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Skeletal PET with 18F-Fluoride: Applying New Technology to an Old Tracer

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The Journal of Nuclear Medicine • Vol. 49 • No. 1 • January 2008.

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

Early Detection and Accurate Description of Extent of Metastatic Bone Disease in Breast Cancer With Fluoride Ion and Positron Emission Tomography

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Jaurnal Clinical Oncoloagy. Val 17, Na 8 (August).1999: pp 2381·2389

Purpose: Previous studies ha ve shown that bone metastases are revealed by magnetic resonance imaging (MRI) or bone marrow scintigraphy several months before they are visible by conventional bone scintigraphy (BS). We present a new approach for detecting bone metastases in patients with breast cancer. We compared findings obtained with fluoride ion (F-18) and positron emission tomography (PET) with those obtained with conventional BS. *Patients and Methods:* Thirty-four breast cancer patients were prospectively examined using F-18-PET andconventional BS. F-18-PET and BS were performed within 3 weeks of each other. Metastatic bone disease was previously known to be present in six patients and was suspected (bone pain or increasing levels of tumor markers, Ca2+, alkaline phosphatase) in 28 patients. Both imaging modalities were compared by patient-bypatient analysis and lesion-by-lesion analysis, using a five-point scale for receiver operating characteristic (ROC) curve analysis. A panel of reference methods was used, including MRI (28 patients), planar x-ray (17 patients), and spiral computed tomography (four patients). *Results:* With F-18-PET, 64 bone metastases were detected in 17 patients. Only 29 metastases were detected in 11 patients with BS. As a result of F-18- imaging, clinical management was changed in four patients (11.7%). For F-18-PET, the area under the ROC curve was 0.99 on a les ion basis (for BS, it was 0.74; P < .05) and 1.00 on a patient basis (for BS, it was 0.82; P <**.05).** ***Conclusion:*** **F-18-PET demonstrates a very early bone reaction when small bone marrow metastases are present, allowing accurate detection of breast cancer bone metastases. This accurate detection has a**

significant effect on clinical management, compared with the effect on management brought about by detection with conventional BS.

The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: 99mTc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT.

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The Journal of Nuclear Medicine • Vol. 47 • No. 2 • February 2006

The aim of this study was to compare the detection of bone metastases by 99mTc-methylene diphosphonate (99mTc-MDP) planar bone scintigraphy (BS), SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT in patients with high-risk prostate cancer. Methods: In a prospective study, BS and 18F-Fluoride PET/CT were performed on the same day in 44 patients with high-risk prostate cancer. In 20 of the latter patients planar BS was followed by single field-of-view (FOV) SPECT and in 24 patients by multi-FOV SPECT of the axial skeleton. Lesions were interpretedseparately on each of the 4 modalities as normal, benign, equivocal, or malignant. Results: In patient2based analysis, 23patients had skeletal metastatic spread (52%) and 21 did not. Categorizing equivocal and malignant interpretation as suggestive for malignancy, the sensitivity, specificity, positive predictive value, and negative predictive value of planar BS were 70%,57%, 64%, and 55%, respectively, of multi-FOV SPECT were92%, 82%, 86%, and 90%, of 18F-Fluoride PET were 100%,62%, 74%, and 100%, and of 18F-Fluoride PET/CT were 100%for all parameters. Using the McNemar test, 18F-Fluoride PET/CT was statistically more sensitive and more specific than planar or SPECT BS (P, 0.05) and more specific than 18F-Fluoride PET (P, 0.001). SPECT was statistically more sensitive and more specific than planar BS (P, 0.05) but was less sensitive than 18F-Fluoride PET (P, 0.05). In lesion2based analysis, 156 lesions with increased uptake of 18F-Fluoride were assessed. Based on the corresponding appearance on CT, lesions were categorized by PET/CT as benign (n 5 99), osteoblastic metastasis (n 5 46), or equivocal when CT was normal (n 5 11). Of the 156 18F-Fluoride lesions, 81 lesions (52%), including 34 metastases, were overlooked with normal appearance on planar BS. SPECT identified 62% of the lesions overlooked by planar BS. 18F-Fluoride PET/CT was more sensitive and more specific than BS (P, 0.001) and more specific than PET alone (P, 0.001). Conclusion: 18F-Fluoride PET/CT is a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer. It is more specific than 18F-Fluoride PET alone and more sensitive and specific than planar and SPECT BS. Detection of bone metastases is improved by SPECT compared with planar BS and by 18F-Fluoride PET compared with SPECT. This added value of 18F-Fluoride PET/CT may beneficially impact the clinical management of patients with high-risk prostate cancer.

18F-Fluoride PET for Monitoring Therapeutic Response in Paget's Disease of Bone

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Journal of Nuclear Medicine Vol. 46 No. 10 1650-1658

A prospective study was undertaken to evaluate PET with 18F -fluoride for monitoring the response to bisphosphonates in Paget's disease ofbones. Methods: Fourteen patients with a monostotic *(n* = 9) or a polyostotic form *(n* = 5) ofPaget's disease were scanned at baseline and

at 1 and 6 mo after the beginning of treatment. Dynamic acquisition and arterial blood sampling were used to calculate the influx constant Ki (by both the Patlak [Ki-PAT] method and the nonlinear regression [Ki-NLR] method). Kinetic modelling was compared with maximal standardized uptake values (SUVmaJ and biochemical markers of bone remodelling. Results: Baseline uptake of 18F-fluoride by pagetic bones was significantly higher than in normal bones *(P* < 0.05). One month after the start of treatment, SUVmax ,Ki-PAT, Ki- NLR, and KI (the unidirectional clearance of fluoride from plasma to the whole of the bone tissue) decreased significantly by 27.8%,27.9%,27.5%, and 23.6%, respectively. Biochemical markers were already normalized in 6 of9 patients with monostotic disease, although all had high 18F-fluoride uptake values. Six months after the start of treatment, 18F-fluoride uptake further diminished by 22.3%-25.6%. Biochemical markers were normal in all but 2 patients, although 10 of 14 patients still showed high 18F_
fluoride uptake. One patient did not respond to treatment and maintained high uptake of 18F-fluoride throughout the study. SUV max correlated with both Ki-PA T and Ki-NLR at baseline, 1 mo, and 6 mo *(P* < 0.05). Moreover, the change of SUV max between baseline and 1 mo, as well as between baseline and 6 mo, also correlated with the change of Ki-PAT and Ki-NLR *(P* < 0.05). Conclusion: Our results show that J8F-fluoride PET can be used to no invasively and accurately monitor the efficacy of treatment with bisphosphonates in Paget's disease of bones. SUV max correlates with Ki-PA T and Ki-NLR and, interestingly, varies in the same manner as kinetic indices. Therefore, the use of SUV max could avoid the need for dynamic acquisition and arterial blood sampling and would facilitate the use of whole-body PET in a clinical setting.

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Fluorocolina

Synthesis and Evaluation of 18F-labeled Choline as an Oncologic Tracer for Positron Emission Tomography: Initial Findings in Prostate Cancer

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Cancer Res. 2001 Jan 1;61(1):110-7

The up-regulation of rates of choline uptake and phosphorylation in certain malignancies has motivated the development of positron-labeled choline analogues for noninvasive detection of cancer using positron emission tomography (PET). The choline analogue, no-carrier-added [18F]fluoromethyl-dimethyl-2-hydroxyethyl-ammonium (FCH), was synthesized through the intermediate [18F]fluorobromomethane. FCH was evaluated in relationship to 2-[18F]fluoro-2-deoxyglucose (FDG) as an oncological probe in cultured PC-3 human prostate cancer cells, a murine PC-3 human prostate cancer xenograft model, and in PET imaging studies of patients with prostate cancer. FCH was synthesized in 20–40% radiochemical yield and >98% radiochemical purity. Accumulation of FCH and FDG were comparable in cultured prostate cancer cells, whereas only FCH was inhibited (90%) by hemicholinium-3, a specific inhibitor of choline transport and phosphorylation. FCH showed similar biodistribution to [14C]choline in the tumor-bearing mouse, with prominent renal and hepatic uptake. Tumor uptake of FCH was similar to choline and FDG in the mouse model, although tumor:blood ratios were moderately higher for FCH. Initial PET imaging studies in prostate cancer patients showed high uptake of FCH in advanced prostate carcinoma and detection of osseous and soft tissue metastases. FCH uptake by tumors was markedly reduced in patients rescanned during androgen deprivation therapy. It is concluded that FCH closely mimics choline uptake by normal tissues and prostate cancer neoplasms. FCH is potentially useful as a PET tracer for detection and localization of prostate cancer and monitoring effects of therapy.

Localization of Primary Prostate Cancer with Dual-Phase 18F-Fluorocholine PET

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J Nucl Med. 2006 Feb;47(2):262-9

This study compared 18F-fluorocholine uptake in malignant and benign areas of the prostate at 2 time points to determine the suitability of delayed or dual-phase 18F-fluorocholine PET for localizing malignancy in the prostate gland. **Methods**: Twenty-six men (15 newly diagnosed with prostate cancer, 2 with recurrent prostate cancer, 6 with no evidence of prostate cancer recurrence after treatment, and 3 with no history of prostate cancer) underwent dual-phase PET consisting of initial whole-body PET starting 7 min after injection of 3.3–4 MBq/kg of 18F-fluorocholine followed by 1-h delayed PET of the pelvis. Tracer uptake in the prostate on the initial and delayed images was measured on a sextant basis. Prostate biopsy or whole-prostate histologic examination after radical prostatectomy was used to classify a prostate sextant as a dominant malignant region or probable benign region. For each sextant, a retention index based on the measured maximum standardized uptake value (SUVmax) was calculated on the initial and delayed images. In 15 prostates with both benign and malignant sextants on histologic examination, a malignant-to-benign ratio of SUVmax was also calculated for each time point. **Results**: A dominant malignant region was found in 17 subjects,

and a probable benign region was found in 24 subjects. The mean SUVmax for dominant malignant regions increased significantly between initial and delayed scans, from 7.6 to 8.6 (mean retention index, 114%; 95% confidence interval, 6%–22%; P 5 0.002). The mean SUVmax for probable benign regions decreased significantly between initial and delayed scans, from 4.8 to 3.9 (mean retention index, 217%; 95% confidence interval, 210% to 223%, P , 0.001). The mean malignant-to-benign ratio increased significantly, from 1.4 on the initial scan to 1.8 on the delayed scan (P 5 0.003). The areas under the receiver operating characteristic curves for distinguishing dominant malignant regions from probable benign regions based on initial SUVmax, delayed SUVmax, and retention index were 0.81, 0.92, and 0.93, respectively**. Conclusion**: On dual-phase PET of the prostate, areas of malignancy consistently demonstrated stable or increasing 18F-fluorocholine uptake, whereas most areas containing benign tissue demonstrated decreasing uptake. Delayed or dual-phase imaging after injection of 18F-fluorocholine may improve the performance of 18F-fluorocholine PET for localizing malignant areas of the prostate.

Role of whole-body 18F-cholinePET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer

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Radiol Med. 2008 Sep;113(6):895-904. Epub 2008 Apr 14

Purpose: The aim of this study was to evaluate the role of whole body 18F-choline(FCH) positron emission tomography-computed tomography (PET-CT) in detecting and localising disease recurrence in patients presenting biochemical relapse after radical treatment for prostate cancer.
Materials and methods: Fifty-six consecutive patients with increased serum prostate-specific antigen (PSA) levels after radical prostatectomy were included in the study. None of them was recei ving hormone treatment at the time f the examination or had been treated during the previous 6 months. All patients underwent whole-body 18F-choline PET imaging, and the pathological findings were compared with those of further imaging exams, biopsy and follow-up. On the basis of the PSA levels, we divided our patient population into three subgroups: PSA≤1, I <PSA≤5, and PSA>5 ng/ml. Results. Overall, the PET scan detected disease relapse in 42.9% of cases (24/56). PET sensitivity was closely related to serum PSA levels, showing values of 20%, 44% and 81.8% in the PSA≤I, I<PSA≤5 and PSA>5ng/ml subgroups, respectively.
***Conclusions*:** In patients with biochemical relapse after radical treatment for prostate cancer, 18F-cholinePET-CT represents a single step, whole-body, non-invasive study that allows disease detection and localisation.
The disease detection rate is related to serum PSA levels.

Fluoromethylcholine (18F) PET/CT for staging hepatocellular carcinoma: prospective comparison with FDG (18F) PET/CT

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***Purpose*:** The sensitivity of fluorodeoxyglucose(18F) (FDG) PET/CT is variable in case of hepatocellular carcinoma (HCC). In a proof-of-concept study,we observed that fluoromethylcholine(18F) (FCH) had a better detection rate.
In the present prospective study, we compared the diagnostic performance of FCH and FDG

PET/CT for staging HCC, according to its diferentiation.
***Methods*:** 34 patients with newly diagnosed (n=27) or recurrent (n=7) HCC were prospectively enrolled. HCC was assessed by histology in 29 cases (11 well-differentiated HCC) and by European Association for the study of the liver ("Barcelona") criteria in 5 cases. All patients underwent whole-body PET/CT 10 min a=er injection of 4 MBq/kg FCH. Within 1 week, all patients underwent whole-body FDG PET/CT 1 h a=er injection of 5 MBq/kg FDG. On basis of histology, 70 hepatic lesions and 3 extra-hepatic lesions were evaluable.
*Results:*The per-patient analysis showed a detection rate of 27/34=79% using FCH PET/CT and 23/34=68% (NS) using FDG PET/CT for both newly diagnosed and recurrent HCC. On a per patient basis, FCH or FDG were positive in 32/34 = 94% HCC patients. !e 2 patients who were "missed" by both FCH and FDG were alive more than 24 months after inclusion. On a per site basis, of the 64/70 = 91% liver lesion sites were detected by FCH or FDG, only 6 lesions being missed by both radiopharmaceuticals. In patients with well-differentiated HCC (11/34) a significant superiority of detection was observed with FCH 11/11=100% vs. 5/11=45% with FDG, p<0,003, on a per patient basis and 30/32=94% vs. 19/32=59% on per liver lesion basis. Furthermore 5 liver HCC lesions appeared photopenic on FCH PET/CT. !e 3 distant metastatic sites were visible with both FCH and FDG. Concordantly with what was observed for liver lesions, the metastatic site corresponding to a primary well-differentiated HCC took up FCH more avidly than FDG (SUV=10.6 vs. 2.7 respectively), and the reverse was true in 2 cases of lung or mediastinum metastases of non-well-differentiated HCC.
Conclusion: FCH has and added value over FDG to stage HCC, in particular for liver sites in well-differentiated HCC. The indications that can be derived from the present study for FCH PET/CT in known HCC are:
- a first line examination for staging well-differentiated HCC-
a second line examination after FDG PET/CT in case of intermediate or poorly differentiated HCC, in particular when liver transplantation is scheduled or when FDG PET/CT is negative.

Fluoromethylcholine (18F) (FCH) PET/CT for the detection of hepatocellular carcinoma (HCC) in patients with a chronic liver disease and liver nodules: prospective comparison with FDG (18F) PET/CT

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Aim: We have shown in a proof-of-concept study that FCH was taken-up by HCC more frequently than FDG. the aim of this prospective study was to compare the diagnostic performance of FCH and FDG to detect HCC in 58 patients with chronic liver disease and nodule(s). *Methods*: 59 patients (40M, 19F, age 33-77) underwent whole-body FCH PET/CT 10 min after injection of 4 MBq/kg and whole-body FDG PET/CT 1 h after injection of 5 MBq/kg FDG. A=er the end of inclusions, both PET/CT examinations were blind read in a random order for each tracer by 2 independent observers using the standard 5 level scale (0: no lesion or most probably benign lesion, 4: most probably malignant lesion) and the consensus of blind readings was reached. Diagnostic performance of each tracer was calculated on per patient and per lesion-site bases. ***Results***: On basis of histology and/or follow-up >6 months, the 59 patients had 34 HCC, 4 cholangiocarcinoma, 2 liver metastasis of colon cancer, 2 pulmonary cancers without primary or secondary liver cancer, 14 liver adenoma and/or focal nodular hyperplasia, and 3 another benign hepatic lesion. Per patient performance of FCH & FDG for detecting presence of HCC, any positive result in another cancer being considered FP.

Positron emission tomography (PET/CT) using fluoro-choline allows to differentiate Adenoma from focal nodular hyperplasia

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Official Journal of the European Association for the Study of the Liver. Volumen 48, Supplement 2, Page S140 (2008)

Background and Aim: Despite of the high performance of current imaging techniques, the differential diagnosis between hepatic adenoma and FNH could remain difficult in particular for nodules of small size, often inaccessible to the liver biopsy. PET/CT using F-18fluoro-2-Dglucose (FDG) is well established as a non-invasive diagnostic tool for the detection of a variety of malignant tumours. However, because of its low sensitivity, this technique is not used for the diagnosis of hepatocellular carcinoma (HCC). We have recently shown that F-18fluoro-methylcholine (FCH) was more sensitive than FDG for HCC detection. The aim of this study was to evaluate the uptake of FCH by hepatocellular benign tumours.
Patients and Methods*:* 20 patients were prospectively explored for one or more nodules developed in a non cirrhotic liver and compatible with an adenoma or a focal nodular hyperplasia (FNH). The nodules were investigated by RMN and CT. A histological confirmation of the lesions was obtained in all patients except six because of the characteristic imaging features of FNH. Two PET/CT were carried out in each patient after injection of FDG and of FCH (4 MBq/kg of body weight) at four days of interval. The uptakes of FCH and of FDG by the tumours were evaluated by the standardized uptake value (SUV).
Results*:* 18 women and 2 men were included and presented with the following hepatic lesions: FNH (n = 11), adenoma (n = 6) including 2 adenomatosis, association of FNH and adenoma (n = 3). All FNH showed an intense and early uptake of FCH (SUV: 8.49□}2.38 at 1 min) in comparison with adjacent normal liver (SUV ratio: 1.55□}0.29). This FCH uptake decreased slowly at late time. In contrast, there was no FCH uptake by the adenomas. Concerning the patients presenting with both adenoma and FNH, an intense uptake of FCH was observed only for the nodule having the features of FNH. None of these tumours (adenoma and FNH) showed an increased uptake of FDG as compared to normal liver.
Conclusions: Our results show that the TEP/TDM using FCH is a sensitive and specific technique able to differentiate FNH from adenoma.

Biodisposition and metabolism of [18F]fluorocholine in 9L glioma cells and 9L glioma-bearing Fisher rats Aditya Bansal, MS1, Wang Shuyan, MD2, Toshiko Hara, MD, Ph.D.2, Robert A. Harris, Ph.D. 1, and Timothy R. DeGrado, Ph.D.[1,2]

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Eur J Nucl Med Mol Imaging. 2008 Jun;35(6):1192-203. Epub 2008 Feb 9

Purpose—[18F]Fluorocholine [18F]FCH) was developed as an analog of [11C]choline for tumor imaging, however, its metabolic handling remains ill-defined. In this study, the metabolism of [18F] FCH is evaluated in cultured 9L glioma cells and Fisher 344 rats bearing 9L glioma tumors.
Methods—9L glioma cells were incubated with [18F]FCH and [14C]choline under normoxic and hypoxic (1% O2) conditions and analyzed for metabolic fate. [18F]FCH and [14C]choline kinetics and metabolism were studied in Fisher 344 rats bearing subcutaneous 9L tumors.

Results—[18F]FCH and [14C]choline were similarly metabolized in 9L cells in both normoxic and hypoxic conditions over a 2 hr incubation period. In normoxia, radioactivity was predominantly in phosphorylated form for both tracers after 5 min incubation. In hypoxia, the tracers remained mainly in nonmetabolized form at early timepoints (< 20 min). Slow dephosphorylation of intracellular 18F]phosphofluorocholine (0.043–0.060 min−1) and [14C]phosphocholine (0.072–0.088 min−1) was evidenced via efflux measurements. In rat, both [18F]FCH and [14C]choline showed high renal and hepatic uptake. Blood clearance of both tracers was rapid with oxidative metabolites, [18F] fluorobetaine and [14C]betaine, representing the majority of radiolabel in plasma after 5 min ostinjection.
Oxidation (in liver) and lipid incorporation (in lung) were somewhat slower for [18F]FCH relative to [14C]choline. The majority of radiolabel in hypoxic subcutaneous tumor, as in hypoxic cultured 9L cells, was found as nonmetabolized [18F]FCH and [14C]choline.
*Conclusions***—**[18F]FCH mimics choline uptake and metabolism by 9L glioma cells and tumors. However, subtle changes in biodistribution, oxidative metabolism, dephosphorylation, lipid incorporation and renal excretion show moderate effects of the presence of the radiofluorine atom in [18F]FCH. The decrease in phosphorylation of exogenous choline by cancer cells should be considered in interpretation of PET images in characteristically hypoxic tumors.

Use of 18F-choline and 11C-choline as contrast agents in positron emission tomography imaging–guided stereotactic biopsy sampling of gliomas

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J Neurosurg. 2003 Sep;99(3):474-9

Object. Neuroimaging-guided stereotactic biopsy procedures are commonly used for diagnosis of gliomas. A number of the imaging modalities currently in use are not reliable enough in depicting these tumors. The authors developed 18Fcholine and 11C-choline as tumor imaging agents for positron mission tomography (PET) scanning, and used them to visualize gliomas prior to stereotactic biopsy procedures.
Methods. The PET studies were performed in 12 patients who were thought to be affected by gliomas observed on computerized tomography and magnetic resonance images. The 18F- and 11C-choline were injected separately, and the PET scanning was started 5 and 20 minutes postinjection. The PET scans gave quantitative information about the distribution of 18F- and 11C-choline in the brain. The tumor uptake was constant between 5 and 20 minutes with both agents. Stereotactic biopsy sampling was performed to obtain tissues from the most radioactive areas on the PET scan; histological diagnoses were made using these tissues. The results were as follows: oligodendroglioma was found in two patients, astrocytoma in one, anaplastic astrocytoma in two, and glioblastoma in seven.
Conclusions. The uptake of contrast agents was always low in low-grade gliomas, and the uptake in high-grade glioma was always high. The tumor/normal (T/N) ratio of 18F-choline was 10.5:12 in anaplastic astrocytoma and 13.2:21 in glioblastoma. The 18F-choline yielded slightly superior results compared with 11C-choline with regard to the T/N ratio. In one case of oligodendroglioma the tumor showed no uptake of 18F- and 11C-choline. With this exception, the PET scans of gliomas
in which 18F- and 11C-choline contrast agents were added would guide the approach to the most malignant areas for stereotactic biopsy sampling.

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Fluoromisonidazol

MINI SYMPOSIUM: PET—THE FUTURE. Tuesday 17 October 2006, 14:00–15:30 PET imaging of tumour hypoxia

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Cancer Imaging (2006) 6, S117–S121

Tumour hypoxia represents a significant challenge to the curability of human tumours leading to treatment resistance and enhanced tumour progression. Tumour hypoxia can be detected by non-invasive and invasive techniques but the inter-relationships between these remains largely undefined. [18F]Fluoromisonidazole-3-fluoro- 1-(20-nitro-10-imidazolyl)-2-propanol ([18F]MISO) and Cu-diacetyl-bis(N4-methylthiosemicarbazone (Cu-ATSM)- positron emission tomography (PET), and blood oxygen level-dependent (BOLD)-magnetic resonance imaging (MRI) are the lead contenders for human application based on their non-invasive nature, ease of use and robustness, measurement of hypoxia status, validity, ability to demonstrate heterogeneity and general availability; PET techniques are the primary focus of this review. Keywords: Hypoxia; radiotherapy; cancer; F-MISO-PET; Cu-ATSM-PET; tumour resistance.

[18F]MISO is the prototype hypoxia imaging agent. Uptake is homogeneous in most normal tissues, reflecting its high partition coefficient (near unity), and delivery to tumours is not limited by perfusion[14]. The initial distribution of [18F]MISO is flow dependent, as with any freely diffusible tracer, but local oxygen tension is the major determinant of its retention above normal background in tissues after 2 h. [18F]MISO accumulates in tissues by binding to intracellular macromolecules when pO2 < 10 mmHg. Retention within tissues is dependent on nitroreductase activity (i.e. on reduction status of a NO2 group on the imidazole ring) and accumulation in hypoxic tissues over a range of blood flows has been noted, including within the intestinal lumen where it is retained in anaerobes. Hypoxia can be imaged with [18F]MISO PET in a procedure that is well tolerated by the patients. Imaging requires 20–30 min and starts anywhere from 75 to 150 min after injection, making it similar to the bone scan with which most cancer patients are familiar. Useful and well-validated images can be achieved with a modest dose of radiation, typically 250 MBq. No arterial sampling or metabolite analysis is required and synthesis is achieved through relatively simple modifications of nucleophilic displacement/deprotection synthesis boxes such as are used for fluorodeoxyglucose ([18F]FDG). In the United States, F-MISO has Investigational New Drug (IND) authorization from the Food and Drug Administration (FDA) as an investigational product for use in humans. Unlike Eppendorf pO2 histography, [18F]MISO is only sensitive to the presence of hypoxia in viable cells; [18F]MISO is not retained in necrosis because the electron transport chain that reduces the nitroimidazole to a bioreductive alkylating agent is no longer active. Limitations of [18F]MISO PET include the modest signal-to-noise ratio of raw [18F]MISO PET images but if a venous blood sample is acquired during the mid-course of the imaging procedure and used to calculate a tumour/blood (T/B) ratio image, then normoxic uptake (T/B < 1) can be electronically subtracted to increase image contrast. Several studies in a range of hypoxic tumours, stroke and hypoxic myocardium[15] have shown that a T/B of >1.2 reliably identifies the presence of hypoxia. The presence of high normal liver uptake impairs complete assessment of liver lesions and urinary excretion interferes with imaging near the bladder.
[18F]MISO PET is able to monitor the changing hypoxia status of lung tumours during radiotherapy[16]. Studies in sarcoma[17] and head and neck cancer[18–20] have demonstrated a correlation of [18F]FMISO uptake with poor outcome to radiation and chemotherapy.

Tumor Hypoxia Imaging with [F-18] Fluoromisonidazole Positron Emission Tomography in Head and Neck Cancer

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Clin Cancer Res 2006;12(5435 18) September 15, 2006

Purpose: Advanced head and neck cancer shows hypoxia that results in biological changes to make the tumor cells more aggressive and less responsive to treatment resulting in poor survival. [F-18] fluoromisonidazole (FMISO) positron emission tomography (PET) has the ability to noninvasively quantify regional hypoxia.We investigated the prognostic effect of pretherapy FMISO-PETon survival in head and neck cancer.Experimental
Design: Seventy-three patients with head and neck cancer had pretherapy FMISO-PETand 53 also had fluorodeoxyglucose (FDG) PETunder a research protocol from April 1994to April 2004.
Results: Significant hypoxia was identified in 58 patients (79%). The mean FMISO tumor/ bloodmax (T/Bmax) was 1.6 and the mean hypoxic volume (HV) was 40.2 mL. There were 28 deaths in the follow-up period.Mean FDG standard uptake value (SUV)max was10.8. The median time for follow-up was 72 weeks. In a univariate analysis,T/Bmax (P = 0.002),HV(P = 0.04), and the presence of nodes (P = 0.01) were strong independent predictors. In a multivariate analysis, including FDG SUVmax, no variable was predictive at P < 0.05.When FDG SUVmax was removed from the model (resulting in n = 73 with 28 events), nodal status andT/Bmax (or HV) were both highly predictive (P = 0.02, 0.006 for node andT/Bmax, respectively; P = 0.02 and 0.001for node and HV, respectively).
Conclusions: Pretherapy FMISO uptake shows a strong trend to be an independent prognostic measure in head and neck cancer.

Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy.

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J nucl med. 2005 feb;46(2):253-60.

In radiotherapy of head and neck cancer (HNC) and non-small cell lung cancer (NSCLC), hypoxia is known to be an important prognostic factor for long-term survival and local tumor control. The PET tracer (18)F-fluoromisonidazole (FMISO) allows noninvasive assessment of tumor hypoxia. This study analyzed whether FMISO PET could predict tumor recurrence after radiotherapy.
METHODS: Forty patients with advanced HNC (n = 26) or NSCLC (n = 14) were studied before curative radiotherapy. Dynamic (0-15 min) and static PET scans were acquired up to 4 h after injection of 400 MBq of FMISO. Standardized uptake values (SUVs) and ratios to reference tissues (mediastinum or muscle) were calculated. In addition, time-activity curves up to 14 min after injection were classified visually. PET data were correlated with clinical follow-up data (presence or absence of local recurrence within 1 y), which were available for 21 patients.
RESULTS: For HNC, patients with local recurrence could be separated from disease-free patients by SUV 4 h after injection (all recurrences had an SUV > 2). For NSCLC, no such correlation was observed. The tumor-to-muscle ratios (T/Mu) and tumor-to-mediastinum ratios (T/Me) at 4 h after injection correlated with the risk of relapse in both tumor entities: All patients with a T/Me greater than 2.0 (NSCLC, n = 5) or with a T/Mu greater than 1.6 (HNC, n = 5) presented with tumor recurrence, whereas only 3 of the remaining 11 patients experienced recurrence (27%). Qualitative analysis of time-activity curves for 37 patients revealed 3 curve types (rapid washout, n = 9; intermediate [delayed washout], n = 12; and accumulation, n = 16). Eighteen patients categorized by curve type could be followed up: In 5 of 6 patients with an

accumulation curve, disease recurred locally within 1 y, compared with 5 of 8 patients with a delayed-washout curve and 0 of 4 with a rapid-washout curve.

CONCLUSION: Our results indicate that outcome after radiotherapy can be predicted on the basis of kinetic behavior of FMISO in tumor tissue. An accumulation-type curve, high SUV, and high T/Mu and T/Me at 4 h after injection are highly suggestive of an incomplete response to treatment and might be used to select patients for intensified therapy protocols.

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Fluorotimidina

Early assessment of therapy response in malignant lymphoma with the thymidine analogue [18F]FLT

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Eur J Nucl Med Mol Imaging (2007) 34:1775–1782

Purpose The aim of this study was to determine whether the thymidine analogue 3′-deoxy-3′ [18F]fluorothymidine ([18F]FLT) is adequate for early evaluation of the response of malignant lymphoma to antiproliferative treatment in a mouse xenotransplant model. Methods Immunodeficient mice bearing a follicular lymphoma xenotransplant were treated with high-dose chemotherapy
(cyclophosphamide, n=10), immunotherapy (CD20mAb, ibritumomab-tiuxetan, n=10) or radioimmunotherapy ([90Y]CD20 mAb, Zevalin, n=10). Forty-eight hours after treatment, antiproliferative effects were assessed with [18F] FLT. Ninety minutes after i.v. injection of 5–10 MBq [18F] FLT, mice were sacrificed and radioactivity within the tumour and normal organs was measured using a gamma counter and calculated as % ID/g. The proliferation fraction in tissue samples derived from treated and untreated tumours was evaluated by Ki-67 immunohistochemistry, which served as the reference for proliferative activity. Results In untreated lymphoma, the mean proliferation fraction was 83.6%. After chemotherapy, the mean proliferation fraction decreased to 39.3% (p=0.0001), after
immunotherapy to 77.6% (p=0.0078) and after radioimmunotherapy to 78.8% (p=0.014). In none of the
animals was a significant change in tumour size observed. In untreated lymphoma, tumoural [18F]FLT uptake was 5.4% ID/g, after chemotherapy it was 1.5% (p=0.0005), after immunotherapy, 3.9% (non-significant), and after radioimmunotherapy, 5.8% (non-significant). Conclusion In a lymphoma xenotransplant model, [18F] FLT detects early antiproliferative drug activity before changes in tumour size are visible. These findings further support the use of [18F]FLT-PET for imaging early response to treatment in malignant lymphoma.

Glioma Proliferation as Assessed by 31-Fluoro-31-DeoxY-l-Thymidine Positron Emission Tomography in Patients with Newly Diagnosed High-Grade Glioma

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Clin Cancer Res 2008;14(7) April1. 2008

Purpose: The aim of this study was to investigate the relationship between the *in vivo* derived kinetic parameters of 3'-deoxy-3'_18F-fluorothymidine C8F-FLT) and the proliferation rate measured *in vitro* by Ki-67 staining in patients with newly diagnosed high-grade gliomas. Experimental Design: Thirteen patients with newly diagnosed high-grade gliomas were investigated with 18F-FLTand *methyl-"C-* L-methionine ("C-MET) positron emission tomography (PET) and T1-, Gd-T1-, and T2-weighted magnetic resonance imaging on consecutive days. Tracer kinetic parameters of 18F-FLTas well as the standardized uptake value and the tumorto-background (T/B) ratio of 18F-FLTand 11C-METwere determined. Data of kinetic modeling, standardized uptake value, and T/B values derived from 18F-FLT-PET were compared with T/B values derived from 11C-MET-PETand to the *in vitro* proliferation marker Ki-67.
Results: A significant correlation was observed between the metabolic rate constant Ki and the proliferation index as measured by Ki-67 immunostaining [Ki, r = 0.79 *(P* = 0.004)]. Also, the phosphorylation rate constant k3 correlated with Ki-67 [k3, r = 0.76 *(P* = 0.006)], whereas the rate constant for transport through the blood brain barrier K1showed a weaker correlation with

Ki-67 [K1. r = 0.62 *(P* = 0.044)]. No significant correlation between I1C-METand 18F-FLTuptake ratios and Ki-67 was observed.

Conclusions: This study shows that kinetic analysis of 18F_FLTtracer uptake is essential for the *in vivo* assessment of tumor proliferation in high-grade gliomas, whereas uptake ratios of I1C-MET and 18F_FLTfailed to correlate with the *in vitro* determined proliferation marker. Thus, kinetic analysis of 18F_FLT might provide an accurate method for the assessment of early response to glioma treatment in the future.

Imaging of Cell Proliferation: Status and Prospects

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The Journal of Nuclear Medicine• Vol. 49 • No. 6 (Suppl) • June 2008

Increased cellular proliferation is an integral part of the cancer phenotype. Several in vitro assays have been developed to measure the rate of tumor growth, but these require biopsies, which are particularly difficult to obtain over time and in different areas of the body in patients with multiple metastatic lesions. Most of the effort to develop imaging methods to noninvasively measure the rate of tumor cell proliferation has focused on the use of PET in conjunction with tracers for the thymidine salvage pathway of DNA synthesis. because thymidine contains the only pyrimidine or purine base that is unique to DNA. Imaging with I1C-thymidine has been tested for detecting tumors and tracking their response to therapy in animals and patients. Its major limitations are the short half-life of 11C and the rapid catabolism of thymidine after injection. These limitations led to the development of analogs that are resistant to degradation and can be labeled with radionuclides more conducive to routine clinical use. such as 18F. At this point, the thymidine analogs that have been studied the most are 3' -deoxy-3' fluorothymidine (FLT) and 1-(2' -deoxy-2' -fluoro-1¡ 3-D-arabinofuranosyl)-thymine (FMAU). 80th are resistant to degradation and track the DNA synthesis pathway. FLT is phosphorylated by thymidine kinase 1. thus being retained in proliferating cells. It is incorporated by the normal proliferating marrow and is glucuronidated in the liver. FMAU can be incorporated into DNA after phosphorylation but shows less marrow uptake. It shows high uptake in the normal heart, kidneys. and liver. In part beca use of the role of mitochondrial thymidine kinase 2. Early clinical data for 18F-FLT demonstrated that its uptake correlates well with in vitro measures of proliferation. Although 18F_ FLT can be used to detect tumors, its tumor-to-normal tissue contrast is generally lower than that of 18F-FDGin most cancers outside the brain. The most promising use for thymidine and its analogs is in monitoring tumor treatment response. as demonstrated in animal studies and pilot human trials. Further work is needed to determine the optimal tracer(s) and timing of imaging after treatment.

Imaging early changes in proliferation at 1 week post chemotherapy: a pilot study in breast cancer patients with 3′-deoxy-3′-[18F]fluorothymidine positron emission tomography.

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Eur J Nucl Med Mol Imaging (2007) 34:1339–1347

Purpose 3′-Deoxy-3′-[18F]fluorothymidine positron emission tomography ([18F]FLT-PET) has been developed for imaging cell proliferation and findings correlate strongly with the Ki-67 labelling index in breast cancer. The aims of this pilot study were to define objective criteria for

[18F] FLT response and to examine whether [18F]FLT-PET can beused to quantify early response of breast cancer tochemotherapy.
Methods Seventeen discrete lesions in 13 patients withstage II–IV breast cancer were scanned prior to and at1 week after treatment with combination 5-fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy. The uptake at 90 min (SUV90) and irreversible trapping (Ki) of [18F]FLT were calculated for each tumour. Thereproducibility of [18F]FLT-PET was determined in ninediscrete lesions from eight patients who were scanned twice before chemotherapy. Clinical response was assessed at 60 days after commencing FEC. Results All tumours showed [18F]FLT uptake and this was reproducible in serial measurements (SD of mean % difference = 10.5% and 15.1%, for SUV90 and Ki, respectively; test–retest correlation coefficient ≥0.97). Six patients had a significant clinical response (complete or partial) at day 60; these patients also had a significant reduction in [18F]FLT uptake at 1 week. Decreases in Ki and SUV90 at 1 week discriminated between clinical response and stable disease (p=0.022 for both parameters). In three patients with multiple lesions there was a mixed [18F]FLT response in primary tumours and metastases. [18F] FLT response generally preceded tumour size changes. Conclusion [18F]FLT-PET can detect changes in breast cancer proliferation at 1 week after FEC chemotherapy.

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En la elaboración de esta información se ha tenido en consideración la publicación de la Sociedad Española de Medicina Nuclear "Propuesta de la SEMN para la aprobación de indicaciones de radiofármacos PET por la vía del uso compasivo". Cristina Asencsio, Antonio Cabrera, y cols. – SEMN. Madrid, febrero 2009