype. 68Ga-DOTATATE PET/CT may be inferior to 18F-FDOPA PET/CT in the detection PHEOs.

Malignant Jugular Paraganglioma: Unusual Presentation on $^{68}$Ga DOTANOC PET/CT.

Jain TK, Basher RK, Shukla J, Mittal BR, Panda NK.

Metastatic jugular paraganglioma are rare tumors and account for less than 1% of the cases of head and neck tumors. We report a 40-year-old woman of jugular paraganglioma, presenting with right-sided neck swelling, hearing loss, and pulsatile tinnitus. Contrast-enhanced CT temporal bone revealed a mass in the right jugular foramina and extending inferiorly to internal jugular vein. Ga DOTANOC PET/CT was performed, which revealed somatostatin receptor expressing lesion in the right internal jugular vein and extension into sigmoid sinus and additional metastatic focus in the sacrum.