and what further benefit may be seen in future years. In addition, the talk will consider developments with gamma camera and other dedicated single photon detectors, such as dedicated cardiac imaging cameras, discussing how improvements may affect the future of Nuclear Medicine.

OP393
PET/CT Instrumentation and Methods

T. Beyer (CH)

1102 - Tuesday, October 13, 2009, 08:00 - 09:30, Hall 112

Symposium 10: Current tools and needs for clinical neuroimaging

OP394
Partial Volume Effect correction reduces multi-centre variability in dopaminergic SPECT quantification.

P. Payoux[1], P. Gantet[1], E. Itti[2], P. Zanotti Fregonara[3], A. Kas[4], M. O. Habert[4], J. P. Esquerré[1]; [1]Purpan University Hospital, Toulouse, FRANCE, [2]Henri Mondor university hospital, Créteil, FRANCE, [3]SHFJ, Orsay, FRANCE, [4]Pitié Salpêtrière university hospital, Paris, FRANCE.

Objectives: In SPECT, the quantification of small volume structures such as striata, is mainly affected by the partial volume effect (PVE). The importance of PVE is directly related to the spatial resolution of the imaging system. The result of the quantification of the binding potential (BP) (specific / nonspecific) varies for the same patient with a camera to other. The objective of this prospective study was to assess the variability of the quantification of BP with and without correction of the PVE, between different centers for the same population of healthy subject. Materials and methods Eight subjects (age 60 ± 3.25 years) were included. All underwent 3 different DaTSCAN procedure on 3 different sites (cameras, reconstruction methods and different spatial resolution). For quantification we used the software Neurotrans3D, Segami ©. This software quantifies dopaminergic activity in the striata by using a 3D striatal deformable anatomical template (SDT). Two manual transformations can be applied to deform this template for easy application to each patient, without changing the ROIs volumes of the template. The NeuroTrans3D software uses a PVE correction based on the technique proposed by Rousset et al. [1]. The FWHM of the PSF used in the PVE correction must be determined to calibrate the NeuroTrans3D software in function of the whole imaging system. The FWHM was determined using a striatal phantom (Radiology Support Devices Inc. Long Beach CA). This software provides BP value for each caudate and putamen with and without PVE correction . Results For each system of the 3 different centers, FWHM was equal to 9.7, 11.5 and 12 mm respectively. The PVE correction increases the striatal BP by a factor ranging from 2 to 3.8 for the area considered (caudate or putamen). For each area of striatum of each patient the correction of PVE reduces differences between sites. The average difference was 11.7% without correction, and 4.9% with correction. The improvement due to the correction of PVE was statistically significative (Wilcoxon test, p <0.0001). Conclusions Correction of PVE not only improves the quality of quantification but also reduces the inter-centre variability. [1] Rousset, O., et al., Correction for partial volume effect in PET : principles and validation. Journal of Nuclear Medicine., 1998. 39(5): p. 904-911.

OP395
Voxel by voxel analysis in clinical perfusion and metabolism

A. Drzezga (GE)

OP396
Construction and Use of Atlas Image Databases

A. Hammers, R. A. Heckemann; Fondation Neurodis, Lyon, FRANCE.

Defining volumes of interest (VOI) within the human brain is a prerequisite for many types of analysis. These include morphometric measurements as well as statistically describing the signal inside the VOI, be it within the image used for defining the VOI itself (usually structural MRI) or in an image which is in register (e.g. PET, SPECT, fMRI). Similarly VOIs can be used to define seed points for DTI measures. The gold standard for defining VOIs remains manual delineation by an expert. However, training of experts and manual delineation itself are time consuming, repetitive, and not scalable for modern image repositories which can contain hundreds or thousands of scans. An alternative to manual delineations are automatic VOI definitions. Since the early 1980s, single subject labelled datasets ("atlases") have been registered with unseen images for this purpose. Such methods are intrinsically limited by intersubject neuroanatomical differences: a single atlas never captures the variability in unseen datasets. Registration via intermediate datasets improves the accuracy of single-subject methods (Collins DL et al. 1999) but is inferior to using single atlases concatenating information from multiple subjects (the "maximum probability map" approach, Hammers A, Allom R et al., 2003). Both approaches are vastly outperformed by individually registering multiple atlases to an unseen target and choosing the atlas label with the highest probability in target space (Rohlfing T et al. 2004, Heckemann RA et al. 2006). Large data bases containing multiple atlases with multiple regions are now becoming available (e.g. Heckemann RA et al. 2006, Gousias IS et al. 2008, Shattuck DW et al. 2008). Differences in the quality of the underlying manual segmentations influence the quality of automatic segmentations (e.g. Klein A et al. 2005). The type of registration between the structural scans underlying the atlases plays a major role for segmentation outcome. While there is no point-to-point correspondence between brains, registration methods using non-rigid mapping and large numbers of degrees of freedom outperform simpler methods (reviewed by Klein A et al. 2009). Multi-atlas methods have been successfully used for screening for pathology (Hammers A et al. 2007) and decision support in radiology (Heckemann RA et al. 2008). Finally, it is possible to "fine-tune" segmentation methods to perform particularly well for a given structure. Such methods can perform better than multi-atlas registration methods (e.g. Chupin M et al. 2009, van der Lijn F et al. 2008) but have yet to be extended to whole-brain anatomical segmentations.

OP397
Ictal SPECT in the presurgical evaluation of refractory partial epilepsy

W. Van Paesschen; UZ Leuven, Leuven, BELGIUM.

Epilepsy is a common chronic neurological disorder that is controlled with medication in around 70% of cases. When partial seizures are recurrent despite anti-epileptic drugs, resection of the epileptogenic cortex may be considered. Single photon emission computed tomography (SPECT) is used to determine the seizure onset zone, which needs to be resected in order to render a patient seizure free. Correct localization of the ictal onset zone using SPECT is associated with a better surgical outcome. Ictal perfusion SPECT imaging using ^{99m}Tc-ethyl cysteinate dimer (ECD) or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) is able to detect the seizure onset zone in a majority of cases, especially in patients with temporal lobe epilepsy. Interictal SPECT imaging, which is more widely available, is unreliable to determine the ictal onset zone and is usually only used for comparison with ictal SPECT images. Assessment of the ictal onset zone using subtracted ictal and interictal studies, overlayed on structural imaging (SISCOM) has proven to be more sensitive and more specific compared to visual assessment. Video-electroencephalography (EEG) monitoring in combination with ictal SPECT imaging, however, is only available in specialized centers. It is important to inject the perfusion tracer as early as possible after the beginning of a seizure and to be aware of patterns of seizure propagation. Propagation patterns typically present as hyperperfusion clusters connected through small trails of hyperperfusion, giving an hour-glass appearance. The largest hyperperfusion cluster with the highest z-score often represents ictal propagation. Full resection of the SISCOM hyperperfusion cluster is usually not required to render a patient seizure free. In conclusion, ictal SPECT is a highly accurate imaging technique in defining brain regions involved in ictal activity. Due to the poor time-resolution of SPECT versus the electrophysiological changes in seizures, ictal SPECT often shows both the ictal onset zone and seizure propagation pathways. A correct interpretation of the ictal SPECT images, therefore, requires knowledge of the results of the full presurgical evaluation. The logistics of ictal SPECT are elaborate and require optimal collaboration between neurologists and nuclear medicine physicians, and explain why ictal SPECT is used in a limited number of centres.

1201 - Tuesday, October 13, 2009, 10:00 - 11:15, Hall 211/212

Plenary 3: Neuroendocrine tumours

OP399
SPECT and PET Imaging of Neuroendocrine Tumours

S. Fanti; Policlinico S.Orsola, Bologna, ITALY.

Nuclear Medicine procedures have been used with great success for studying Neuroendocrine Tumours (NET). Several SPECT and PET tracers were found useful for evaluation of NET, allowing to image different characterisctics of these neoplasms. MIBG was the first radiopharmaceutical used to identify and localize NET, and in particular tumours secreting catecholamine; MIBG SPECT can still be considered as first-choice imaging technique for diagnosis and follow-up of pheochromocytomas, paragangliomas, and neuroblastomas. Tracers based on radiolabelled somatostatin analogs were introduced to study NET expressing a high density of somatostatin receptors (SSR) and gained a widespread acceptance, especially for NET arising in the gastro-entero-pancreatic district. SSR SPECT is currently used routinely for studying carcinoids and other NETs, and in particular for localizing primary tumor, staging at presentation, evaluating relapse or disease extension, monitoring the effect of treatment and selecting patients for therapy. PET tracers were introduced more recently for the imaging of NET. FDG is not well suited for studying NET, as most NET shows a faint uptake of FDG, as glycolisis is significantly increased only in poorly differentiated NET, usually rapidly growing and highly aggressive; therefore a role for FDG PET may be suggested only for prognostic evaluation, in case of aggressive NET tumours. Other tracers have been developed to evaluate the different metabolic pathways of NETs, such as F-DOPA, C-HTP and C-HED, with good results in various NET (C-HTP in pheochromocytomas and paragangliomas, C-HTP in carcinoids, F-DOPA in almost all NETs). However these tracers are still not widely used for difficult and expensive production, limiting the diffusion of these approaches.SSR PET tracers have also been recently developed, mainly labelled with 68Gallium, and are increasingly used in many centers in Europe for PET/CT imaging. The advantages of these PET radiopharmaceuticals, as compared to SSR SPECT radiotracers, are better spatial resolution, reduced patient exposure and lower costs. Therefore they are rapidly gaining interest for the high diagnostic sensitivity especially in gastro-enteropancreatic NETs and paraganglioma, but problems remains for the regulatory issues related with the routine use of these tracers.

OP400
Radionuclide Therapy

I. Virgolini; Department of Nuclear Med., Med. Univ. Innsbruck, AUSTRIA.

Above all, the highly variable natural course of neuroendocrine tumours (NETs) should always be considered. Today, there can be no doubt about the wide therapeutic index and high efficacy of somatostatin (SST) analogues for symptomatic management. In addition, the results of peptide receptor related therapy (PRRT) with long-acting SST analogues indicate that these molecular therapies have its place in the treatment of NET for size reduction, improvement of quality of life and overall prognosis. Serious side effects are rare, especially in combination with amino acids for kidney protection. Patients should always be evaluated by proceeding SSTR scintigraphy and dosimetry using respective octreotide or lanreotide analogues, preferably the ^{68}Ga-labelled ones for PET. ^{18}FDG-PET scanning shows a poor sensitivity to detect NETs with a low metabolic activity and slow growth rate, while together with the ^{68}Ga-labelled SST-analogues ^{18}FDG-PET has clinical potential for the restaging of patients undergoing PRRT. Since 1997 Innsbruck has treated patients with either ^{90}Y-DOTA-lanreotide or ^{90}Y-DOTA-TOC. The 2009 treatment schedule foresees 3-5 cycles (3.7 GBq, 10 weeks interval, long-acting SST analogs in between) given under kidney protection with amino acids up to a cumulative kidney dose of 30 Gy. Restaging is done

with ^{68}Ga-DOTA-TOC-PET and ^{18}F-FDG PET, and repeated dosimetry with ^{111}In-DOTA-TOC. ^{177}Lu-DOTA-TOC is given to patients with smaller sized tumours (7.4 GBq, 10 weeks interval, long-acting SST analogs in between), or to patients with progressive disease pretreated with ^{90}Y-DOTA-SST analogs, after at least a 6 months follow-up period. The response rates to PRRT are about 50% stabilization and 25% partial remission or minor response. Long-term follow-up (10 years) indicate the therapeutic potential in NETs treated with different SST analogs over time. In general, there is a need for randomized trials in order to establish which treatment scheme and which radiolabelled SST analogue, or combination of analogues, is optimal for PRRT. There is evolving also a great demand on multi-institutional trials on the concomitant use of molecular therapeuticals, whereas the availability of adequate facilities, legislation, are restricting the progress. One of the major problems is still the availability of these radiopeptides in general, and the request for new and cheaper therapeutic radionuclides in particular. For certain tumour entities ^{131}I-mIBG therapy is appropriate, and combination therapies with PRRT are discussed. The future treatment of NETs will be more individualized where the tumour biology and molecular genetics play a major role.

OP401
Dosimetry in Radiopeptide Therapy

M. Cremonesi; European Institute of Oncology, Milano, ITALY.

Peptide Receptor Radionuclide Therapy (PRRT) has proven efficacy for patients with somatostatin receptor expressing tumours. Promising results have been obtained, especially with ^{177}Lu- and ^{90}Y-peptides. Possible renal impairment represents the principal side effect, while haematological toxicity is usually low. The large patient variability of tumour and non-target organ uptake, which emerged from clinical trials, sustains the need of reliable dosimetry for tailored therapy, with improved safety and efficacy. Different dosimetry methods, practical or sophisticated, can be applied depending on purposes and technological availability. Input data set includes blood/urine samples, and scintigraphic images, adequately scheduled up to almost 3 days. Planar images, not ideal, may be useful to derive biokinetics over the time, while SPECT and SPECT/CT fused images, although time-consuming, offer detailed intra-organ activity distribution. The MIRD scheme represents the reference formalism for internal dosimetry. Dedicated software (OLINDA/EXM) has been used to derive mean absorbed dose estimates for ^{177}Lu- and ^{90}Y-peptides, based on standard kinetic models, several phantoms, multiregional organs, and possible patient-specific adjustments. To improve accuracy towards a real patient-specific dosimetry, methods may be refined by including actual organ shape and size, inhomogeneous activity distributions, and Monte Carlo simulations. Other aspects besides the mean absorbed doses influence the biological effects, improving the predictivity of dosimetry as regards immediate, delayed or chronic toxicity. In facts, specific tissue radiosensitivity, dose-rate, detailed intra-organ activity distribution, multi-cycle schemes, and also associated risk factors, have been shown to affect the specific tissue response of tumours and irradiated organs (the kidneys, in particular). Addressing the linear quadratic radiobiological model to PRRT, a correlation between the Biological Effective Dose (BED) evaluated in kidneys and renal toxicity has been found for patients treated with ^{90}Y-peptides. Results are similar to the dose(BED)-effect curve obtained in external beam radiation therapy. These findings in PRRT have encouraged sharing information from different therapies and enlarging the study of surviving fraction (SF), normal tissue control probability (NTCP), and tumour control probability (TCP) curves. A further issue to be deepened is the possible influence of inhomogeneous dose distribution, especially in kidneys and tumours. An important contribute can be provided by the voxel dosimetry, allowing to depict dose and BED volume histograms, the correspondent SF, and the Equivalent Uniform Biologically Effective Dose (EUD).

1301 - Tuesday, October 13, 2009, 11:30 – 13:00, Hall 211/212

CME 10: LUNG (Interactive): The Role of Nuclear Medicine in Pulmonary Disease: Embolism, Inflammation and Infection, Cancer

OP402
Embolism

M. Bajc (SE)

OP403
Inflammation/Infection

J. Buscombe (UK)

OP404
Cancer

M. Farsad (IT)

1302 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 112

Symposium 11: Advances in Cardiac PET-CT

OP405
Assessment and quantification of myocardial perfusion

G. Sambuceti (IT)

OP406
Assessment of myocardial metabolism with PET

P. G. Camici; Imperial College - Hammersmith Campus, London, UK.

A number of positron labelled tracers has been developed for the noninvasive assessment of myocardial metabolism in humans. The positron-emitting radionuclides of the biologically ubiquitous elements oxygen (^{15}O), carbon (^{11}C), and nitrogen (^{13}N), as well as fluorine (^{18}F) substituting for hydrogen, can be incorporated into a wide variety of substrates or substrate analogs that participate in diverse metabolic pathways without altering the biochemical properties of the substrate of interest. These ligands enable the assessment of different metabolic processes including free fatty acid metabolism (^{11}C-palmitate and ^{11}C-acetate), oxygen metabolism ($^{15}O_2$ and ^{11}C-acetate) and glucose utilization (^{18}F-fluorodeoxyglucose and ^{11}C-glucose). The short physical half-life of the positron emitting radionuclides facilitates the performance of sequential studies with a favorable radiation exposure to the subject when compared with conventional single photon radionuclides. Accordingly, some of these tracers have been used in combination to probe more than one metabolic pathway simultaneously. The similarity of positron emitters with their non radioactive equivalents means that the labelled products are chemically and biochemically almost identical to the original compounds and therefore the information gained using the radiolabelled compounds reflects accurately that of the original non labelled molecules. By combining the knowledge of the metabolic pathways of interest with kinetic models that carefully describe the fate of the tracer in myocardial tissue and blood, an accurate interpretation of the tracer kinetics as they relate to the metabolic process of interest can be achieved. Exploiting the PET detection scheme which permits accurate quantification of activity in the field of view with appropriate kinetic models it is therefore possible to quantify the metabolic parameters (e.g. µmol/g/min). Most of these tracers have been used for pathophysiological studies and only ^{18}F-fluorodeoxyglucose is used routinely in clinical practice for studying myocardial viability.

OP407
PET-CT: a new opportunity for cardiac application

M. Hacker; University of Munich, Munich, GERMANY.

Appropriate diagnosis and therapy of coronary artery disease (CAD) frequently require information about both the morphological and functional status of the coronary artery tree. Thus, combined imaging consisting of invasive coronary angiography (ICA) plus myocardial perfusion imaging (MPI) is practiced in clinical routine diagnostic of patients with stable angina since many years and can therefore be accepted as the reference standard in the diagnosis of hemodynamically relevant coronary artery stenoses. Both morphological and functional information are mandatory for the decision of performing an interventional therapy or initiating/maintaining medical treatment in numerous symptomatic patients. The hemodynamically relevance of coronary artery lesions is a major condition to decide whether an interventional therapy should be performed or not. A non-invasive concept providing both information could provide accurate allocation of perfusion defects to their determining coronary lesion and specific morphological and functional classification of patients with coronary artery disease. Myocardial perfusion PET with ^{13}N-ammonia or ^{82}Rb has shown high sensitivity and specificity in the detection of coronary artery stenoses and has shown superior compared to SPECT due to a higher accuracy and the opportunity to provide absolute quantification data. In addition, PET/CT scanners are widely available, attributable primarily to the technology's widely accepted role in clinical oncology, so that CT attenuation correction and calcium scoring can simply be performed. There are also initial data, showing the feasibility of combined PET/CT angiography as an alternative non-invasive concept in clinical decision making and therapy planning of coronary artery disease. Additionally, the implementation of coronary calcium scoring to ^{82}Rb perfusion PET has shown incremental prognostic value as compared to perfusion PET alone. In Europe, however, ^{82}Rb is not yet regulary distributed and ^{13}N-ammonia requires an in-house cyclotron, which is not available in most sites. Otherwise, PET/CT has great potential for extended myocardial viability diagnostics in patients with more advanced stages of CAD leading to severely reduced left ventricular function. ^{18}F-FDG, mostly in combination with SPECT perfusion techniques, is widely accepted as a gold standard in myocardial viability diagnostics and has proven powerful in the prediction of left ventricular function recovery after both revascularisatioin and resynchronisation therapy (CRT). In combination with CT angiography, a "viablility one-stop-shop" could be a possible option. In addition, coronary veins can be displayed during CT angiography, which in combination with FDG "scar mapping" could be helpful for planning CRT lead positioning or guiding myocardial ablation therapies.

OP408
Molecular and receptor imaging

F.M. Bengel (USA)

1303 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 111

Featured: new PET tracers

OP409
Invited Talk

P. Schubiger (CH)

OP410
Development of an improved amyloid probe, [^{11}C]AZD2184. From pre-clinical to clinical in vivo PET measurements in AD patients

J. Andersson[1], K. Varnäs[1], Z. Cselényi[2], B. Gulyás[1], B. Swahn[3], S. Finnema[1], S. Nyberg[2], L. Farde[2], C. Halldin[1]; [1]Karolinska Institutet, Stockholm, SWEDEN, [2]AstraZeneca Pharmaceuticals Neuroscience Clinical, Södertälje, SWEDEN, [3]Department of Medicinal Chemistry AstraZeneca R&D, Södertälje, SWEDEN.

High levels of white matter retention limits the utility of currently used amyloid PET tracers (e.g. [^{11}C]PIB). AZD2184 (2-(6-(methylamino)pyridin-3-yl)benzo[d]thiazol-6-ol), has shown an improved signal to noise window due to lower background binding compared to PIB in autoradiography studies using tritiated compounds (Johnson et al. 2009). **Aim:** To label AZD2184 with carbon-11 and perform in vivo PET characterization in cynomolgus monkeys and Alzheimer's patients. **Materials and methods:** [^{11}C]AZD2184 was prepared by a two step radiosynthesis starting with the reaction of 5-(6-(tert-butyldimethylsilyloxy)benzo[d]thiazol-2-yl)pyridin-2-amine with [^{11}C]methyl iodide followed by deprotection of the tert-butyldimethylsilyl group (Gravenfors et al. 2007). Four brain PET measurements in two cynomolgus monkeys and one whole body dosimetry study were performed with [^{11}C]AZD2184. Preliminary clinical PET evaluation of the radioligand was carried out in AD patients. **Results:** The total synthesis time of [^{11}C]AZD2184 was 33 minutes with a specific radioactivity of 1643-3371 GBq/umol at EOS and a radiochemical purity >99%. The distribution of brain radioactivity in cynomolgus macaque was fairly uniform, with early to late brain concentration ratios (peak vs 60 min.) significantly higher for [^{11}C]AZD2184 than reported [^{11}C]PIB values (Mathis et al. 2003) (8.2 and 4.6 respectively), indicating low levels of white matter retention. Metabolism of [^{11}C]AZD2184 was fast with less than 10% remaining in the plasma 15 minutes after administration. Whole body dosimetry in cynomolgus macaque indicated that an effective dose in an adult male would be 6.2 μSv/MBq. Summation images from AD patients clearly visualize high brain uptake of [^{11}C]AZD2184 mainly in cortical regions, while a homogenuos uptake and a fast washout was evident in young control subjects. **Conclusion:** [^{11}C]AZD2184 shows a pre-clinical and clinical profile that suggests an improved signal in PET compared to currently used radiotracers. **References:** • Johnson, A. E., Jeppsson, F., Sandell, J., Wensbo, D., Neelissen, J. A. M., Juréus, A., Ström, P., Norman, H., Farde, L., Svensson, S. *P. S. J. Neurochem.* 108: 1177-86, 2009. • Gravenfors, Y.; Jonasson, C.; Malmström, J.; Nordvall, G.; Pyring, D.; Slivo, C.; Sohn, D.; Ström, P.; Wensbo, D. *Int. PCT Appl.* WO 2007086800. • Mathis, C. A., Wang, Y., Holt, D. P., Huang, G. F., Debnath, M. L., Klunk. W. E. J *Med Chem* 46(13): 2740-54, 2003.

OP411

Synthesis and preliminary biological evaluation of [^{18}F]JNJ41510417as a radioligand for positron emission tomography imaging of phosphodiesterase-10A in the brain

S. Celen[1], M. De Angelis[2], S. K. Chitneni[3], J. Alcazar[2], M. Koole[4], S. Dedeurwaerdere[5], T. Steckler[5], M. Schmidt[5], K. Van Laere[4], A. Verbruggen[1], X. Langlois[5], J. I. Andrés[2], G. Bormans[1]; [1]KULeuven,Laboratory for Radiopharmacy, Leuven, BELGIUM, [2]Johnson & Johnson Pharmaceutical Research & Development, Toledo, SPAIN, [3]Duke University Medical Center, Durham, NC, UNITED STATES, [4]KU Leuven, Nuclear Medicine, Leuven, BELGIUM, [5]Johnson & Johnson Pharmaceutical Research & Development, Beerse, BELGIUM.

Aim. PDE10A (phosphodiesterase-10A) inhibitors hold potential for treating neurological and psychiatric disorders like schizophrenia. We have synthesized and evaluated [^{18}F]JNJ41510417 as a positron emission tomography (PET) tracer for in vivo quantification of PDE10 in brain. **Materials & Methods**. [^{18}F]JNJ41510417 was synthesized via direct nucleophilic substitution of the O-mesylated precursor with [^{18}F]fluoride in DMF at 90 °C, followed by purification using semi-preparative high-performance liquid chromatography (HPLC). The biodistribution of the tracer in rats was evaluated at 2, 30 and 60 min post injection. Rat plasma, cerebrum and cerebellum homogenates were analysed by HPLC to quantify radiometabolites. Dynamic imaging after injection of [^{18}F]JNJ41510417 in rats and PDE10 knock-out mice was performed on a FOCUS 220 microPET scanner (Siemens). Blocking and displacement experiments were done by subcutaneous or intravenous injection of cold JNJ41510417 and other compounds with known affinity for PDE10. Image analysis was done using PMOD v2.9 software. Uptake in brain slices of knock-out mice was visualized using autoradiography (Cyclone, Perkin Elmer). **Results**. [^{18}F]JNJ41510417 was obtained with a radiochemical yield of 14 %, a radiochemical purity of >99 % and a specific activity of 320 GBq/μmol. Tissue distribution studies showed a steadily increasing uptake of the tracer in striatum over time, while there was a clear wash-out of non-specific binding from other brain regions. Polar metabolites were detected in plasma and in brain. Dynamic microPET imaging showed high intensity signal in striatum (peak max time 100 min p.i.) with only background radioactivity in the cortical regions as well as in cerebellum. Pretreatment of the rats with PDE10A inhibitors resulted in a significant decrease in striatum-to-cerebellum ratio from ~5 (baseline) to <2 (pretreatment). After injection of the chase compounds, the activity in striatum was washed out rapidly with a significant reduction in striatum-to-cerebellum ratio from ~3 to <1.5. Imaging and autoradiography in PDE knock-out and wild-type mice showed uptake only in the wild-type brain. Binding to wild-type striatum was about 30 times higher compared to knock-out striatum. **Conclusion**. Experiments in rats and PDE10 knock-out mice indicate that [^{18}F]JNJ41510417 binds specifically and reversibly to PDE10 in striatum, strongly suggesting that this new fluorinated quinoline derivative is a promising candidate for in vivo imaging of PDE10 using PET.

OP412

11C-Phenethyl-Orvinol: A Full Agonist Diprenorphine Analogue for PET-Imaging of Opioid Receptors

J. Marton[1], **B. W. Schoultz[2],** T. Hjørnevik[3], A. Drzezga[4], H. J. Wester[4], F. Willoch[3], G. Henriksen[4]; [1]ABX advanced biochemical compounds Biomedizinische Forschungsreagenzien GmbH, Radeberg, GERMANY, [2]Department of Chemistry, University of Oslo, Oslo, NORWAY, [3]Centre for Molecular Biology and Neuroscience & Institute of Basic Medical Sciences, University of Oslo, Oslo, NORWAY, [4]Klinikum rechts der Isar, Technische Universität München, München, GERMANY.

Aim: Investigations of structurally matched opioid agonist/antagonist pairs could clarify whether the agonist provides superior sensitivity for quantification of receptor occupancy. We here report on the synthesis and characterisation of [11C]phenethyl-orvinol ([11C]PEO), an agonist radiotracer which is structurally related to the μ-antagonist diprenorphine and the partial μ-agonist buprenorphine. Material&Methods: [11C]PEO was obtained by reacting the corresponding 3-O-trityl-6-O-desmethyl-precursor with [11C]MeI. Inhibition constants and agonist potency for PEO-binding to cloned human opioid receptors were determined. The regional brain distribution of [11C]PEO was investigated in vivo with PET and in ex vivo studies. Results: PEO binds with high affinity binding to κ-OR (Ki=0.12±0.08 nM) and μ-OR (Ki= 0.18±0.06 nM), and with moderate affinity to δ-OR (Ki=5.1±0.6 nM). PEO has 105 and 113 % of the potency of the full agonists DAMGO (μ-OR) and U69593 (κ-OR), respectively. The initial uptake of [11C]PEO in the brain of rats was high, ranging from 0.82±0.02% in the frontal cortex to 0.67±0.03 % in the cerebellum at 5 min after injection. The ratio of radioactivity in striatum, thalamus and frontal cortex to that in the cerebellum, which can be used as a measure of specific binding, was in the range 2.95±0.18-3.78±0.22 and 4.47±0.23-5.23±0.27 at 20 and 60 min p.i., respectively. When rats were treated with the μ-antagonist Cyprodime (2 mg/kg, i.v.) 10 min before the injection of [11C]PEO and sacrificed 20 min after, specific binding of the radioligand in the striatum, thalamus and frontal cortex was reduced by 86, 84 and 82% compared to the control group. On the other hand, when the rats were treated with Salvinorine A, a κ-OR selective agonist at a dose of 2 mg/kg, the binding of the [11C]PEO in striatum, thalamus and frontal cortex was reduced by only 5, 7 and 11 %, respectively. Micro-PET imaging experiments in vivo in rats confirmed the rapid brain entry of [11C]PEO as well as its uptake in brain regions containing a high concentration of the μ-OR. Conclusions: We have provided a 11C-labelled orvinol which has a saturable and μ-OR selective binding in rat brain. A study on the sensitivity of 11C-PEO for detecting changes to the availability of μ-OR is in progress.

OP413

[18F]FE@SUPPY - the first PET tracer for the Adenosine A3 receptor

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Aim: Changes of the adenosine A_3 receptor (A3R) expression have been shown in neurological and affective disorders, cardiac and oncological diseases and inflammation processes. However, so far there are no reliable data on absolute amounts of receptor protein. The state of the art method for visualization and quantification of receptor systems in-vivo is PET. 5-(2-fluoroethyl)2,4-diethyl-3-(ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate (FE@SUPPY) was recently presented as a high affinity ligand (K_i 4.22nM) displaying good selectivity (ratio 2700 A1R/A3R) for the A3R. Thus, we developed and evaluated [^{18}F]FE@SUPPY as the first PET tracer for the A3R. **Materials and Methods:** A suitable labeling precursor, 5-(2-tosyloxyethyl)2,4-diethyl-3-(ethylsulfanylcarbonyl)-6-phenylpyridine-5-carboxylate (Tos@SUPPY) and the reference standard compound, FE@SUPPY, were synthesized. Radiosynthesis of [^{18}F]FE@SUPPY was conducted in a one-pot reaction and for ex vivo biodistribution studies male Sprague-Dawley rats were used. In-vitro metabolic stability studies were conducted using carboxylesterase and samples were analyzed by HPLC. For ex-vivo metabolic stability experiments, male wild-type rats were injected with [^{18}F]FE@SUPPY and sacrificed after various time points. Brains were removed, blood was collected and samples were analysed by radio-HPLC. In-vitro autoradiography was performed on rat and human brain slices and compared with [^{125}I]AB-MECA. Finally, micro-PET experiments were conducted in rats. **Results:** Starting from 49.2±13.9GBq [^{18}F]fluoride, 8.9±4.0GBq of [^{18}F]FE@SUPPY (34.9±14.8%, specific radioactivity 60.8±18.0GBq/μmol) were achieved. Organ with highest uptake was liver (1.41±0.57% I.D./g, 30min). Tissues with lowest uptake were colon and testes. Intermediate brain uptake was observed throughout the examined time span. Carboxylesterase studies showed a K_m of 20,12μM and a V_{max} of 0.038μM/min. In blood samples we found one hydrophilic radioactive metabolite coeluting with fluoroethanol. In brain, no metabolites were found. Autoradiographic studies showed a radioactivity distribution mainly matching the described mRNA-distribution pattern of the A3R. Blocking experiments confirmed high selectivity and specificity of [^{18}F]FE@SUPPY towards the A3R. Autoradiographic studies showed that [^{18}F]FE@SUPPY displayed a different uptake pattern compared to [^{125}I]AB-MECA. Micro-PET experiments displayed high uptake in fat-rich regions and medium uptake in brain. **Conclusion:** [^{18}F]FE@SUPPY was prepared with yields and radiochemical purities sufficient for preclinical and routine clinical applications and binding of [^{18}F]FE@SUPPY was selective and specific. Therefore [^{18}F]FE@SUPPY, the first PET tracer for the Adenosine A_3 receptor, serves as a promising tracer for further investigations. This project is partly sponsored by the Austrian Academy of Sciences (DOC-fFORTE Nr. 22347) awarded to D. Haeusler and by the Austrian Science Fund (FWF P19383-B09) awarded to M. Mitterhauser.

OP414

Synthesis and evaluation of a carbon-11 labeled PET-radioligand with affinity for the transient receptor potential vanilloid subfamily type 1 receptor.

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Objectives. The TRPV1 (Transient Receptor Potential Vanilloid subfamily type 1) receptor is a non-selective cation channel, mainly expressed on primary sensory neurons, which plays a key role in the integration of noxious stimuli of chronic inflammatory pain or tissue injury. However, the exact role of this receptor in the brain remains elusive. TRPV1 has been visualized using *in vitro* autoradiography, but there is currently no radioligand available that allows *in vivo* visualization of this receptor using PET. Therefore, we have synthesized and evaluated a carbon-11 labeled analog of N-(3-methoxyphenyl)-4-chlorocinnamide which was reported to be a high affinity (18 nM) antagonist for hTRPV1. **Methods.** N-(3-methoxyphenyl)-4-chlorocinnamide (***1***) was synthesized as previously described (Gunthorpe MJ, Neuropharmacology 2004, 46:133-149). The labeling precursor (N-(3-hydroxyphenyl)-4-chlorocinnamide (***2***) was synthesized in four steps starting from 3-acetamidophenol. Both compounds were purified by column chromatography on silica gel and their structures were confirmed by MS and ^{1}H NMR. Carbon-11 was produced by a ^{14}N(p,α)^{11}C nuclear reaction in a Cyclone 18/9 cyclotron (IBA, Louvain-la-Neuve, Belgium) yielding [^{11}C]CH_4, which was converted to [^{11}C]MeI or [^{11}C]MeOTf in a home-built recirculation module. The obtained [^{11}C]MeI or [^{11}C]MeOTf was then bubbled through a solution of ***2*** in DMF in the presence of Cs_2CO_3. The reaction mixture was heated at 70 °C, diluted with water and purified

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with RP-HPLC. The log P and biodistribution in mice at 2 and 60 min p.i of [^{11}C]-***1*** were studied. Calcium imaging experiments, using fura-2 as dye, were performed with HEK293 cells expressing hTRPV1 to determine the IC_{50} of ***1***. **Results.** ***1*** was shown to act as an antagonist of hTRPV1. Ca^{2+} responses to 100 nM capsaicine were inhibited in a concentration-dependent manner, with an IC_{50} of ± 180 nM. The log $P_{octanol/buffer}$ value of [^{11}C]-***1*** was 1.82, suggesting that it may cross the BBB. After intravenous injection in mice, brain uptake was high (2.3% ID at 2 min p.i.) and wash-out was rapid (0.2% ID at 60 min p.i.). [^{11}C]-1 was also efficiently cleared from plasma (2 min: 4.7% ID; 60 min: 0.5% ID), mainly by the hepatobiliary pathway. **Conclusion.** N-(3-hydroxyphenyl)-4-chlorocinnamide (***2***) was synthesized and efficiently labeled with carbon-11 to obtain compound [^{11}C]-***1***, which has favourable biodistribution characteristics in normal mice. Work is in progress to further evaluate the biological properties of [^{11}C]-***1***. A µPET study in rats and metabolite study are in progress.

OP415
[^{18}F]-fludarabine for PET imaging of lymphoma

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Background [^{18}F]-FDG PET a functional and metabolic imaging tool has taken a major position in the pretreatment staging, restaging, therapy monitoring as well as post-therapy surveillance of lymphoma. However, the observed results remain sometimes equivocal, depending, among other criteria, on the histological subtype of the lymphoma, leading to false negative results in low grade lymphomas (SLL, MALT). Moreover, the lack of specificity of [^{18}F]-FDG leads to false positives in the case of increased glycolysis. Therefore there is an unmet need for a more specific tracer that would overcome these problems. **Aim** The aim of our work was to develop from fludarabine, a drug used in low-grade non-Hodgkin's lymphoma treatment, a novel PET radiopharmaceutical ([^{18}F]-fludarabine) and evaluate its potential in preclinical studies. **Methods** fludarabine was labelled with [^{18}F]-KF *via* the substitution of the corresponding 2-nitro derivative followed by deprotection, HPLC purification and formulation. The radiotracer was injected in a) normal mice (controls), b) SCID mice (displaying lymphoid depletion), and c) SCID mice bearing human xenografted RL lymphomas, for in vivo evaluation by microPET and biodistribution after dissection. **Results** [^{18}F]-fludarabine was efficiently synthesized (60% yield decay corrected, radiochemical purity>99%). In animals studies, data revealed at 60min post injection - in controls a relatively high uptake in lymphoid organs such as the spleen (9.2%±0.03ID/g), - in SCID mice this uptake is strongly reduced (2.2%±0.3ID/g) - in xenografted SCID mice a maximum tumor uptake is reached after 20min with an higher degree in tumor (6.6%±0.6ID/g) *versus* others organs at 60min. **Conclusion** An efficient method for the radiosynthesis of [^{18}F]-fludarabine was developed. The preliminary biological evaluation as a new PET tracer for lymphoma is very promising.

1304 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 117

Technologists Oral Session 3

T17
Study of the Influence of Patient Hydration in Bone Scintigraphy

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Introduction Bone Scintigraphy is a noninvasive and very sensitive Nuclear Medicine diagnostic method in detecting early bone lesions. Between the important technical details to consider when dealing with patient preparation there is the hydration level. The aim of this study is focused on assessing the value of hydration on clinical image quality of bone scans. Material and Methods Fifty five patients (30 females and 25 males, aged between 30 to 80 years old, with an average age of 61,6 years) with indication to perform bone scintigraphy were imaged and previously divided into three groups according to the level and moment of hydration: group 1 (3 females and 3 males) with insufficient hydration (below 500 mL); group 2 (15 females and 12 males) with hydration (21 mL/kg) after radiopharmaceutical administration; group 3 (12 females and 10 males) with hydration (7 mL/kg; 45 minutes) before and after (21 mL/kg) radiopharmaceutical administration. Each patient received 740 to 925 MBq of 99mTc-HDP and whole body images were acquired 2.5 to 3 hours after using standardized acquisition parameters. Regions of interest (ROI) were drawn in the diaphysis of the left femur, on soft tissue of the right lower limb and externally to the right knee (background ROI). Bone/soft tissue ratio, bone/background ratio and soft tissue/background ratios were calculated. Statistical analysis was performed using a test of hypotheses for the difference between means in independent samples and the chi-square test to investigate in each group, the relation/dependence of bone/soft tissue ratio and the gender of patients. Results There are statistical significant differences between the three groups of patients concerning the average bone/soft tissue ratio in three groups (u1 = 2.8859; u2 = 3.3864; u3 = 3.4264). Concerning chi-square test we found that bone/soft tissue ratios are independent of the gender (X2 (df) of 0.5985). Conclusion Based on these results it is possible to conclude that bone/soft tissue ratio in fact increases with the level of hydration and so the related image quality. Furthermore, we found that starting hydration even before radiopharmaceutical administration can help to improve image contrast and image quality.

T18
Optimization of injected F18-FDG patient dose using NECR curve to individual patient scans

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Aim: Patient dose for F18-FDG is mostly administered calculated as a standard dose per kg patient weight. Modern PET-scanners are introduced with terms as 'half dose imaging' or 'half time imaging'. However, the NECR curves of a PET-scanner show where the scanner is functioning optimal. Aim is to objectively calculate the patient dose to be administered based on the NECR of the PET scanner. Methods: NECR curves and values of the PET-scanner (Siemens Biograph 40 TrueV) were measured according to the NEMA NU-2 2007 protocol. F18-FDG patient studies were acquired with a standard patient dose of 3,5 MBq / kg with a standard protocol of 4 min / bed position. Totals and delayed randoms counts were recorded in separate sinograms. For each patient and bed position, with exception of the head region, an individual NECR curve is calculated similar to [1]. Patient length, weight, body mass index (BMI) and dose were registered The dose which should give optimal response was determined retrospectively. Correlations between the proposed optimal dose and given patient parameters were calculated. Results: Different to [1] is the use of a new generation PET-scanner. Also we found out that the individual patient scatter fraction is not relevant due to normalisation of the NECR curve. Further we used the individual totals sinogram to create the masks. The NECR of this PET scanner is much higher than the one used in [1]. Images were reported of good clinical quality. The individual patient NECR was found to be at 66% of maximal NECR. Injected dose was accordingly at 33% of dose at maximum NECR. We found a higher correlation of calculated dose with weight than with BMI. Conclusions: The methodology developed allows estimating injected dose by patient weight, adapted to the NECR curve of the scanner. This estimated injected dose is at 66% of the maximum NECR of the scanner. Dose reduction results in operating at lower percentages of the maximum NECR. Image quality phantom studies are necessary to determine the achievability of this dose reduction. References: [1] Watson et al; Optimizing Injected dose in clinical PET by accurately modelling the counting-rate response function specific to individual patient scans, JNM 2005, 46, 1825-1834

T19
Staff radiation dose during cardiac PET examinations with Rubidium 82

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Aim Myocardial perfusion PET-CT with Rb-82 is a promising diagnostic tool newly available in Europe. Our aim was to estimate radiation dose to staff involved in rest-stress myocardial perfusion studies with Rb-82 PET-CT in our center. Materials & methods We considered 4 different "worker" categories (physician, technologist, nurse and "quality controller"). The physician controls the infusion device that delivers the eluted activity, being present in the PET room during stress and rest acquisition. The nurse prepares the patient for ECG and arterial pressure monitoring, and is present in the PET room during stress and rest acquisition. Both the physician and the nurse stood >2-3m away from the patient during and shortly after the Rb-82 infusion, when possible. The technologist installs the patient on the PET-CT, and controls the acquisition from an adjacent room. Additionally, a quality controller verifies the conformity of the eluate once a day, performing 3 to 4 blank elutions before allowing the system to be used in patients. Each staff member had a personal digital torso dosimeter. Measurements were discarded as soon as FDG was present in the PET unit or a staff member had to leave the controlled area during the procedure. Results Staff exposure was measured during clinical examinations of 32 patients. All patients received the same activity for stress and rest (1600 MBq). Measured doses per elution for each "worker" category are presented in following table.

	Mean ± SD (uSv)	MIN - MAX (uSv)
Quality controller	0.61 ± 0.36	0 - 1.5
Physician	1.05 ± 0.62	0.17 - 2
Technologist	0.02 ± 0.06	0 - 0.17
Nurse	0.38 ± 0.25	0 - 0.75

Conclusion The radiation dose remains small, even for the physician standing in the injection room during Rb-82 infusion. The physician dose for a stress-rest study is similar to those obtained by other groups for Tc-99m-MIBI stress-rest scintigraphy. Doses to physician and nurse might be further reduced using a shield or stressing the importance of increasing the distance from injection device and patient after injection. As expected, doses to technologists who stay in the shielded control room are very low.

T20
Comparing three stress test protocol in Myocardial Perfusion Imaging: patient's tolerance and image quality

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Aim: Adenosine is commonly used for pharmacologic stress testing in Myocardial Perfusion Imaging (MPI). However, this vasodilator agent may cause several side-effects and has been associated with an increased subdiaphragmatic tracer uptake that may interfere with image interpretation and overall test quality. The aim of this study was to compare stress induced by treadmill exercise, adenosine and adenosine plus low level treadmill exercise in terms of side effects referred by patients and to evaluate the corresponding image quality. ***Materials & Methods:*** One hundred and two (102) patients that underwent MPI were divided in three groups according to the stress test performed: Group 1 - Treadmill exercise (n=23); Group 2 - Adenosine infusion (n=57); Group 3 (n=22) - Adenosine infusion combined with low level treadmill exercise. Each group was further divided according to the presence or absence of side effects, their number and the need to administer pharmacologic therapy to control symptoms: A -No side effects; B - One side effect; C - two or more side effects and/or pharmacologic therapy needed. Image quality was evaluated according to the requirement of a new stress acquisition due to

extra-cardiac activity that interfered with image quality and interpretation. ***Results:*** The most common effects were facial flushing, abdominal/ throat pressure and discomfort in the arms.

		Group 1 (Treadmill)	*Group 2 (Adenosine)*	*Group 3 (Adenosine+low-level Treadmill)*
	A	*78,3%*	*14%*	*36,4%*
Side effects	*B*	*13%*	*15,8%*	*45,5*
	C	*8,7%*	*70,2%*	*22,7%*
Image Quality: Stress acquisition repeated		*4,3%*	*17,5%*	*0*

Conclusions: The best stress modality, considering patient's tolerance and image quality is treadmill exercise. When this is not possible and a pharmacologic stress test has to be considered, association of a low-level treadmill exercise to the adenosine infusion is safe, reduces the side-effects and allows for reduced extra-cardiac activity, giving better image quality compared with the adenosine infusion alone. This alternative stress protocol turns the pharmacological stress test more tolerable and reduces the camera total occupation time per patient.

T21

Ejection fraction measurement with a dynamic cardiac phantom : Comparison of Tc-99m, F-18 and Rb-82 tracers.

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Background: Myocardial perfusion can be studied with SPECT or PET tracers. Cardiac wall motion and variations of ejection fraction (EF) between stress and rest are useful for diagnosis or follow-up and should be determined accurately. Our aim was to compare EF obtained by different tracers used in clinical use at our center, especially Rb-82 that became recently available. **Methods:** We used a dynamic cardiac phantom (BSI, Lübbecke, Germany) with a known EF of 67%, EDV 112ml, ESV 37 ml, beating at 60 bpm, filled with 15 MBq F-18, 1600 MBq of Rb-82 and 30 MBq Tc-99m in the inner membrane chamber fixed in a water filled torso-anthropomorphic phantom. Gated acquisitions (8 frames/cycle) were performed with PET (PET/CT Discovery LS, GEMS), and SPECT (ECAM, Siemens). One single acquisition was performed for F-18 and Tc-99m. For Rb-82 we compared a 5- and 10-min gated acquisition. PET images were acquired in 2D mode, and reconstructed with OSEM (2 iterations, 28 subsets). CT was used for attenuation correction for PET, whereas no attenuation correction was used for SPECT. Data were evaluated with a dedicated cardiac software tool **Results:** Using reconstruction parameters applied in routine clinical evaluations (Butterworth, critical frequency 0.52, power 5,), we obtained EF of 66%, 62% and 70% for Tc-99m, F-18 and Rb-82, respectively, corresponding to a 7.5 % underestimation for F-18, and a 4.5% overestimation of for Rb-82. 5 and 10 min.gated Rb-PET results were identical (70%).

	Reconstruction	Filter	EF (%)	EDV (ml)	ESV (ml)
Tc-99m	FBP	BW (0.52 / 5)	66	71	24
Tc-99m	OSEM (2i/28s)	BW (0.52/10)	69	75	23
Tc-99m	OSEM (2i/28s)	BW (0.52/5)	70	69	21
F-18	OSEM (2i/28s)	Gauss (FWHM 4.36mm)	62	87	33
Rb-82	OSEM (2i/28s)	Gauss (FWHM 4.36mm)	70	82	35

EDV and ESV are both underestimated in SPECT. In PET examinations ESV are closer to the real volume but the EDV is still underestimated resulting in an underestimated EF with F-18 and a slightly overestimation of EF with Rb-82. **Conclusion:** EF was measured accurately with Tc-99m and Rb-82, although EDV (and ESV with Tc-99m) were underestimated. Physician should be aware of EF underestimation when measured with F-18 PET. Difference between the two PET tracers might be due to the higher energy of Rb-82 positrons as compared to F-18.

T22

Standardization of patient dose in PET/CT-scans

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Aim: The majority of departments performing PET/CT-scans, administer a dose of 370-400 MBq ^{18}F-FDG intravenously and use a scan time of 2½ to 3 minutes per bed position. In our department we administer 400 MBq ^{18}F-FDG and scan 2½ minutes per bed position. The radiation dose from ^{18}F-FDG equals 7.5 mSv to the patient but also results in a considerable radiation dose to technologists. In our department technologists receive approximately 0.6 mSv/month when working with PET/CT-patients. We wanted to investigate the possibility to administer 4 MBq/kg to the patients in order to decrease the dose to both patient and technologist and still obtain images that can be used diagnostically. **Materials and methods:** Sixty patients scheduled for PET/CT-scan were included. After a fast of at least 6 hours, patients were given 4 MBq/kg ^{18}F-FDG intravenously. All patients were scanned 60-75 minutes after injection. CT-scan was followed immediately by a PET-scan acquired in listmode with an acquisition time of 3 min per bed position. Data was histogrammed in to acquisition times of ½, 1, 1½, 2, 2½ and 3 min and reconstructed using 3D OSEM. For each patient the image were reviewed randomly and independently by two physicians. The equivalent doses to five technologists were measured with personal film badges. The technologists were also carrying electronic dosimeter and wrote a daily radiation journal. Average doses were calculated for each technologist and a comparison between a period of administering 400 MBq and a period administering 4 MBq/kg was performed. **Results:** The images were scored 1 to 5, with 1 designated a high observer confidence in the diagnostic quality of the images and 5 designated a low observer confidence. All images obtained a score of 1 or 2. The equivalent dose to the technologist decreased from approximately 0.6 mSv/month when administering 400 MBq to the patients to approximately 0,4 mSv/month when administering 4 MBq/kg to the patients. **Conclusion:** It is possible to standardize the administered dose to the patient without any loss of diagnostic quality in the images. The decrease in radiation activity handled per patient resulted in a decreased dose to the technologist.

T23

Investigation of Central Sleep Apnea with Brain FDG-PET - technical aspects for setting-up a service

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Introduction: central sleep apnea (CSA) is poorly understood and significantly less frequent than obstructive sleep apnea. Unfortunately CSA health effects are often serious and similarly damaging. Reductions and pauses in breathing disturb sleep and interfere with day life activities. Diagnosis is a multidisciplinary approach and requests detailed registration of sleep patterns that include a polysomnogram. There are several treatment options with variable efficacy. Aim: to investigate changes in regional brain glucose metabolism during episodes of central sleep apnea and compare them with baseline. Material and methods: setting-up for these studies is highly demanding because it requests a group effort well timed. Patients arrive to the polysomnogram room where they are prepared for registration (electrodes placed on the scalp, lying flat on a bed, significantly reduced light and noise). Two people are always nearby, the polysomnogram technician and a nuclear medicine technician with the FDG dose prepared for intravenous administration. FDG has to be administered during the episode of central sleep apnea registered on the polysomnogram - only a few seconds duration. PET imaging is performed at 30 minutes and 3 hours post-injection during central sleep apnea episode. The same protocol is followed at baseline. Qualitative image evaluation by an experience nuclear medicine physician is complemented by quantitative analysis using a home-made registration protocol. Results: so far, we were successful in obtaining central sleep apnea data in three subjects for comparison with baseline. The overall evaluation reveals that FDG uptake is generally higher after central sleep apnea episode than at baseline. This is observed in the cortical and subcortical gray-matter structures. In one of the individuals there was regional differences, mainly in the brainstem and thalamus. Conclusion: we demonstrate that investigation of brain glucose metabolism during central sleep apnea episodes is feasible by implementing a team work effort that includes polysomnographic registration of sleep patterns. Overall glucose metabolism is stimulated during central sleep apnea. Regional differences (brainstem and thalamus) deserve further investigation and are ongoing.

T24

Comparison of methods for uptake calculation in lymphatic mapping using SPECT/CT

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Aim: Quantify the difference in the uptake of sentinel lymph nodes using different calculation procedures available with SPECT/CT. *Methods:* A series of 40 breast cancer patients undergoing indicated lymphatic mapping was examined with planar scintigraphy and SPECT/CT. The uptake of the sentinel nodes was determined from the attenuation corrected SPECT images using two methods: In a first approach all coronal slices were added and a 2D ROI was drawn around the sentinel nodes. In a second approach the uptake was calculated defining 3D ROIs in an ad hoc volumetric analysis tool. The uptake was calculated as the amount of counts in the ROI divided by the counts of the complete image. *Results:* At least 1 sentinel node was seen in 37 of the 40 patients. In the 3D visualization a total of 68 nodes could be mapped, whereas in the 2D one only 53 nodes were mapped. In 5 patients the 2D visualization did not allow to discriminate nodes in a conglomerate (11 nodes). In 3 patients it was impossible to separate conglomerates in 3D (5 nodes). The uptake in 3D was in average 82,8% lower (std. dev. 172%) than the one calculated using the 2D method. In all but in 3 cases the 2D uptake was always higher than the 3D uptake. Overflow was not present in any calculation using the 3D method, while it was reported in all 2D sumation images. In a few cases the SPECT images were reconstructed in a thinner matrix eliminating the overflow in the 2D sumation images. However, reconstruction in matrices with higher resolution involved reconstruction time approximately 16x or 64x longer (depending if resolution was increased by 2 or 4 times). The time to calculate the uptake in 2D was 60% shorter in average than the time needed to determine it in 3D. *Conclusions:* The calculation of uptake using volumetric tools is closer to reality than in the 2D approach. The main reason for this is the appearance of overflow in the sumation. Distinguishing nodes in conglomerates seems also to be easier with the 3D method. As a summary, despite the longer time for evaluation the 3D quantification of uptake is superior than the 2D evaluation and seems to be the right choice towards quantitative imaging with SPECT/CT.

1305 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 113

Molecular Imaging: preclinical - non oncology

OP416

Preclinical evaluation of ABY-025, a second generation Affibody molecule having a re-engineered scaffold

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Aim The sequence of the HER2 binding Affibody molecule ABY-025 is the result of a profound scaffold re-engineering, making it more amenable for peptide synthesis, reducing deamidation and other posttranslational changes, and increasing the overall hydrophilicity. It is known that substitution of single amino acids can alter the biodistribution and targeting capacity dramatically. Therefore it was of great importance to perform this preclinical evaluation of ABY-025. **Material and methods** Recombinantly produced Z_{02891}-Cys was conjugated with maleimide-DOTA (MMA-DOTA-Z_{02891}-Cys = ABY-025) and labelled with ^{111}In at 60ºC. *In vitro* tests were performed to evaluate labelling stability as well as binding specificity and binding capacity to HER2-expressing cells. *In vivo* targeting capacity and kinetics was evaluated in mice bearing

SKOV-3 xenografts. Specificity of tumour uptake of ^{111}In-ABY-025 was investigated by *in vivo* blocking with an excess of non-labelled Affibody molecule. A comparative biodistribution was performed to compare ^{111}In-ABY-025 with the previously evaluated tracers ^{111}In-DOTA-$Z_{HER2:342-pep2}$ and ^{111}In-MMA-DOTA-$Z_{HER2:2395}$-Cys. **Results** ABY-025 was labelled with quantitative yield already after 0.5h of incubation and the conjugate was stable when incubated in complete cell media at 37ºC for 24h. The radiolabelled conjugate retained capacity for specific binding to HER2-expressing cells. In SKOV-3 xenografts, ^{111}In-ABY-025 showed excellent targeting capacity and the tumour uptake was specific (Table 1). The blood clearance was rapid resulting in a tumour-to-blood ratio of 6.3 already 0.5h p.i. which was further increased for later time points reaching 88 at 4h p.i. The biodistribution pattern of ^{111}In-ABY-025 was in very good agreement with the compared tracers. Xenografts were clearly visualized both 0.5h and 4h p.i. **Conclusions** Despite profound re-engineering of the Affibody molecule, the ^{111}In-ABY-025 biodistribution pattern is in a remarkable good agreement with the other compared tracers. In vivo, ^{111}In-ABY-025 shows high and specific targeting capacity to HER2 with rapid blood clearance, leading to high tumour-to-organ-ratios and very good imaging contrast. **Table 1 Biodistribution of ^{111}In-ABY-025 in SKOV-3 xenografted mice 1h p.i.**

	non-blocked (%IA/g)	blocked (%IA/g)
tumour	16.7±2.5*	2.4±0.2
blood	1.1±0.1	0.8±0.1
liver	1.9±0.2	1.3±0.2
spleen	0.8±0.1	0.5±0.1
kidney	186±24	194±51
muscle	0.36±0.05	0.23±0.04
bone	0.5±0.2	0.34±0.09

Data are expressed as percent of injected activity per gram tissue (%IA/g) and presented as an average from four animals ± SD.
* $p<10^{-4}$

OP417

Nuclear imaging of intratracheal siRNA delivery with PEG-PEI copolymers

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Delivery is still the major hurdle in RNAi therapy. Due to instability of siRNA and rapid excretion upon systemic injection, most of the clinical trials involving siRNA based drugs apply local administration to the eyes targeting macular degeneration and diabetic retinopathy or direct delivery to the brain or the lung. The lung with its vast surface area and strong perfusion is indeed well suited for drug uptake concerning small, hydrophobic molecules. It is, on the other hand, only to a limited extent permeable for large, hydrophilic biopharmaceuticals, such as siRNA. Yet, successful local therapy, e.g. protection from SARS infection, inhibition of RSV and influenza A virus replication has been reported. In our study, we have investigated how formulation of siRNA with polyethylene imine (PEI) and polyethylene glycol (PEG) grafted PEI (PEG-PEI) into nanosized complexes influences biodistribution, absorption and clearance of vector and load after intratracheal instillation. These parameters were studied by non-invasive nuclear imaging and were compared for PEG-PEIs of different grafting degrees. Non-invasive imaging allows for investigation of biodistribution in the same animal at different time points. SPECT images show slow elimination of the 111In-DTPA-labeled material. After 24 hours, radioactive signal can still be observed in the mounth and the upper trachea. The kidneys are slightly visible. Another 24 hours later, radiolabeled material is excreted via the kidneys, and the liver becomes slightly visible. The strongest signal is observed in the lung, and only in the lower trachea radioactive material is still present. To quantify biodistribution of radiolabeled siRNA and polymers, organs were dissected 48 hours after treatment showing that, depending on the polymer, still 5-22 % of the vector and 1-11 % of the load is present in the left lung, which - for anatomical reasons - was filled with a bigger part of the polyplex solution. The first-pass effect, which is very prominent after i.v. injection, was decreased to about 5 % uptake of labeled polymers and a negligible percentage of siRNA by the liver. PEI and PEG-PEI polyplexes seem to be suitable for local sustained release siRNA delivery. Clearance of radioactive material was observed to be much slower than after systemic administration, the first-pass effect was circumvented, local concentrations were high for 48 hours and no pathologic effects in the lung were observed histologically. Knock down efficiency in GFP mice after instillation of siGFP/(PEG-)PEI polyplexes, which was observed qualitatively, remains to be quantified.

OP418

Evaluation of Dose-Dependent Effects of 111In on Canine Endothelial Progenitor Cells for Cell Tracking

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Introduction Transplantation of endothelial progenitor cells to assist angiogenesis has been evaluated in models of myocardial infarction. Cell tracking with the use of radiolabels like 111In have been instrumental in determining the retention of labeled cells at the infarction site. However, cellular safety limits of such radiolabels must be established to ensure that transplanted cells remain functional. We describe the dose dependent effects of 111In cytotoxicity on canine endothelial progenitor cells (cEPC) in vitro for autologous transplantation of cEPCs in a canine model of myocardial infarction. Methods Peripheral blood was taken from one female mongrel dog (30 ml) and mononuclear cells were isolated using density gradient centrifugation. Isolated cells were cultured in EBM-2 media supplemented with 10% FBS and penicillin/streptomycin and adherent cEPCs were culture expanded up to passage 9. On day 0, cEPCs were collected and divided into 4 groups consisting of 3 radiolabeled groups and a control group (5.79x106 cells/group). Radiolabeled groups were labeled with 111In-tropolone for 30 minutes, washed twice with PBS, and cell pellet and supernatant activity was determined using a dose calibrator. Cell proliferation was assessed using the MTT assay at days 1, 4, 8, and 10 and cell counting with a hemacytometer days 1, 4, and 9. Viability was assessed using the trypan blue exclusion assay days 1, 4, and 9. Results Labeling efficiency for each radiolabeled group of cells was 94.3, 92.8, and 91.2% with cellular activities of 0.036, 0.08, and 0.198 Bq/cell respectively. MTT results demonstrated that cEPC proliferation was affected by 111In in a dose-dependent manner with the 0.198 Bq/cell group being significantly different from control at all time-points ($p<0.05$). Lower cellular doses indicated a slight lag at early time-points after labeling (day 1 control vs. 0.08, $p<0.01$; day 4 control vs. 0.032 and 0.08 $p<0.05$), however were not significantly different from control at later time-points. Cell counting data also confirmed these results. Cell viability remained between 80-100% over the observation period. Conclusion Dose-dependent effects of 111In were seen on cell function such that cEPCs exhibited significantly slower proliferation rates at the highest dose. Viability data at late time-points suggest little direct effects from 111In at the levels tested over the period of observation. These data suggest the importance of safe cellular limits for angiogenic therapies using labeled transplanted cells.

OP419

Type 2 Cannabinoid Receptor Based Reporter Gene Constructs for Brain PET Imaging

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Aim: Reporter genes have become a standard tool in various molecular biology protocols with the aim of determining the location, duration and extent of gene expression within living subjects. However, for the brain no successful PET reporter systems are available with low endogenous background gene expression and good blood-brain-barrier (BBB) penetration of the PET probe. The aim of this study was to develop a new PET reporter gene system which can be applied to the brain. The type 2 cannabinoid receptor (CB2) has a very low brain expression in physiological conditions and CB2 PET radioligands crossing the BBB were recently developed. **Methods:** We constructed an adeno-associated viral vector (AAV) transfer plasmid encoding human CB2, harboring a point mutation at position 80 (D80N) referred to as CB2(D80N), as such or in combination with enhanced green fluorescent protein (eGFP) or firefly luciferase (FLuc). Two rats were stereotactically injected with 5 µl of AAV-eGFP-T2A-CB2(D80N) in the right striatum and 5 µl of AAV control vector in the left striatum. At different time points (6, 13, 18 and 96 days) after stereotactic injection of the AAV, a selective ^{11}C-labeled CB2 inverse agonist (2,3-dichloro-phenyl)-[5-[^{11}C]methoxy-2-methyl-3-(2-morpholin-4-yl-ethyl)-indol-1-yl]methanone was injected intravenously and dynamic µPET images (Focus 220, Siemens) were acquired. Time-activity curves (TAC) and parametric binding potential maps were determined. The animals were sacrificed and perfused and double immunohistochemical staining against CB2 and eGFP of the brain sections was performed. **Results:** The observed CB2 binding potential increased over time and reached a maximum in right striatum at 18 days after vector injection in the brain. The time-activity curves persistently expressed an increased uptake in right striatum compared to control left striatum and cerebellum. Immunohistochemical analysis showed colocalization of both CB2 and eGFP in the right striatum. In contrast, only eGFP expression was seen in the contralateral hemisphere. **Conclusion:** We have successfully developed a new PET reporter gene system consisting of an adeno-associated viral vector expressing the CB2 receptor as the reporter gene which can be quantified for at least 3 months.

OP420

^{99m}Tc- Annexin A5 imaging is positive in acute and chronic phase of experimental immunoallergic myocarditis

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Purpose: Acute myocarditis is one of the most challenging diagnosis in cardiology, due to its wide non-specific clinical, electrocardiographic and echocardiographic features. SPECT using ^{111}In-antimyosin-antibodies (specific for cardiomyocytes death) used to be accurate for this purpose but is no longer available. Our aim is to evaluate the sensitivity of ^{99m}Tc-Annexin A5 (ANX) scintigraphy during acute and chronic phase of experimental autoimmune myocarditis. **Methods** : Myocarditis was induced by injection of purified rat cardiac myosin in 24 Lewis rats who were then studied on day10, day15, day20, 1 month, 3 months or 6 months after immunization by echocardiography and ANX imaging (microSPECT/CT Biospace Lab). SPECT/CT images were qualitatively and quantitatively analyzed, using myocardial-to-muscle activity ratio (MMR) on axial slices. In vivo imaging data were compared to autoradiographic and histological findings (Hematoxilin Eosin, Sirius Red) in terms of location, extent, and intensity of lesions. **Results:** Both echography and ANX SPECT/CT were negative in all rats on day10 and in 2 of 4 rats at 6months after immunization. ANX-SPECT/CT was positive in 16 of 17 rats from day15 to 3 months after immunization, while echocardiography was normal in 6 of them with limited (<3/17 myocardial segments) histological lesions. MMR was 7.9±2.1 in the 11 rats with >3 segments lesions, 5.6±1.1 in the 6 rats with <3segments lesions, versus 3.8±0.7 in 8 controls ($p<0.01$ and $p<0.03$). It peaked at 21days then decreased. Six months after immunization, 2 of 4 rats had dilated hypokinetic fibrotic ventricles with positive ANX imaging in 1 case. On autoradiography of axial myocardial sections, ANX activity was located in areas of mixed dead myocytes and inflammatory cells. **Conclusion**: ANX-SPECT/CT was positive during acute and chronic (3 months) phase of immunoallergic myocarditis in rats. This suggests potential clinical role of ANX imaging for the detection of acute and chronic active myocarditis.

OP421

Scintigraphic Imaging of Myocardial and Pulmonary Fibrosis Using a Peptidomimetic of Human Platelets Glycoprotein VI

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Objectives : We have radiolabelled with Tc-99m a biotinylated peptide (called collagelin) which mimics the collagen binding site of glycoprotein VI and specifically binds to collagen in vitro. Our aim was to test the ability of 99mTc-collagelin (Coll) to target collagen in vivo using a rat model of myocardial fibrotic scar and a mouse model of pulmonary fibrosis. **Methods :** Myocardial infarctions (MI) were induced after thoracotomy by coronary ligature in 8 Wistar rats. Lung fibrosis was induced in 2 male C57BL/6J mice by intratracheal administration of bleomycin (Bellon, Aventis, France). One month after coronary ligature, and 14 days after bleomycin tracheal instillation, alive animals were IV injected either with Coll (70MBq in 8 rats, 8MBq in 5 mice) or with irrelevant peptide (IP in 8 rats and 5 mice). Then planar and SPECT thoracic images were obtained 1-2h after tracer injection , using a dedicated small animal system. Heart-to-lung activity ratios (HLR), and lung-to-muscle activity ratios (LMR) were calculated on planar images in rats and mice respectively. Then frozen axial heart and lung sections were used for quantitative autoradiography, and histology (hematoxilin eosin, Sirius red). The whole procedure was also performed in 6 sham-operated rats, and 7 saline serum instillated mice. **Results :** After IV injection Coll demonstrated fast blood clearance (half life: 5±0.5 min), early high gallbladder then bowel excretion, low liver and low renal uptake. No thyroid or gastric uptake was observed until 6h post-injection. Significant Coll uptake was observed in the cardiac area of all but 1 of the rats with MI scars, compared to sham-operated rats (n=6). In mice, mild pulmonary Coll uptake was visible in 3 of 5 mice. HLR were 2.08 ± 0.17 in rats with MI scars versus 1.61 ± 0.23 in control rats ($p<0.01$). LMR was 3.42±0.57 mice that received bleomycin and 1.81±0.25 in controls ($p<0.01$). Comparison of autoradiography and histology findings showed that Coll activity coincided with collagen (Sirius Red coloration). There was little uptake of Pc in myocardial scars with infarct-to-remote myocardium activity ratio of 1.83 ± 0.3 versus 2.92 ± 0.53 for collagelin ($p<0.008$). No Pc uptake was observed in pulmonary fibrosis on autoradiography. **Conclusions** : 99mTc-Collagelin was able to specifically target rat MI fibrotic scars and mouse lung fibrosis in vivo. This offers perspectives for further development of non invasive molecular imaging of fibrosis.

OP422

Intrapancreatic distribution and metabolism of 11C-dihydrotetrabenazine in rat

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In diabetes mellitus (DM), pancreatic islet beta cells are destroyed resulting in loss of insulin production. 11C-dihydrotetrabenazine ([11C]DTBZ) is a radioligand specific for the vesicular monoamine transporter 2 (VMAT2) expressed in beta cells. The aim of this study was to evaluate the metabolism and distribution of [11C]DTBZ in the pancreas of healthy rats. The specific radioactivity of [11C]DTBZ was 380 ± 210 MBq/nmol (mean ± SD) and radiochemical purity exceeded 95%. To evaluate the biodistribution of [11C]DTBZ ex vivo, male Sprague-Dawley rats (n = 5-7/time point) weighing 250-300 g were injected intravenously with 46 ± 24 MBq [11C]DTBZ (mean injected mass = 180 ng; range 5-400 ng) and sacrificed at 10 or 60 min post injection. The organ-specific biodistribution of radioactivity was measured as a percentage of the injected dose per gram of tissue (% ID/g). For autoradiographic analysis, the pancreases were cut into 20-µm thick cryosections and the regions of interest were outlined on digital images using image analysis software. To establish histological references for the analyzed regions, the same or adjacent sections were subsequently stained with haematoxylin and eosin. Insulin and VMAT2 antibody staining defined VMAT2 expression in rat islets. Radioactive metabolites in the pancreas were analyzed by radio thin layer chromatography. For in vitro autoradiography studies, 20-µm thick cryosections of rat pancreas (and brain and adrenal gland as references) were incubated with various concentrations of [11C]DTBZ. [11C]DTBZ uptake at 10 min in whole pancreas was 3.0 ± 0.6 and in blood 0.20 ± 0.02 % ID/g, and at 60 min 3.0 ± 0.5 and 0.10 ± 0.01 % ID/g, respectively. Tissue measurements and autoradiographic analysis of pancreas slices showed that radioactivity uptake in the pancreas was heterogeneous. At 10 min p.i. the uptake was 2-fold higher in the head than in the tail of the pancreas. No difference in the amount of unchanged tracer was found between the different parts of pancreas. The ex vivo and in vitro autoradiography, combined with histological stainings, demonstrated that radioactivity uptake did not accumulate in islets. Previous studies have suggested that quantification of VMAT2 expression in beta cells using [11C]DTBZ represents a method to estimate changes of beta cell mass. Our results suggest that initial regional uptake of [11C]DTBZ is largely determined by local vascularization of pancreas. Unspecific exocrine uptake then dominates and specific endocrine uptake is not observed, at least within the time frame achievable with the short lived [11C]DTBZ.

OP423

Experimental validation of ^{99m}Tc-NTP 15-5 as a SPECT radiotracer for *in vivo* assessment of degenerative and tumoural pathologies of cartilage.

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Introduction: When considering the pathophysiologic basis of both the degenerative and tumoural pathologies of cartilage, proteoglycans (PG) appear as one of the primary targets for the degradation and proliferation processes respectively. Our lab develops a "cartilage imaging strategy" with the ^{99m}Tc-NTP 15-5 tracer that selectively binds to cartilage PG in vitro and in vivo. **Methods:** We have assessed the pertinence of ^{99m}Tc-NTP 15-5 radiotracer for cartilage SPECT imaging in: (i) healthy animals, (ii) animals developing osteoarthritis, and (iii) animals with primary and recurrent grade II orthotopic chondrosarcoma. Considering pathological animal models, ^{99m}Tc-NTP 15-5 imaging was performed at regular intervals after pathology induction and tracer uptake followed as a function of time. ^{99m}Tc-NTP 15-5 imaging was compared with ^{99m}Tc-HMDP scintigraphy. **Results:** In healthy animals, a high and specific accumulation of ^{99m}Tc-NTP 15-5 was observed in cartilage (about 5.5 +/- 1.7 % of ID/g of tissue at 15 min after iv injection), with a highly contrasted joint imaging being obtained in all animal species studied (i.e. rabbit, guinea pig, rat and also mice using high resolution 1mm-pinhole SPECT acquisition). In the meniscectomized guinea pig model of osteoarthritis, ^{99m}Tc-NTP 15-5 imaging (being performed over 6 months) allowed in vivo the assessment of PG changes associated to both the hypertrophic and decompensation responses of degenerative cartilage. In the orthotopic swarm rat chondrosarcoma models (both the primary growth and recurrent models) ^{99m}Tc-NTP 15-5 imaging evidenced a significant uptake of the tracer at the tumoural site at very early stage, with the tracer uptake being strongly correlated with tumour growth. It should be mentionned that ^{99m}Tc-HMDP imaging was negative during the whole study, even at the later stage of tumoural development or recurrence. **Conclusions:** These experimental results in relevant animal models underlined the potential of ^{99m}Tc-NTP 15-5 as the first and only radiopharmaceutical able to provide in vivo a specific diagnosis and staging of the degenerative and tumoural pathologies of cartilage. **Grants:** INCa, Ligue Contre Le Cancer ; Fondation pour la recherche Medicale ; Regional Innovation fund OSEO

1306 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 114

Oncology PET: lymphoma 1

OP424

Diagnostic accuracy of 89Zr-rituximab-PET/CT imaging in patients with relapsed CD20+ B-Cell non-Hodgkin's lymphoma: comparison with 18FDG-PET/CT.

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Background: 89Zr-rituximab-PET/CT combines the high sensitivity of PET/CT with the specificity of the chimeric monoclonal antibody (mAb) rituximab for the CD20-antigen expressed on the surface of CD20+ B-cell non-Hodgkin's lymphoma (NHL). Zirconium-89 (89Zr) is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed for a mAb to achieve optimal tumour-to-background ratios. The aim of this study was to compare the diagnostic accuracy of 89Zr-rituximab-PET/CT with 18FDG-PET/CT in patients with CD20+ B-cell NHL. Materials and Methods: Six patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma (1 mantle cell and 5 follicular lymphomas) were included in this study. Similarly to the Zevalin® treatment schedule, each patient received a first infusion of unlabelled (cold) rituximab at 250 mg/m² followed by the injection of 3-4 mCi 89Zr-rituximab and one week later, the same infusion of cold rituximab followed by radioimmunotherapy with 90Y-rituximab (0.3-0.4 mCi/kg). 89Zr-rituximab-PET/CT was performed at 4 time points: 1 hour, 24 hours, 3 days and 6 days after intravenous administration of 89Zr-rituximab. A baseline 18FDG-PET/CT was performed 1 to 4 weeks before the 89Zr-rituximab immuno-PET/CT. Standard uptake values (SUV) were assessed for all PET-positive lesions and compared for both tracers. Results: 18FDG-PET/CT revealed 24 hypermetabolic lesions (SUVmax: 8±4, range: 2.1 - 15.9) in the 6 evaluated patients. All FDG-positive lesions showed significant uptake on 89Zr-rituximab-PET/CT, with highest SUV on the late images (6 days post injection of 89Zr-rituximab; SUVmax: 8.9±5.3, range: 2,6 - 26,1). Linear regression analysis of SUV in 89Zr-rituximab- and 18FDG-positive lesions showed a very poor correlation (R2 = 0,14) between the level of CD20 antigen-expression and metabolic activity. Moreover, in 2 out of 6 patients, 89Zr-rituximab-PET/CT revealed 8 supplementary CD20+ lesions which were strictly negative on 18FDG-PET/CT and corresponded to particularly small (≤ 1cm) lymph nodes and mesenteric nodules on CT. Conclusion: 89Zr-rituximab-PET/CT provides an excellent imaging tool for accurate quantification of CD20 antigen-expression, which is of particular interest for dosimetry as a prelude to radioimmunotherapy with 90Y-Rituximab. The preliminary results of this pilot study suggest that 89Zr-rituximab-PET/CT is more accurate than 18FDG-PET/CT for the detection of viable lymphoma in patients with predominantly indolent NHL.

OP425

The diagnostic accuracy of 18F-FDG PET/CT in patients with primary extranodal lymphoma

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Purpose: To evaluate the diagnostic accuracy of 18F-FDG-PET/CT in patients with primary extranodal lymphoma(PEL). Methods: All patients presenting to our institution over a 5 year period with a clinical/histological diagnosis of PEL who underwent 18F-FDG-PET/CT scanning were included. Of 30 patients (15 male,15 female, mean age 60), 9 had gastrointestinal PEL, 3 each had pulmonary, cutaneous and bone PEL, 2 each had brain, orbital, breast and pancreatic PEL, and one each had thyroid, testicular, parotid and muscular PEL. Of 45 PET/CT scans, 19 were for staging, 13 for monitoring post-therapy response and 13 to look for suspected recurrence. Ability to detect PEL, exclude secondary nodal lymphoma, detect recurrence and assess treatment response was recorded. Final diagnosis was based on histology/cytology, and clinical and imaging follow-up (median 52 months, range 8-78 months). Results: Staging PET/CT correctly detected PEL and excluded secondary spread from nodal lymphoma in 16/19 cases. In one case of orbital lymphoma PET/CT confirmed secondary involvement. In one DLBCL of small bowel, PET/CT failed to detect bone marrow disease. Findings were indeterminate in 1 case (duodenal uptake could not be resolved as inflammatory or neoplastic). In the post-treatment response group, PET/CT was true positive(TP) in 3 patients, true negative(TN) in 8, false positive in one(small bowel uptake due to fibrosis/granulation tissue), and indeterminate in one(pulmonary uptake could not be resolved as inflammation/residual lymphoma). Of 13 scans for recurrence, 4 were TP, 7 TN and 2 were indeterminate(one showing acute gastritis or recurrent lymphoma in a patient with treated lung PEL, the other either post-treatment inflammation or recurrence in brain PEL). Conclusions: 18F-FDG-PET/CT showed a high degree of accuracy in staging PEL and assessing both disease recurrence and post-treatment response. This is important as treatment for localized PEL, advanced-stage PEL and secondary extranodal involvement by systemic lymphoma differs radically. PELs often show preferential spread to other extranodal organs, where they may be difficult to visualize by cross-sectional imaging. The additional information provided by PET/CT is valuable in this scenario.

OP426

The role of FDG-PET imaging for assessing the aggressivenes of lymphomas

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AIM Our study aimed to evaluate if standardized uptake value (SUV) discriminates well between aggressive and indolent lymphomas, and if there is a correlation between the SUVmax, as an indicator of cellular glucose uptake, and Ki67, as a cellular proliferation indicator, in non-Hodgkin's lymphoma (NHL). MATERIAL & METHODS We retrospectively studied 177 patients (54% males, 46% females, average age 50 years, SD 19,4) with biopsy-confirmed lymphoma, typified according to the 2008 WHO Classification, who underwent PET/CT for staging. We noted only the highest SUVmax value in patients with more than one pathological FDG accumulation. In 72 cases of NHL, Ki67 proliferative index was also recorded. For the statistical analysis we used the receiver operating characteristic (ROC) curve, Student-t test, and the 1-way analysis of variance (ANOVA) with a post hoc lowest square difference (LSD) or Tamhane test. Significance was obtained when p≤0.05. RESULTS The mean SUVmax value was higher in aggressive (n=109, mean SUVmax=12.2) than in indolent (n=68, mean SUVmax=5.4) lymphomas (P<0.01). In the NHL group (n=129), we found also the same difference when comparing aggressive (n=61, mean SUVmax=14.5) and indolent (n=68, mean SUVmax=5.4) (P<0.01). The ROC curve showed that SUVmax of 8 discriminates aggressive from indolent lymphoma patients with a sensitivity and specificity of 79% in NHL.

	NHL		DLBCL	
%Ki67	n	mean SUVmax	n	mean SUVmax
0-30	19	6.2	13	7
31-80	29	9.9		
81-100	24	18.7	21	7.7

72 cases of NHL, according to the percentage of Ki-67, were grouped in 0-30 %, 31-80%, and 81-100%, observing an upward tendency in SUVmax values according to the Ki67 percentage increase (P<0.01). In DLBCL group, also founded the same tendency between 0-80% and 81-100% values of Ki67(P=0.05). CONCLUSION SUVmax is lower in indolent than in aggressive lymphoma. Patients with NHL and SUVmax>8 have a high likelihood for aggressive disease. This study also suggests a good correlation between glucose metabolic activity and cellular proliferation measured by Ki67. Furthermore, it can separate low, medium and high percentages of Ki67, which is considered very useful for therapeutic management of NHL. Larger studies of DLBCL are needed to assess the relation between Ki67 and SUV max. This information may be helpful if there is discordance between biopsy and clinical behavior.

OP427

Evaluation of unenhanced low-dose PET/CT as the only imaging technique for staging lymphoma patients

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AIM: This study prospectively compares the agreement between contrast-enhanced full-dose PET/CT (PET/CECT) and unenhanced low-dose PET/CT (PET/NCECT) in lesion detection and initial staging of Hodgkin's disease and non-Hodgkin's lymphoma. MATERIAL AND METHODS: Fifty-two biopsy-proven lymphoma patients (19 Hodgkin disease, 12 follicular non-Hodgkin lymphoma and 21 diffuse large B-cell non-Hodgkin lymphoma) underwent a 18F-FDG PET/CT study that included unenhanced low-dose CT and enhanced full-dose CT for initial staging. For every patient, each modality of PET/CT images was evaluated by a pair of readers, comprising 1 experienced radiologist and 1 experienced nuclear physician. While evaluating one of the 2 types of PET/CT, the readers were unaware of the results of the other type. Lesion detection, number of sites affected in each anatomic region, and disease stage were assessed. Agreement between techniques was determined by the kappa-statistic. RESULTS: For region-based analysis, PET/NCECT detected cervical lesions in 32 patients, thoracic lesions in 25 and abdominal lesions in 21, while PET/CECT detected cervical lesions in 32 patients, thoracic lesions in 24 and abdominal in 21. PET/NCECT detected 13 cases of extranodal disease and PET/CECT detected 12 cases. The total number of indeterminate findings for region-based analysis was 4 for PET/NCECT and 9 for PET/CECT. Agreement between the 2 types of PET/CT in lesion detection was almost perfect for each region considered (kappa > 0.9; p< 0.05), as well as for disease stage (kappa = 0.85; P < 0.05) which in six cases both techniques showed discordant findings. CONCLUSION: Our study showed a good agreement between unenhanced low-dose PET/CT and contrast-enhanced full-dose PET/CT for lymph node and extranodal disease in Hodgkin and non-Hodgkin lymphoma. These results suggest that unenhanced low-dose PET/CT should be enough in most patients as the only imaging technique for the initial staging of lymphomas.

OP428

Diagnostic Usefulness Of Quantitative 18F-FDG PET/CT Data In The Detection Of Bone Marrow Involvement In Primary Staging Of Lymphoma Patients

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Aim: Fluorine-18 Fluorodeoxyglucose (FDG) PET-CT examination is widely used in the primary staging of lymphoma patients. Although it has shown to be superior to conventional staging in detection of nodal and extranodal involvement, its role in detection of bone marrow involvement needs further evaluation. In this study we aimed to evaluate role of FDG PET-CT in detection of marrow involvement of Hodgkin's and non-Hodgkin's lymphoma. Material-methods: FDG PET/CT images of 62 lymphoma patients who were examined for primary staging purposes and had bone marrow biopsies were analyzed. Patients taking any chemotherapeutics or bone marrow stimulants before the PET/CT scan were excluded. We measured bone marrow FDG uptake by drawing cubic volume of interests over lumbar 3rd, 4th and 5th vertebrae and calculated the mean standardized uptake values (bmSUV). Focal pathological findings were excluded from this quantitative analysis. Additionally, mean SUVs were calculated for mediastinal blood pool (bloodSUV) and liver (liverSUV). Receiver operating characteristics (ROC) curve analyses were used to assess the diagnostic accuracies of bone marrow uptake using bmSUV values, bmSUV/bloodSUV and bmSUV/liverSUV ratios. Bone marrow biopsy findings were used as the diagnostic reference. Results: The study group involved 19 Hodgkin's and 43 non-Hodgkin's lymphoma patients. Bone marrow biopsy showed infiltration in 13 of 62 patients (21%) and negative in 49 (79%). ROC curve analysis using bmSUV produced an area under curve (AUC) value of 0,722 (p=0,014). With a cut-off value of bmSUV ≥ 2,5 FDG PET-CT demonstrated 69% sensitivity and 63% specificity in the detection of bone marrow involvement. AUC value was slightly better (0,754 with p=0,005) for the bmSUV/ bloodSUV ratio and slightly lower (0,706 with p=0,023) for bmSUV/ liverSUV. Using a cut-off value of bmSUV/bloodSUV ≥ 1,8 increased specificity to 69% without a change in sensitivity. Conclusion: Quantitative analysis of FDG PET-CT images showed moderate sensitivity and specificity in diagnosis of bone marrow involvement in lymphoma patients. Using bone marrow to blood pool FDG uptake ratio instead of bone marrow 18F-FDG uptake increased the specificity value.

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Computer aided assessment of therapy response in PET-CT in patients with lymphoma - clinical benefit or more confusion ?

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The assessment of the response to therapy in PET-CT in patients is not often easy. Several studies needs to be compared and frequently the findings are unequivocal. The aim of study was to assess the dedicated software for PET-CT studies comparison against the clinical outcome. Method: We studied 30 consecutive patients with the baseline study who were referred for the therapy response assessment in the PET-CT. Fourteen patients had 3 PET-CT scans. The acquisition was performed on the same PET-CT scanner with the same uptake time. The injected FDG activity ranged between 300 and 380 MBq. The PET VCAR software was compared against the clinical assessment. The assessment was conducted in every site showing uptake (lesion comparison) at the baseline study and the overall (summary comparison) performance of the software. Results The lesion comparison was significantly different than summary comparison results (p<0.05). The errors were caused by including the tonsillar and other inflamatory uptake into analysis (3 patients). There was an excellent correlation between the clinical outcome and PET VCAR results based on the lesion comparison but not the summary comparison. It was caused by averaging of the response in the four cases of mixed response cases (i.e. partial response with new lesions). Conclusion: Dedicated study comparison software is concordant with the clinical outcome and may be helpful only if done on the per lesion basis. The summary results should be always verified.

OP430

The role of 18F-FDG PET/CT in the change of staging and therapeutic management in patients with Hodgkin Lymphoma

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Aim: To assess the sensitivity and specificity of CT and 18F-FDG-PET/CT in identifying nodal sub diaphragmatic lesions and/or extra nodal lesions in patients with Hodgkin lymphoma, leading to a consequent change of staging and therapeutic management. Materials and methods: 137 examinations 18F-FDG-PET/CT in 100 patients with Hodgkin lymphoma, range age 8-78 years, 65 enrolled for follow-up/restaging, 37 for staging, 35 for post-therapy assessments (chemotherapy and/or radiotherapy and/or stem cell transplant). All patients performed a contrast medium total-body CT, within six months (range 1 - 6 months) of PET/CT total-body. The performance of the methods was assessed considering a follow-up of 6 months - 2 years. Results: in 97/137 examinations (70.8%) the two methods were in agreement (85/97 negative, 12/97 positive) with a K-Cohen of 0.65 (substantial agreement). In 40/137 examinations (29.2%), the two methods were in disagreement. Specifically in 21/40 examinations (15.32% of total examinations), CT reported lesions were not confirmed by PET/CT. In the follow-up in 14/21 patients 18F-FDG-PET/CT determined a change of management and these patients were considered in partial remission (free therapy), in 6/21 patients there was a change of staging, but not of the management, in 1/21 there was a false negative PET/CT result. In 19/40 examinations (13.86% of total examinations) 18F-FDG-PET/CT reported lesions not detected by CT. Specifically in the follow-up in 6/19 patients PET/CT determined a modify of management with a change of staging and therapy, while in 9/19 patients there wasn't a change of therapy, but in 7/9 there was a change in the staging, finally in 4/19 patients the management of patients did not considered the PET/CT results, but only the results of CT. The differences in performance between the methods were analyzed with the McNeamar test with p <0.05 considered statistically significant. PET/CT reported values of sensitivity (78.12%), specificity (94.28%), accuracy (90.51%), positive predictive value (80.64%) and negative predictive value (90.51%) that were higher than CT values of the same parameters (59.37%, 86.66%, 80.29%, 57.57% e 80.29% respectively). The McNeamar test calculated a better performance of 18F-FDG-PET/CT for the sensitivity and positive predictive value. Conclusions. 18F-FDG-PET/CT is significantly superior to CT in determining presence or absence of nodal sub diaphragmatic and/or extra nodal lesions in patients with Hodgkin lymphoma, indicating higher probability that a person presents disease in those locations with better discrimination of true positive and false positive patients.

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The role of FDG PET and PET/CT in initial staging of childhood lymphomas

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Aim: Positron emission tomography (PET) and integrated positron emission tomography with computed tomography (PET/CT) using fluorine-18-fluorodeoxyglucose (FDG) offer information on

the metabolic activity of tumor cells and was proven useful in staging of lymphomas in adults. Increased metabolic activity frequently precedes the delayed morphological and anatomical changes and metabolic changes may occur even if anatomic size does not change significantly.Whole-body PET and PET/CT can also detect lesions at unexpected sites. The aim of our study was to assess the usefulness of PET and PET/CT for initial staging of pediatric lymphomas and its possible impact on the clinical management. Materials and methods: Over a period of 5 years eighty-six children and adolescents with lymphoma (58 with Hodgkin's lymphoma, 28 with non-Hodgkin's lymphoma) had complete diagnostic work-up including FDG-PET (31 pts.) or PET/CT (55 pts.) and were included into this study. Mean age was 15 years (4-19). PET and PET/CT findings were correlated with standard staging methods (CSM) including CT, ultrasound, and bone marrow examination. Discordant findings were verified by MRI and follow-up radiographic studies including PET and PET/CT. Results: There were concordant findings in 57/86 (66%) children. In 26 patients PET and PET/CT revealed 40 additional lymphoma manifestations (22 normal-sized lymph nodes, 13 focal bone marrow infiltrates, and 5 extra-nodal lesions) and correctly upstaged 13 of 86 children (15%). Only two out of 86 patients (2%) were not accurately staged by PET, when PET failed to visualize diffuse bone marrow infiltration (extent of 15% cells) in 1 patient (CT negative), and missed small pulmonary metastases (≤6 mm) in 1 child, that were correctly described by CT component of integrated imaging. Compared with CSM, pre-treatment PET had significantly higher sensitivity (97% vs. 83%), specificity (100% vs. 89%), and significantly higher accuracy (98% vs. 84%). Clinical management was modified in 11/86 (13%) of patients as a result of PET findings. Conclusions: The inclusion of FDG PET and PET/CT in the imaging evaluation of children with lymphoma can have significant impact on the clinical management. Our study showed that PET and PET/CT imaging have the ability to detect both nodal and extra-nodal lymphoma manifestations and is useful and complementary to other imaging studies for primary staging of pediatric lymphomas. Supported by grants: IGA NS/9997-4 and MZO FNM 2005

1307 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 115

Oncology SPECT: molecular imaging - new clinical methods, new radiopharmaceuticals

OP432

Preparation and in vivo evaluation of ^{99m}Tc-DTPA-Gd for possible multimodal imaging use

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Objective The purpose of this study was to observe the biologic characteristics of Gd-DTPA-Dimeglumine of magnetic resonance contrast enhancer labeled with technetium-99m. **Method** The labeled compounds was prepared by reducing ^{99m}Tc in the presence of Gd-DTPA-Dimeglumine with stannous chloride. The labelling efficiency and stability of ^{99m}Tc-Gd-DTPA-Dimeglumine and ^{99m}Tc-DTPA were measured by thin paper chromatography. The plasma protein binding rates were measured by the trichloroacetic acid method, the biodistribution in mice was observed by the blood sampling and major organs that were taken out from mice at 1min, 5min, 10min, 15min, 30min, and 60min after intravenous injection of labeled compounds, and renal dynamic scintigraphy in rabbit were administrated. All of the experimentations compared with ^{99m}Tc-DTPA. **Results** The labelling efficiency of ^{99m}Tc-Gd-DTPA-Dimeglumine was 97% and stable at room temperature within 6h. The plasma protein binding rate of ^{99m}Tc-Gd-DTPA-Dimeglumine and ^{99m}Tc-DTPA were 3.48±0.24% and 2.25±0.21%, respectively, and have significant difference. Statistical indicated that the amount of ^{99m}Tc-Gd-DTPA-Dimeglumine deposited in brain, heart, lung higher than that of ^{99m}Tc-DTPA at 1min after injection, and ^{99m}Tc-Gd-DTPA-Dimeglumine deposited in muscle , blood, heart deposited higher than that of latter at 5min, 10min, 15min respectively. Renal dynamic scintigraphy showed that two labeled compounds were quickly excreted by kidney, and the time to peak less than 5min, the half time of clearance is about 10min. **Conclusion** The magnetic resonance contrast enhancement of Gd-DTPA-dimeglumine may be labeled with with technetium-99m. ^{99m}Tc-Gd-DTPA-Dimeglumine may be a significant way to study its biodistribution *in vitro* and *in vivo.* ^{99m}Tc-Gd-DTPA-Dimeglumine could be detected with both SPECT and MRI which increase imaging resolution and sensitivity.

OP433

Facile synthesis of DO3MP-AME-DO3MP and its preclinical evaluation as multidentate imaging agent for skeletal metastases using SPECT

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Aim: A variety of bone-seeking radiopharmaceuticals have been used in attempts to diagnose and palliate the pain of patients with skeletal metastases. The phosphorus based tracers especially phosphonate compounds are routinely used for this purpose. The presence of uncoordinated phosphonate oxygen atoms allow a mechanism for absorption of the complexes on the surface of newly formed hydroxyapatite. The diagnostic imaging of the lesions before the therapy is useful in giving information about the extent of damage and radiation doses to be delivered during therapy. The metastable radionuclide 99mTc has become the mainstay of diagnostic nuclear medicine. Design of a phosphonate derivative having diagnostic application in bone imaging is the aim of our research. **Methods:** As part of our efforts to explore the application of chelating agents, this work describes the potential of 99mTc- DO3MP-AME-DO3MP as diagnostic pharmaceutical by evaluating its deposition in bony tissues after the synthesis and radiolabeling of 10-bis(acetamido)ethane-bis[1,4,7-tri(methylenephosphonicacid)-1,4,7,10-tetraazacyclododecane (DO3MP-AME-DO3MP). 1,4,7,10-Tetraazacyclododecane was converted to tris(t-butyl) ester of 1, 4, 7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane. Fourth unsubstituted arm was bound with ethylene diamine based linker and was attached to one more unit of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane to give the compound , 10-bis(acetamido)ethane-bis[1,4,7-tri(carboxymethane)-1,4,7,10-tetraazacyclododecane (DO3A-AME-DO3A). Finally its phosphonic acid derivative, DO3MP-AME-DO3MP, was synthesized with PCl_3. **Results:** DO3MP-AME-DO3MP was synthesized and characterized by NMR spectroscopy. The radiolabeling efficiency was found to be > 97% and the stability in serum indicated that 99mTc remained bound to the chelate, DO3MP-AME-DO3MP up to 24h. Blood clearance showed a quick wash out from the circulation and biological half life were determined. Biodistribution characteristics of 99mTc- DO3MP-AME-DO3MP were examined in BALB/c mice and it shows prominent bone localization. The drug was excreted mainly through renal routes. The scintigraphic images of 99mTc- DO3MP-AME-DO3MP in rabbit showed rapid accumulation of radioactivity in bone. Within 30 min the compound 99mTc- DO3MP-AME-DO3MP was localized in the whole skeleton rapidly. The images also show that non-osseous tissue uptake of 99mTc-chelate was minimal and when assessed with its rapid blood clearance, accounts for the low soft tissue activity. **Conclusions:** 99mTc- chelated DO3MP-AME-DO3MP has high bone accumulation property, since it displays selective uptake in the skeletal system and has low nontarget uptake and rapid nonosseous tissue. Therefore, it can be useful in bone metastases pretherapy diagnostic imaging. Attempts are being made to use it for therapeutic purpose with radiometals (β-emitters) like Ho-166, Re-186 and other metal ions.

OP434

Facile synthesis of methionine conjugate with macrocyclic chelate (DO3A-Act-Met): Its Preclinical evaluation as SPECT/PET radiopharmaceutical for tumor imaging

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Aim: Single Photon Emission Computed Tomography (SPECT) has become a powerful scientific and clinical tool for probing biochemical processes in the human body. 80% of radiopharmaceuticals used in nuclear medicine are ^{99m}Tc labeled because of its favorable physical and radiation characteristics. The metastable radionuclide ^{99m}Tc has become the mainstay of diagnostic nuclear medicine. So far many radiolabeled amino acids have been exploited for determining protein synthesis pathways and believed to better reflect the malignant nature and increased proliferation of cancer cells, methionine based are one of them. Methionine is known for its active participation in protein synthesis, it acts as methyl group donor in the biosynthetic pathways. The metabolic rate at cancerous tissues is more and so the uptake of methionine. Currently, many methionine based compounds have found application in SPECT and L-[methyl-^{11}C]-methionine (MET) is the most popular AA- imaging modality for tumors in PET, although its use is restricted to PET centers with an in-house cyclotron facility. The objective is to synthesize 4-methylsulfanyl-2-[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-butyric acid, (DO3A-Act-Met) having application in SPECT and PET. **Method:** This work describes the potential of ^{99m}Tc- DO3A-Act-Met as diagnostic pharmaceutical by evaluating its deposition in cancerous tissues after the synthesis and radiolabeling of 4-methylsulfanyl-2-[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-butyric acid, DO3A-Act-Met. 1,4,7,10-Tetraazacyclododecane was converted to tris(t-butyl) ester of 1, 4, 7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane. Fourth unsubstituted arm was bound with chloroacetyl derivative of methionine methyl ester to give the compound, 4-methylsulfanyl-2-[2-(4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetylamino]-butyric acid, DO3A-Act-Met. Finally, the compound is radiolabeled with ^{99m}Tc for scintigraphic studies. **Results:** DO3A-Act-Met was synthesized and characterized by NMR and Mass spectroscopy. Radiolabeling efficiency with ^{99m}Tc was found to be > 97% and the stability in serum indicated that ^{99m}Tc remained bound to DO3A-Act-Met up to 24h. Initial investigation of blood clearance showed a quick wash out from the circulation and biological half life were determined. Biodistribution characteristics of ^{99m}Tc- DO3A-Act-Met were examined in BALB/c mice and it shows prominent tumor (EAT) localization. The drug was excreted mainly through renal routes and the accumulation of ^{99m}Tc- DO3A-Act-Met in tumor was determined at various time intervals. **Conclusions:** ^{99m}Tc- DO3A-Act-Met has high tumor (EAT) accumulation property. Further investigation on the BMG glioblastoma is being carried out. Attempts are also being made to use the cavity of 1,4,7,10-tetraazacyclododecane to introduce 68Ga and 64Cu to determine the application of DO3A-Act-Met in PET imaging.

OP435

MDR and MDR reversal kinetics in human adenocarcinoma cell lines

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Aim: Multidrug resistance (MDR) is a condition characterized by the presence of cross-resistance to several non-structurally related drugs, representing one of the major setbacks to the success of chemotherapy. One of the mechanisms responsible for MDR is the overexpression of efflux pumps such as P-glycoprotein (Pgp), multiple resistance-related protein 1 (MRP1) and lung resistance-related protein (LRP). These proteins confer resistance to a similar spectrum of substrates, despite their different intracellular locations and extrusion mechanisms. Verapamil is a L-type calcium-channel blocker, ¬known as a substrate for Pgp, reversing its activity. L-Buthionine-sulfoximine (BSO) is a γ–glutamylcysteine synthetase inhibitor and can be used as blocker for cellular MRP1. In this study we aim to compare transport kinetics for a resistant human colorectal adenocarcinoma cell line, in the presence and absence of two MDR reversers, verapamil and BSO, through 99mTc-Sestamibi. Methods: MDR proteins expression was evaluated in resistant (ATCC-LS1034) and sensitive (ATCC-WiDr) human colorectal adenocarcinoma cell lines. Cytoplasmatic and membrane Pgp, MRP1 and LRP, was analyzed by flow-cytometry. Pgp expression was also analyzed using western blotting techniques. Cellular transport kinetics was analyzed in the presence and absence of MDR modulators, verapamil and BSO. Retention studies were performed after cell incubation with the previously referred drugs, for different time intervals (10 and 60 minutes) and concentrations (10, 25, 50 and 100 μM) with 99mTc-Sestamibi. For that cells were incubated for 60 minutes, washed after and resuspended with 99mTc-Sestamibi-free medium. Samples were collected and cell metabolism stopped at different time-points in order to obtain retention percentage, which was measured by gamma-counting adjusted for 140 keV. Retention studies were also performed using LigandTracer® Yellow (Ridgeview Instruments AB, Uppsala-Sweden), an equipment that enables real-time measurements in order to obtain continuous retention curves. Data was analyzed using

appropriate software. Results: Pgp and LRP expression was significantly higher ($p<0.05$) in resistant cells when compared to the sensitive ones, although MRP1 being also expressed. Western blotting analysis confirmed flow-cytometry results. 99mTc-MIBI retention percentage was significantly higher ($p<0.05$) in the resistant cell line when compared with the sensitive one for all time-points considered. In resistant cells incubated with MDR modulators there are no statistically significant differences ($p>0.05$) when all points of the retention curves are considered. However, in the first minutes that there are differences among the MDR modulators used. Conclusions: The data obtained until now suggest that with the modulators evaluated, they must be used immediately before the cytotoxic drug administrated.

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Targeting Metastatic Prostate Cancer (PCa) Using ^{123}I-MIP-1072 & ^{123}I-MIP-1095: A Phase I Clinical Study in Patients

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Background: The rapid and accurate detection of metastatic PCa remains a clinical challenge. An exploratory clinical study using two I-123 labeled small molecule inhibitors of prostate specific membrane antigen (PSMA), previously shown to selectively target PSMA(+) PCa xenografts has been completed. The compounds are based on glutamate-urea-lysine heterodimers (J Med Chem 2008). **Methods**: Organ and blood pharmacokinetics and urinary excretion were studied after an intravenous dose of 10mCi of ^{123}I-MIP-1072 and ^{123}I-MIP-1095 in 7 patients with confirmed metastatic PCa in a crossover design. Serial whole body (WB) planar images, blood and urine were collected over 3 days. ROI analysis was used to estimate organ and WB retention. Radiation absorbed doses were estimated using OLINDA/EXM. Target to background ratios were calculated based on the mean tumor ROI (counts/pixel) divided by the mean adjacent background of comparable size. Lesion visualization (LV) was scored on a 0-4 scale using 2 blinded readers with a score of 2 being classified as good. **Results**: After IV injection, both agents were observed to localize in both solid tumors (S) and bony metastases (B) as early as 0.5hr. At 1hr LV was scored at 2 for all confirmed lesions with T/B of S 1.7, B 1.8 and S 1.7, B 1.4 for MIP-1072 and MIP-1095. 4-6hr was determined to be the optimal imaging time with an LV of 3 and T/B of S 1.9, B 2.2 and S 1.9, B 1.7 for MIP-1072 and MIP-1095. At 48 hr T/B was still > 2.0 due to the compounds internalization in the tumor. Both agents cleared the blood in a biphasic manner, MIP-1072 was~5X faster (36 vs 7ml/hr/kg.). MIP-1072 was excreted in the urine unchanged with 54% and 74% in the urine by 24 and 72hr. In contrast, only 7% and 20% of MIP-1095 was renally excreted at 24 and 72 hr with some metabolism observed. Estimated absorbed doses were 74 vs 148mGy/MBq in kidneys (MIP-1072 vs MIP-1095) 33 vs 78mGy/MBq in liver; 81 vs 218mGy/MBq in salivary glands and 30 vs 44mSv/MBq effective dose. **Conclusion**: Both agents rapidly detect metastatic prostate cancer in soft tissues and bone confirming that targeting the extracellular domain of PSMA with small molecules is a viable approach for molecular imaging of metastatic prostate cancer. Extrapolation to ^{131}I therapy demonstrates that the kidney will be the dose-limiting organ (assumes thyroid blockade) at administered doses for ^{131}I-MIP-1072 of 31GBq and for ^{131}I-MIP-1095 of 7GBq.

OP437

Pretherapeutic Evaluation of extra-hepatic Accumulation in SIRT-Patients by Tc-99m-MAA-Perfusion-Scintigraphy: Is there an Impact of SPECT-MRI/CT-Image Fusion?

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Aim: Pretherapeutic patient evaluation by Tc-99m-MAA-perfusion-scintigraphy is a prerequisite for the successful and safe performance of selective internal radio therapy (SIRT). The aim of our study was to evaluate the benefit of SPECT-MRI/CT-image fusion in comparison to planar whole body scintigraphy. **Patients and Methods:** In our retrospective study 120 patients (m: 74, f: 46; mean age: 61.6y, 17-85y) with primary (n=29) or secondary (n=91) liver malignancies were included. All patients had been examined with Tc-99m-MAA-perfusion scintigraphy between 01/2007 and 09/2008. The imaging protocol consisted of planar whole body scintigraphy and SPECT of the abdomen. Additionally, contemporary abdominal MRI- or CT-images were acquired. After software based manual fusion of SPECT and MRI/CT, both planar images and fused SPECT-MRI/CT-images were assessed for the presence of extra-hepatic nuclide accumulation in a consensus reading. Comparative statistics were applied for data analysis. **Results:** In 45 of 120 patients (37%) extra-hepatic nuclide accumulation was suspected according to planar scans. We found a confirmation of extra-hepatic nuclide accumulation in planar scans by fused images in 21 of the 45 patients (47%) and no confirmation in 24 of the 45 patients (53%). In 12 of the 75 patients (16%) without extra-hepatic nuclide accumulation in planar scans an extra-hepatic nuclide accumulation was found in fused SPECT-MRI/CT images. As a consequence, image fusion changed the therapeutic strategy in 36 of the 120 patients (30%). 24 of the 36 false positive patients (67%) in planar scintigraphy could be treated by SIRT without reservations. In 10 of the 36 patients (28%) SIRT was possible after angiographic reassessment. In 2 of the 36 patients (5%) SIRT was not possible despite angiographic re-evaluation. **Conclusion:** Fusion of Tc-99m-MAA-SPECT- and MRI/CT-images is superior to planar scintigraphy for the detection/exclusion of extra-hepatic nuclide accumulation. As the therapeutic strategy was altered in 30% of our patients, SPECT-MRI/CT-image fusion is in our opinion mandatory for the correct pretherapeutic evaluation of patients before SIRT.

OP438

Improved diagnostic accuracy for neuroendocrine tumours using fused SPECT/CT (low dose) with Tc-99m-Tektrotyd

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Somatostatin receptor scintigraphy (STRS) of neuroendocrine tumours (NETs) is often challenging because of lesion size and poor anatomic delineation. Tc-99m-Tektrotyd is a recently developed tracer for imaging tumours with overexpression of somatostatin receptors, especially subtype 2. The aim of this study was to evaluate the added value of single-photon emission computed tomography (SPECT)/CT hybrid imaging with Tc-99m-Tektrotyd for staging patients with NETs. **Material and Methods:** Eleven patients (10m,1f; age 19-74 a) with histologically proven NETs (G1,2 patients; G2,5 patients; G3,4 patient, according to WHO Classification. Functioning NET,3 patients; nonfunctioning NET,8 patients) were investigated for staging of disease before (6 patients) or after (5 patients) surgery of primary tumour. STRS was performed in all patients at 1h and in 5 patients also at 3h p.i. of 555 MBq Tc-99m-Tektrotyd. All patients underwent whole-body scan (AP and PA) and SPECT/CT (low dose) imaging of thorax, abdomen and in selected cases of head and neck also. SPECT images were first interpreted alone and then re-evaluated with the addition of fused SPECT/CT images. **Results:** Abnormal SPECT findings were reported in 23 sites (primaries,4; metastases,19) in 10 patients. CT anatomical maps provided more precise anatomical localization than SPECT alone in 9 of these abnormal findings. SPECT/CT hybrid imaging allowed the characterization of the significance of 5 lesions found with diagnostic CT and enabled the exclusion of tumour disease in 3 of the sites with abnormal tracer uptake. The minimum size of the lesions that were detected was 6 mm. **Conclusions:** The imaging properties of Tc-99m and the one-day imaging protocol with Tc-99m-Tektrotyd offer opportunities for more widespread application of STRS. Fused SPECT/CT (low dose) images allow a highly accurate localization of tumour sites and improve the diagnostic accuracy of Tc-99m-Tektrotyd SPECT in patients with NETs.

1308 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 116

Neurology/psychiatry: miscellaneous

OP439

Monitoring of treatment response in brain tumors by 18F-FET PET/CT

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Aim: The aim of this retrospective analysis was the monitoring of the response of patients with brain tumors after irradiation or chemotherapy with FET (O-(2-[(18)F]fluoroethyl)-L-tyrosine) PET/CT and the comparison with the results of MRI. **Material and Methods:** We included 15 patients (10 men and 5 women) with a mean age of 43 years (range: 25 to 63 years). The tumors were classified as astrocytomas grade II (4), astrocytomas grade III (2), glioblastomas (7), oligodendroglioma grade II (1) and oligoastrocytoma grade II (1). The patients were treated with chemotherapy alone (n=9), radiotherapy (n=4) or chemotherapy combined with radiotherapy (n=2). 185 MBq 18-F-FET were injected i.v., followed by PET/CT imaging of the brain (Philips Gemini GXL) 30 minutes later. Each patient was examined two times by a FET PET between July 2005 and February 2009. The mean time lag was 10 (1 to 36) months. A visual interpretation with a semi-quantitative analysis (SUV) was performed. The patients were classified into responders and nonresponders. The results were compared to the findings on MRI. A stable disease was concerned to be a response to therapy. **Results**: In 14 of 15 (93%) patients FET PET results were concordant to the MRI changes. We found 7 patients in the responder group and 7 patients in the nonresponder group. In one patient (7%) FET PET showed a response, while MRI suggested a progression. The mean SUV in the responder group decreased by 31% (0 - 65%) and increased in the nonresponder group by 89% (19 - 217%). **Conclusion**: The FET PET results were concordant to the MRI results in the vast majority of patients, but one patient under newly initiated Bevacizumab therapy showed early metabolic response to chemotherapy while the structural response has to be awaited. FET PET and MRI are considered complementary modalities. They should be performed concerted in patients with brain tumors, especially because of the ability of FET PET to show metabolic response even before structural changes become detectable.

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Brain tumour delineation over dual time point ^{18}FDG PET

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Tumour delineation for therapy planning is normally related to non-^{18}FDG-PET tracers since normal brain has a high metabolic uptake of ^{18}FDG. Nevertheless, delayed ^{18}FDG-PET has shown better contrast of tumour to normal brain uptake (T/N) ratio. Objective To compare several strategies for tumour delineation based on quantitative criteria applied over dual time point ^{18}FDG-PET images. Materials and methods An automated tumour segmentation method was designed based on the differences between standard and delayed ^{18}FDG-PET images. Four different segmentation criteria were considered: any SUV increase, SUV increase greater that 10%, any T/N ratio increase and T/N ratio increase greater that 10 %. In order to validate the paradigm, ten patients with suspected glioblastoma multiforme recurrence and uncertain MRI findings were studied. All patients underwent a dual time point ^{18}FDG-PET study, with standard images acquired at a median of 46.5 minutes (38 to 56) after injection and delayed images acquired at a median of 343.2 minutes (229.8 to 387.0) after injection. A ^{11}C-Metionine-PET study was also performed. In order to assess comparisons on a voxel basis, parametric images of SUV and *T/N* ratio were obtained and images from each subject were registered and spatially normalised (SPM2). Tumour extension was analysed attending to each criterion, and compared

to the volume segmented over the ^{11}C-Methionine-PET, considering a T/N ratio of 1.4 as threshold for malignancy. Results All tumours showed areas with T/N ratio increase greater that 10% between early and delayed ^{18}FDG-PET. Besides, 9 tumours presented areas with SUV increase, and 8 lesions presented a SUV increase greater than 10%. The volume defined with T/N ratio increase on dual time ^{18}FDG-PET was similar (1/10) or smaller (9/10) than the volume delimited over ^{11}C-Methionine-PET. SUV increase based criteria yielded smaller tumour extension than T/N ratio criteria in 9/10 patients. Therefore, all criteria considered were too restrictive in segmenting the tumour extension. However, in most patients (8/10) the segmented volume matched with the highest uptake in ^{11}C-Methionine-PET, corresponding to the most malignant area in tumour. Conclusion Dual time point ^{18}FDG-PET is useful for tumour delineation in glioblastoma multiforme recurrence. Comparing to ^{11}C-Methionine-PET, the increase in the T/N ratio over dual time point ^{18}FDG-PET provides the best criteria for tumour delineation.

OP441

Reduced thalamic FDG uptake in adults with neurofibromatosis type 1 and correlation with peripheral tumor load

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Aim: Previous FDG-PET studies suggest that cerebral glucose metabolism in subjects with neurofibromatosis type 1 (NF1) is reduced specifically in the thalamus. However, these studies are limited by small sample size and poorly matched control groups. In addition, they did not attempt to explain this specific effect. The aim of the present study was to analyze cerebral FDG uptake in a large sample of adults with NF1 compared to a well-matched control group. In order to test the hypothesis that reduced thalamic activity in NF1 is caused by nerve-tumor-related reduction of peripheral input due to PNF/MPNST, thalamic FDG uptake was tested for correlation with total tumor burden. **Materials and Methods**: Whole-body FDG-PET/CT including the brain had been performed in 30 NF1 subjects for detection of MPNST. Brain FDG uptake was normal by visual inspection in 24 subjects who were included in the present analysis (14 females, 37.9±16.2 years). Twenty-four control subjects were selected in reverse chronological order using a match-by-subject approach with respect to gender and age. FDG-PET/CT had been performed for a non-NF1/non-CNS oncological indication. Subjects with any finding in the brain were excluded. NF1 subjects and controls did not differ with respect to gender, age, blood glucose level, or FDG dose. Individual brain FDG uptake images were stereotactically normalized using SPM2, and scaled to a common median uptake value within a predefined gray+white matter mask. Scaled FDG uptake was compared voxel-by-voxel between the NF1 group and the controls at the uncorrected significance level α=0.001. VOI-based analysis was performed using the thalamus VOI of the AAL-atlas. Total tumor burden was quantified in 8 NF1 subjects from whole-body MRI. **Results:** Voxel-based testing revealed a single 6.8 ml cluster of reduced FDG uptake in the NF1 subjects located in the thalamus. There was no increase of FDG uptake in the NF1 subjects. VOI-analysis showed a 7.2% reduction of thalamic FDG uptake in the NF1 group (t =-3.273, df= 46, p=0.002). Total tumor burden ranged between 7ml and 1.4L. Thalamic FDG-uptake did not correlate with total tumor burden (Pearson r=0.241, p=0.612). The power to detect a correlation of r=-0.7 at the 0.05 level was 79%. **Conclusion:** Adult subjects with NF1 show reduced FDG uptake specifically in the thalamus. Apparently there is no strong association between thalamic FDG uptake and total tumor burden. However, larger sample size is required to further test the hypothesis of impaired peripheral input to the thalamus in NF1.

OP442

Association between reduced cortical α4β2* nicotinic acetylcholine receptor binding and impaired memory and attention in early stage multiple sclerosis: a 2-[18F]F-A-85380 PET study

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Aim: Cognitive dysfunction is a common feature even in early stage multiple sclerosis (MS). Lower cortical and subcortical α4β2* nicotinic acetylcholine receptor binding (α4β2*-nAChR) may be associated with cognitive impairment. To investigate α4β2*-nAChR availability in MS and its relationship to cognitive symptoms, patients with early stage MS with negligible MRI-based cortical or global atrophy were studied using α4β2*-nAChR specific 2-[18F]F-A-85380 (2FA) PET and multiple cognitive testing. Methods and Materials: Seven non-smoking early stage MS (37±16 ys; 3/4 m/f; EDSS 1.9±1.6; MMSE 29.3±0.8; DemTect 15.0±2.3), seven age-comparable, non-smoking normal controls (NC; 46±10 ys; 4/3 m/f; MMSE 29.6±0.8; DemTect 16.4±2.1) underwent 2FA-PET. Parametric images of the distribution volume were determined (Logan plot) with the arterial input function corrected for plasma protein binding and radiolabeled metabolites. Binding potential (2FA-BP) was calculated using the corpus callosum as reference region. VOI-/SPM-analyses were performed. To assess different cognitive domains, MS and NC were tested with a multiple cognitive test battery (DemTect - 5 subtests, WAIS-III, WMS-III, DOT, TMTA/B). T1/T2-weighted MRI were analyzed semiquantitatively for regional cortical and global atrophy. Significance was accepted at p<0.05 (for SPM p<0.001). Results: Compared to NC, in MS 2FA-BP was significantly reduced in frontal cortex (superior, middle, inferior), cingulate cortex (anterior, middle and posterior), temporal cortex (superior, pole, middle, inferior), sensorimotor cortex (supplementary motor area; SMA), parietal and occipital cortex (cuneus) and cerebellum. Compared to NC, MS patients performed significantly worse in cognitive testing such as WAIS-III digit span forward, word list - immediate recall and Wechsler Memory Scale III - immediate recall implicating impaired attention and verbal/working memory. These cognitive measures correlated significantly with reduced 2FA-BP in frontal and cingulate cortex, temporal, parietal and occipital cortex. There was negligible MR-based cortical/global atrophy in MS compared to NC (p>0.3) Conclusion: In early stage MS, there is significantly reduced α4β2*-nAChR binding in frontal and cingulate cortex (anterior, middle and posterior), in temporal, parietal and occipital cortex (cuneus), in sensorimotor cortex (SMA) and the cerebellum. Since these MS patients demonstrate only negligible cortical/global atrophy, these cortical and cerebellar α4β2*-nAChR diminutions may precede significant cerebral atrophy. Furthermore, in early stage MS cognitive testing revealed significant impaired attention, verbal and working memory that are associated with lower α4β2*-nAChR binding especially in the frontal and cingulate cortex, temporal, parietal and occipital cortex. These preliminary 2FA-PET data suggest that α4β2*-nAChR might become a new target for early assessment and drug development of cognitive impairment in MS.

OP443

In- vivo diagnosis of atypical Alzheimer disease using pathology-sensitive brain imaging, 11C-PIB and short TE spectroscopy MR imaging in Posterior Cortical Atrophy

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Atypical presentations of Alzheimer's disease (AD) may account for 15-20% of cases and can be diagnostically challenging when non-memory symptoms are the initial presenting feature. Recognized clinical syndromes include Posterior Cortical Atrophy (PCA), characterized by deficits of visuospatial function associated with typical AD histopathological changes. There is a role for pathology sensitive imaging techniques to support in vivo diagnosis. Such techniques include ^{11}C-PIB PET, a marker of beta amyloid (Abeta) plaques, as well as Proton Magnetic Resonance Spectroscopy (MRS), which allows non-invasive measurement of cerebral metabolites N-Acetylaspartate (NAA) and Myoinositol (MI). Aim This study aims to identify the role of pathology-sensitive imaging biomarkers in atypical lobar atrophy syndromes for improving early diagnosis. Materials & Methods Two patients with PCA were recruited from the memory clinics of Imperial College Healthcare NHS Trust. We evaluated brain amyloid load with ^{11}C-PIB PET and regional NAA/MI ratios with MRS. Both PCA patients had a neuropsychological assessment and MRI (3T) including isotropic volume T1-weighted MP-RAGE and short TE 2D MR spectroscopic imaging. Amyloid load was assessed by 60-90min target: cerebellum RATIO and ROI analysis. Retention of ^{11}C-PIB was compared with that of typical AD (N=10) and normal control subjects (N=17) from our database using statistical parametric mapping(SPM2). Results The PCA patients, both women, were aged 54 and 60 years and had MMSE scores of 27/30 and 25/30 respectively. Neuropsychological testing showed profound deficits in visuospatial function with relatively preserved memory. Cortical ^{11}C-PIB binding was raised in the frontal, parietal, temporal and occipital cortex compared with the controls($P < 0.000$). The PCA ^{11}C-PIB binding pattern was similar to Alzheimer disease (parietal, temporal and frontal cortex) but retention was higher in the occipital cortex($P < 0.001$). Low N-Acetylaspartate (NAA) and elevated Myoinositol (MI) ratios were found in spectra acquired from voxels, which included the posterior cingulate gyrus. Both patients showed regional parietal cortical atrophy; more marked in one case than the other. Conclusion We have demonstrated increased ^{11}C-PIB retention reflecting raised amyloid in two Posterior Cortical Atrophy patients. Uptake was higher in the occipital cortex compared with typical Alzheimer disease patients, reflecting the pattern of neuropsychological deficit. In addition, brain metabolic MRI profiles showed regional decreases in N-Acetylaspartate (NAA), increases in Myoinositol (MI), known to be associated with AD. Pathology-sensitive in-vivo techniques have the potential to facilitate differential diagnosis of atypical dementia and identify patients who could benefit from specific anti-amyloid therapeutic strategies.

OP444

The detection of 18F-FDG foci on carotid bifurcations and on aortic arch is associated with an enhanced risk of subsequent ischemic stroke: a case-control study

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Aims - When documented in atherosclerotic plaques, a high uptake of 18F-fluorodesoxyglucose (FDG) is likely to relate to an inflammatory cells infiltrate and thus, to potentially unstable plaques. However, the relation with an enhanced risk of subsequent ischemic event is not yet established. This case-control study was aimed to determine whether the previous arterial FDG uptake of patients presenting a subsequent ischemic stroke is higher than that of event-free follow-up controls. Methods - We retrospectively included 26 patients, who had been referred to a conventional hybrid FDG-PET/CT imaging for an oncologic indication: (i) 8 case-patients, selected on the basis of a subsequent hospitalization for a documented ischemic stroke, and (ii) 18 event-free controls, who were matched to each case (2 to 3 per case) according to age, gender, type of cancer and date of PET imaging. The baseline clinical data, as well as data extracted from the CT and PET images of carotids and aortic arch, were compared between cases and controls. Results - Compared with controls, the case-patients exhibited: (i) trends toward a higher incidence of previous cardiovascular disease (75% vs. 29%, P=0.06) and a higher number of cardiovascular risk factors (2.6±1.4 vs.1.5±1.1, P = 0.08), (ii) equivalent CT calcium scores on carotids and aortic arch and (iii) higher rates of FDG foci on carotid bifurcations (63% vs.12%, P = 0.02) and aortic arch (75% vs. 26%, P = 0.02). Among the 5 case-patients who had a stroke of Sylvian location, 4 (80%) had FDG foci on ipsilateral carotid bifurcations and short delay times between PET and stroke (from 7 days to 14 months). This delay time was much longer (21 months) for the 5th patient who had no arterial FDG focus. Conclusion - To our knowledge, this case-control study is the first one showing that the detection of FDG foci on carotid bifurcations and on aortic arch are both associated with an enhanced risk of ischemic stroke. Further studies are required to precise the clinical usefulness of hybrid PET/CT imaging in this setting.

OP445

Cerebral perfusion changes after carotid endarterectomy, using Tc-99m ECD brain SPECT with voxel-based analysis

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Purpose: The aim of the present study was to determine preoperative hypoperfusion and perfusion changes after carotid endarterectomy (CEA) in patients with internal carotid artery stenosis. **Material.** Examined group included 27 patients (5 women and 22 men) at the age of 44-80 years with internal carotid artery stenosis 70%. Eight participants had a history of stroke and 16 of transient ischemic attacks (TIA). Preoperative computed tomography (CT) was normal in 15 cases, including 3 asymptomatic patients. **Methods.** Brain perfusion SPECT with 99mTc-ECD was performed 1-3 days before CEA and 3-5 days after the surgery. Radiopharmaceutical dose was 740 MBq. Brain SPECT was carried out 20-30 min after injection using a rotating, double-head, large field of view gamma camera (Varicam, GE Medical Systems) equipped with low-energy, high-resolution collimators. The data were collected in a 128 × 128 matrix through 360° rotation at 3° intervals for 25 s per view. Data reconstruction was performed by filtered back projection with Metz filter. Regional cerebral blood flow was evaluated visually and semiquantitatively using voxel- based analysis with Brain SPECT Quantification software (Compart, Poland). The change of perfusion between basal and control studies was considered significant when relative difference (RD) was higher than 10% in a cluster volume (CV) greater than 10 ml. **Results.** No side effects were observed after the surgery. Preoperative SPECT was normal in one asymptomatic patient and in one with TIA and normal CT. Hypoperfusion ipsilateral to CEA was seen in 23 cases, including 11 patients with normal CT. Hypoperfusion contralateral to CEA was seen in 14 cases, including 10 patients with normal CT. After the surgery perfusion did not change in 8 patients. Improvement of perfusion was observed ipsilaterally to CEA in 17 cases (CV=10.2-194.9ml, mean 62±54, RD=14.4-30%, mean 18.2±4), contralaterally in 10 patients (CV=10.2-194.9ml, mean 73.5±51.9, RD=14.2-19,1%, mean 16.1±1.8). Deterioration of perfusion was seen ipsilaterally to CEA in 2 patients (CV=16.6-17ml, mean 16.8±0.3, RD=14.4-16%, mean 15.2±1.1) and contralaterally in 2 patients (CV=24.6-28.1ml, mean 26.4±2.5, RD=13.8-15%, mean 14.4±0.8). **Conclusions**: Brain perfusion SPECT with voxel-based analysis allows for detection of hypoperfusion in patients with internal carotid artery stenosis (including asymptomatic and those without morphological changes in CT). In short - term observation perfusion disturbances tend to improve after CEA.

OP446

Brain F-18- FDG PET/CT imaging in haemolytic uraemic syndrome (HUS) during and after the acute phase.

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Introduction/background: Haemolytic-Uraemic Syndrome (HUS) is a multisystemic disease clinically characterized by uraemia, thrombocytopenia and haemolytic anaemia and it is the most common cause of acute renal failure in children between 1 and 4 years of age. Besides the kidneys, the central nervous system (CNS) is clinically involved in 20-50% of HUS cases. Common signs of severe CNS injury are seizures, alteration of consciousness, hemiparesis, visual disturbances and brainstem symptoms, with 4-10% of acute mortality. Morphologic brain imaging (CT and MRI) can show structural changes in basal ganglia, cerebellum, thalami and brainstem in 20-60% of HUS cases with severe CSN involvement. **Aim:** Functional imaging of brain perfusion/metabolism was rarely applied in HUS and aim of the study is to assess brain functional involvement by means of F-18- Fluoro-deoxi-glucose (F18-FDG) brain PET imaging. **Methods**: Six patients with HUS (3 males, mean age 6 years) were studied in acute phase and after clinical resolution (1-12 months later). Two patients had neurologic symptoms/signs but none deceased for complications. PET/CT brain imaging was obtained 40-60 min after FDG intravenous administration (Biograph TruePoint PET-CT, Siemens, Erlangen, DE). Visual and VOI-based analysis of PET data were performed comparing early and late PET/CT studies**. Results**: Acute PET/CT study showed a mild symmetric and diffuse impairment of cortical perfusion/metabolism in cerebellum and posterior cortex (parieto-occipital); one patient showed also relevant asymmetric hypometabolism in left temporal cortex. Subcortical involvement was mild and limited to the caudate nuclei. Recovery PET/CT studies showed normalization of perfusion patterns in parieto-occipital cortex and subcortical gray matter, whereas the cerebellum hypometabolism persisted. Our results seem consistent with both models of brain injury suggested in HUS, featuring both mild/symmetric and reversible involvement of gray matter in most patients (metabolic injury) and further focal/asymmetric cortical involvement in patients with relevant neurologic symptoms in acute phase (thrombotic focal vascular damage). **Conclusion**: Functional brain imaging in acute HUS using F18-FDG PET/CT showed a main pattern (including patients with no neurological signs/symptoms) of significant and diffuse/symmetric impairment of perfusion/metabolism in posterior cortex and cerebellum, with minor impairment in basal ganglia and recovery within some months. Focal/asymmetric pattern of cortical hypoperfusion/hypometabolism in HUS seems associated with more relevant neurological symptoms/signs in acute phase.

1309 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 120/121

Radionuclide therapy/dosimetry: bone & joint

OP447

The role of serum PINP in ^{89}Sr pain palliation therapy of prostate cancer patients with bone metastatic disease

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Introduction. Bone metastatic disease is a complication of prostate cancer. The diagnosis usually relies on skeletal x-ray and bone scintigraphy. The clinical management of bone metastatic disease is difficult, therefore markers of bone remodeling could contribute in diagnosis and follow up of bone metastases. The major structural protein in bone is type I collagen. It is synthesized by osteoblasts and accounts for ~ 90% of the organic matrix. The amino-terminal propeptide of type I procollagen (PINP) represents a marker of early bone formation during osteoblast proliferation. **Aim.** This study investigates the role of serum amino-terminal propeptide of type I procollagen (PINP) as indicator of response to bone pain palliation treatment with ^{89}Sr-chloride in prostate cancer patients. **Method.** Overall 34 prostate cancer patients (mean age 63 years) with bone metastases were treated with ^{89}Sr-chloride. All patients were undergoing hormone treatment before entering this study. Hematological toxicity and side effects were reported according to WHO guidelines. Correlation between serum PINP, PSA and the response to ^{89}Sr therapy was also studied. **Results.** Treatment efficacy was complete in 45 % of patients, partial in 35 % and negative in 20 % of patients. A mild hematological toxicity was apparent in 4 patients. Platelet and white blood cell counts returned to baseline levels within 6 - 11 weeks after therapy. The results demonstrated a decrease in serum PINP in clinical responders, while in clinical non-responders there was no significant change in PINP concentrations. **Conclusion.** ^{89}Sr-chloride is effective and safe in bone pain palliation. Serum PINP may prove useful as a bone formation marker in early diagnosis of bone metastases. An additional benefit may be in optimization of bone pain palliative therapy in prostate cancer patients. More studies are needed in order to evaluate its full potential.

OP448

The Palliation of Painful Bone Metastases Using ^{89}Strontium-chloride in Patients with Various Malignacies

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INTRODUCTION: Strontium-89 (Metastron®) is a pure beta- emitter selectively absorbed at bone locations with increased osteoblastic activity, used for palliative therapy. The aim of this study was to review the radionuclide therapy using Strontium- 89 chloride in the palliation of painful bone metastases in patients with various malignancies. METHODOLOGY: One hundred and two treatments with Strontium- 89 chloride were performed in our Institution between 1989. and 2000. We retrospectively analyzed the data of 69 patients (aged 22 to 85 years, middle age 61.2 years) with painful bone metastases due to prostatic (44.9%), lung (23.1%), breast (10.1%) and other (21.9%) cancers. Forty five patients received single intravenous dose of Strontium- 89 chloride activity of 148 MBq and 24 patients multiple (up to 4) doses in the average interval of 3.2 months. Pain relief, consumption of analgesic drugs and improvement of mobility and life quality were used for estimating the effects of therapy (scale 0-5; 0- no effect to 5-excellent effect). Blood counts were taken after three and after six weeks. RESULTS: Palliative therapy using Strontium-89 chloride showed response rate of over 80%. The effect was described as excellent in 19 (27.5%) patients, and as no effect in 10 (14.5%) patients . Bone pain palliation to some degree (mean 3.37) was induced in the remaining 40 patients. The average duration of palliation after first treatment was 3.7 months. Hematological toxities were in generally mild, making repetitive treatment relatively safe. Severe hematological toxicity (thrombocytopenia and pancytopenia) was registered only in two patients. CONCLUSION: administration of Strontium- 89 chloride was shown as effective in pain palliation without induction of severe side effects. Better effects would be expected in patients under good clinical conditions and life expectancy over three months.

OP449

Bone markers may predict response of skeletal metastases to ^{153}Sm-EDTMP / zoledronic acid

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Purpose The evaluation of the effect of bone seeking radiopharmaceuticals has relied mainly on more or less subjective endpoints such as the multidimensional pain model and quality of life questionnaires. In order to obtain more objective endpoints that correlate well with the subjective endpoints in the palliation of pain caused by skeletal metastases specific bone markers were investigated in a clinical phase I study combining ^{153}Sm-EDTMP (Quadramet®) and zoledronic acid (Zometa®) in hormone-refractory prostate cancer patients. Bone marker changes were compared with PSA changes and with clinical effect. *Methods* Patients with hormone-refractory prostate cancer were treated with 18.5 MBq/kg ^{153}Sm-EDTMP in weeks 1 and 3 and with 37 MBq/kg in week 15. Treatment with 4 mg zoledronic acid started at week 3 and continued every 4 weeks through week 23. Clinical response was recorded by EORTC questionnaires. PSA and bone marker levels (serum bone specific alkaline phosphatase [BAP], serum procollagen type I N propeptide [PINP] and urinary creatinine corrected N-terminal type I collagen peptide [NTX]) were measured every 4 weeks. Bone marker changes, PSA changes and clinical effect were compared in week 11 (mid-treatment) and week 23 (end-treatment). Kappa-coefficient was used as a measurement of agreement between two tests for response (95%-confidence interval). It was used as a chance-corrected proportional agreement between clinical effect and PSA / bone marker changes. *Results* 12/18 treated patients were evaluable. Median PSA change was +7% in week 11 and +109% in week 23. Urinary creatinine corrected NTX (-72%; -63%), serum BAP (-25%; -46%) and serum PINP (-26%; -43%) values decreased in week 11 and 23, compared to baseline. A significant agreement with clinical effect was found for BAP and PINP changes in week 23 ($p<0.05$). BAP correlated very well with PINP changes, but less with NTX. Bone marker changes did not correlate with PSA changes. BAP decrease was more pronounced than what may be expected from mono-therapy with zoledronic acid, further supporting the feasibility of bone markers for response monitoring. *Conclusion* Markers of bone metabolism are feasible for response monitoring in radionuclide therapy for metastatic bone disease. A clinical response after treatment with ^{153}Sm-EDTMP and zoledronic acid correlated best with BAP and PINP changes.

OP450

Is Soft Tissue Accumulation Of 153 Sm-EDTMP Negligible For Dosimetric Estimate?

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Images taken after administration of 153 Sm-EDTMP show a faint or undetectable activity outside the skeleton. For this reason it has been suggested that the contribution to retained dose can be neglected for dosimetric estimate. Aim of this work was to evaluate the tracer behaviour in the bone (B), soft tissues (S) and urine (U) during the first 24 hrs after administration. **Methods**. Seventy two patients (47 males and 25 females, age 65.5 +/-11.7 yrs) with multiple bone metastases and preserved renal function were studied 5 (t0) , 280 (t1) and 1380 (t2) minutes (median value) after therapeutic administration of 37 MBq/Kg of 153 Sm-EDTMP. Additional 56 pts with the same characteristics were studied at t1 only. The first measurement was acquired immediately following administration and before bladder emptying to obtain the reading corresponding to 100% activity. The further scans were acquired after bladder emptying. Care was taken to accurately reproduce the patient-contour geometry at each time point. Data corrected per decay were calculated employing the Brenner's method to obtain values of cumulative urine excretion (U), soft tissues (S) and bone (B) uptake expressed as percentage of the t0 counts (injected dose). **Results**. Cumulative U excretion does not increase significantly from t1 to t2 (34.5+/-14 and 35 +/-16 respectively) while S decreases from a median value of 19.6 to 8.6 ($p<0.0001$, not Gaussian distribution) and B increases from 45.8 +/-14 to 54.8+/-15 ($p<0.0001$),with a faster increase rate during the first hours p.i. (9.7 points/h or 17.6%/h considering the max value observed as 100%) than in the 2nd phase (0.44 and 0.81/h respectively, $p<0.0001$). Neglecting the contribution of S and assuming that whole body (WB) retention reflects only B uptake, there is an overestimation of true B accumulation of 32.89+/- 13.4 and 15.2+/- 9.4 % at t1 and t2 respectively. **Discussion**. The B accumulation rate is faster (up to 50 times) during t0-t1 than in t1-t2 and S activity represents a significant pool of the WB retained dose at each time point. Despite the fact that B uptake cannot differentiate between tumor burden and normal bone, which have different kinetics and uptake values, the dose rate to bone marrow should be calculated separately during the two (or more?) phases without neglecting the contribution of S pool which may be responsible of an overestimation of B uptake.

OP451

The value of scintigraphic studies in discriminating Multiple Myeloma patients that will benefit from Sm-153 EDTMP infusion.

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INTRODUCTION: Encouraging results are obtained by the use of Sm-153 EDTMP in Multiple Myeloma (MM) patients to achieve pain control, while bortezomib and Sm-153 combination has been proposed to overcome resistance and to minimize non-tumor tissue toxicity among refractory and relapsed MM patients. In a study of ours, we proposed the combined use of Tc-99m MIBI, that reflects myeloma disease activity, and Tc-99m (V) DMSA in the evaluation of the effectiveness of chemotherapy. The aim of our study was to identify the best imaging modalities in order to access MM pts that will benefit from the use of Sm-153, based on the hypothesis that pts with active disease and osteoblastic bone lesions will have the maximum benefit. MATERIALS AND METHODS: Twenty-three pts were included in the study (12 F/11 M, mean age 63.6±14.2). 18/23 pts had received or were under chemotherapy (pretreated) and 5 pts were untreated (newly diagnosed). Tc-99m MIBI, Tc-99m (V) DMSA and bone scintigraphies were obtained on separate days. X-rays exams were also available. RESULTS: Overall, abnormal scintigraphic findings were found in 16 MIBI scans (12/18 pretreated pts and 4/5 untreated pts), in 18 (V) DMSA scans (16/18 and 2/5 pts respectively) and in 20 bone scans (all pretreated and 2/5 untreated pts). Abnormal X-rays, with osteoblastic reaction were diagnosed in 17 pts (all pretreated). The 16 pts with disease activity (MIBI positive scans) had: 13 positive /1 negative (V) DMSA scans, 15 positive / 1 negative bone scans and 10 positive / 6 negative X-rays. Regarding negative MIBI scans, 5/7 were positive in both (V) DMSA and bone scans and 7/7 had positive X-rays. CONCLUSION: MIBI scan can discriminate pts that will benefit from the use of Sm-153 EDTMP; yet, bone scan can be a further inclusion or exclusion criterion rather better than (V) DMSA scintigraphy or X-ray exams.

OP452

Assessment of response to systemic metabolic radiotherapy with 153Sm-EDTMP in oncology patients with osseous metastases, as regards to the extent of scintigraphic findings and the sort of primary malignancy.

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AIM: To investigate the consequence of 153Sm-EDTMP in the management of pain associated with osteoblastic skeletal metastases. The multiplicity of therapeutic reply was recorded concerning the seriousness of bone participation and the cancer type. Interesting peripheral data (side-effects, radionuclide's cooperative action with other curative interventions), were incidentally registered. MATERIAL AND METHODS: During 2007-2008, 67 patients (44 males, 23 females, age range 52-88 years, median 70 years) with metastatic bone pain were examined about the 153Sm-EDTMP efficiency. 32 patients suffered from prostate cancer, 15 patients from breast cancer, 9 patients from lung cancer and 11 patients from other malignancies. Exclusion criteria were: WBC<4000 cells/μL, Hgb<10 g/dl, Hct<30%, PLT<100.000/mm3, SCr>2.0 mg/dL, life expectancy <2 months. Concerning the performance status were fixed three images: A-PS, B-PS, C-PS, >70%, 50%-70%, <50% respectively, according to Karnofsky index. Three reply types were defined regarding the analgesic outcome: complete relief - drug therapy withdrawal (TI), medium improvement (TII), no response (TIII). Our patiensts were classified into three groups regarding the number of metastases: GI (<5 foci), GII (5-10 foci), GIII (generalized metastatic disease). All parameters were evaluated before treatment, followed up daily for a 4-week period and reconsidered after three months. RESULTS: GI group presented 19 A-PS, 1 B-PS, 1 C-PS images, and 15 TI, 5 TII, 1 TIII reply types. Correspondingly, we had 13-3-9 images, 11-8-6 replies in GII group, and 4-3-14 images, 7-7-7 replies in GIII group. Prostate cancer patients presented 22 A-PS, 3 B-PS, 7 C-PS images, as well 23 TI, 8 TII, 1 TIII replies, while breast cancer patients 11-2-2 images and 8-4-3 replies. In patients suffered from lung cancer (2-0-7 images, 1-4-4 replies) or other malignancies (1-2-8 images, 1-4-6 replies), results weren't encouraging. Flare phenomenon and myelotoxicity weren't remarkable. Palliative impact achieved within the first week and continued during the surveillance time in most cases. Coexistence with EBRT or chemotherapy was generally positive. In contrast, bisphosphonates seem to diminish radionuclide's effectiveness possibly because of similar strong affinity to bone's calcium phosphate. CONCLUSIONS: Samarium therapy in osseous metastatic disease is briefly satisfying, with apparent improvement in life quality. Patients with fewer metastatic lesions, appear to have better answer. Prostate and breast cancer without noticeable variations, had stronger response. Potential combination with other treating options, undeniably creates profits, except bisphosphonates. In this case, we suggest mediating at least a 2-week period.

OP453

Radiosynoviorthesis in inflammatory joint diseases

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Introduction Radioisotopic synoviectomy is an interesting therapeutic option in inflammatory joint diseases. In patients (pts) with joint function impairment and severe pain due to various benign bone diseases resistant to steroid and no steroid anti-inflammatory drugs, it can improve life quality aging on spontaneous and movement related pain, so that artroprostesis can be delayed with particular benefit in young population. Aim To validate efficacy in pain reduction of benign joint diseases and in delaying time of surgical correction in young patients. Methods 24 pts (age 35-75) enrolled in the study were affected by: rheumatoid arthritis (8 pts), osteo-arthritis (8pts), polyetilene disease (4 pts) and femore necrosis (4 pts). Ankle and knee were the joints communely affected, treated with tradional therapy consisting of systemic steroid or no steroid drugs and intra-articular steroid injection without benefit for the pts. So these conventional therapy resistent pts received intrarticularly administration of Renium 156 (185 MBq) in ankle (16 pts) and Yttrium 90 (185 MBq) in knee (8 pts). The immobilitation time required after injection was 48 hours for all of them. Pts underwent tree phase bone scintigraphy before and 6 months after therapy and clinical controls after 2 days, 7 days, 3 and 12 months. Results At involved joint tree phase bone scan showed increased vascular and blood-pool phase before radiosynoviortesis and normal scan at post-therapy control. No early collateral effects were observed and no pain was referred by pts during 1year follow-up. No pts underwent to surgical artroprostesis, including pts affected with polyetilene disease and femore necrosis, in which radiosynoviortesis is an unusual approach. Conclusion Radiosynoviortesis can be a valid therapeutic chance in articular pain and function impairement of joints affected with inflammatory diseases and can delay surgical option when needed. So it can be suggested particularly in young population for which delay is a crucial point of therapeutic strategy. Moreover our preliminary results indicate that polyetilene disease and femore necrosis can be succexfully treated as new therapeutic approach.

OP454

Rhenium [186RE] sulfide colloid-radiosynoviorthesis for treatment of hemophilic hemarthrosis

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Aim: The radionuclide synovectomy, which is also known as radiosynoviorthesis (RSO), has been used effectively for a long time in the treatment of recurrent hemarthrosis in hemophiliac patients. We report the results of 186-Rhenium radiosynoviorthesis in hemophiliac patients of medium sized joints. Material and methods: Between May 2007 to April 2009 we administered 12 RSO injections in 7 children and 2 adults {mean age: 14.11 ± 9.8 years (min: 9, max: 29)}. The treatment was repeated in one patient and in three patients two joints were treated. 186-Re colloid in 1 cc dosage was used for ankle and elbow joints. The joint was then manipulated through a full range of extension and flexion, to distribute the particules homogeneously throughout the joint space, and splinted for 72 hours to minimize the leakage. All the patients had severe hemophilia A, with grade 2 or grade 3 synovitis. None of the hemophiliac A patients had previously had an inhibitor. Before RSO, patients had mean hemorrhage incidence of 4.4 / monthly, in the last 6 months. Two hours earlier than the treatment all patients began to receive factor prophylaxis and they have continued to receive factor prophylaxis for three days. All the procedures were performed under aseptic conditions. Results: Mean patient follow-up after RSO was 15.7 ± 7.8 months (min:2 max:22). After RSO, patients had mean hemorrhage incidence of 1.8 / monthly. In 5th day of the injection one patient suffered from hemorrhage in his ankle. Excluding that patient none of the patients encountered any acute or chronic hemorrhage or other complications. Re-injection was planned to decrease synovial volume in a patient with prolonged chronic synovitis. Conclusion: RSO is an effective and promising method for chronic synovitis and recurrent hemorrhage in hemophiliac patients, particularly with frequent intra-articular bleedings. The anti-hemophiliac factor consumption was markedly reduced in patients after RSO therapy. Radiosynoviorthesis is well tolerated by patients suffering from hemophiliac hemarthrosis.

1310 - Tuesday, October 13, 2009, 11:30 - 13:00, Hall 122/123

Clinical science: bone & joint

OP455

SPECT/CT contribution to conventional knee bone scintigraphy.

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Aim Due to its anatomical complexity, knee joint was chosen to study the diagnostic contribution of SPECT-CT in a conventional gammagraphic procedure. The aim of this study was to detect pathological findings in a group of patients suffering benign disorders. *Matherials and methods* Thirty-five patients (medium age: 57y [19-81y]) suffering previous traumatism (n=16), knee prosthesis (n=4) or chronic pain (n=15) were included. Bone scintigraphy studies were performed in all patients by means of planar images in different proyections (AP/PA/Lateral) and SPECT-CT. Complementary dynamic exploration was performed to 30 patients. All patients were explored in a hybrid system (SYMBIATruePoint SPECT-CT SIEMENS^{TM}). SPECT-CT protocol included a fast acquisition SPECT and low-dose CT. *Results* Triple-phase and planar studies were evaluated and compared with SPECT-CT images. Pathological findings were associated in our series to osteoid osteoma (n=1), loosening prosthesis (n=4), joint inflammation (n=16), insertional disorders (n=4), osteochondritis (n=14) and osteonecrosis (n=1). In 9 of the 35 patients (26%) conventional images contributed to complete a final diagnosis of the process. However, SPECT/CT improved the location of these pathological findings in 26 of the 35 patients (74%). Moreover, fusion images contributed to detect new findings as insertional pathologies, osteochondritis or osteoid osteoma. *Conclusion* SPECT-CT is an important tool to explore knee joint in benign disorders. According to these preliminary results, insertional lesions and non-suspected osteochondritis focus were considered the principal contribution of this method.

OP456

Value of lateral blood pool imaging in patients with suspected stress fractures of Tibia

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Aim:To critically evaluate the use of lateral blood pool imaging in athletes with lower limb pain with a clinical suspicion of stress fractures Methods: 2 experienced nuclear medicine physicians evaluated the three phase bone scan using 99mTc -MDP performed in 50 consecutive patients referred from a specialist sports injury clinic for suspected tibial stress fracture.The vascularity to the tibia as seen on the blood pool images in the anterior and posterior views were compared to the lateral view assessments. Results:24 stress fractures in 24 patients and 66 shin splints in 40 patients were diagnosed. Of the 24 patients diagnosed with stress fractures, lateral blood pool imaging was positive in 21/24 patients, anterior images were positive in 11/21 patients and posterior images were positive in 7 patients (p<0.001). Conclusion: Lateral views of the tibia provide the optimal quality images for evaluation of vascularity and our study results support this.

OP457

Three-phase bone scintigraphy with SPECT in patients with avascular necrosis of the hip

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Avascular necrosis (AVN) which is also called osteonecrosis or aseptic necrosis, is a condition in which the death of bone cells due to decreased blood flow can lead to pain and collapse of areas of bone. This collapse of bone can lead to degenerative arthritis of nearby joints. Avascular necrosis is most common in the hip joint. Conditions commonly associated with AVN are serious trauma, extended and/or high doses of corticosteroid medications, and excessive alcohol consumption. AVN is suspected most often when a person with risk factors for the condition experiences localized bone-type pain, often felt in the groin. Diagnosis is obtained by radiography of the painful hip. Because early x-rays are usually normal in the early stage of the disease, bone scintigraphy (BS) and MRI are the diagnostic modalities of choice since both can detect minimal changes at early stages of the disease. A variety of methods are now used to treat AVN, and the most common is the total hip replacement. More precise AVN staging can be achived by use of three-phase BS with SPECT. In patients with AVN of the hip three-phase BS with SPECT is significant in early detection and separation of patients with spontaneus healing from those who need surgery.The aim of study was detection and staging of AVN of the hip using three-phase BS with SPECT in patients with suspected AVN. MATERIALS AND METHODS: Three-phase BS and SPECT of the hips were done in 24 patients with suspected AVN. AVN was due to high doses of corticosteroid therapy in 12 pts, due to hip trauma in 6 pts, as a result of SLE in 2 pts, and in 4 pts AVN was idiopathic. In 14 pts AVN was diagnosed by BS, and in 10 pts AVN was diagnosed previously by MRI and confirm by BS. Positive scintigraphic results were classified in three scintigraphic stages: 1-early, 2-intermediate and 3-late stage of AVN. RESULTS: Three-phase BS with SPECT was positive in all patients (100%). In 6 pts (25%), AVN was in early stage. Twelve pts (50%) had intermediate stage, and 6 pts (25%) had late scintigraphic stage of AVN. Twenty pts had unilateral and 4 pts had bilateral AVN of the hip. CONCLUSION: Three-phase bone scintigraphy with SPECT is very sensitive method for AVN detection. Three-phase BS with SPECT can establish stage and prognosis of AVN and influence further therapy.

OP458

Quantitative Three Phase Bone Scan and SPECT Studies in Complex Regional Pain Syndrome

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INTRODUCTION: Complex Regional Pain Syndrome (CRPS) is a chronic progressive disease characterized by severe pain, swelling, vasomotor dysfunction and changes in the skin of the affected limb. We aimed to evaluate the changes in activity accumulation in foot bones besides periarticular areas on Tc-99m MDP TPBS for early diagnosis of cases with posttraumatic lower extremity CRPS type I. **MATERIAL&METHOD:** 42 cases with lower extremity CRPS type I.and healthy 10 cases (9 M, 1 F) underwent to bilateral foot radiography, Tc-99m TPBS and MDP SPECT. Dynamic and static plantar and lateral scintigraphic images were obtained after IV 740 MBq Tc-99m MDP injection. Following visual evaluation, ROIs were drawn on bilateral foot phalances, metatarsal and tarsal bones, calcaneus and distal tibias. Mean net counts were calculated for all cases. Affected and normal extremity values were compared. **RESULTS:** 4 cases detected fracture on SPECT images were excluded from study. Mean age was 35 ± 13 yrs for remained 38 patients (29 M, 9 F), 29 ± 3 yrs for control group Direct graphies were normal in all control cases and 29 patients, only 9 patients were osteoporotic. Although counts of affected extremity was not different from normal extremity on first-pass (FP) and blood-pool (BP), significant difference was detected in late static images in CRPS cases (Table 1). Normal extremity values were similar with control group. Metatarsal values of affected extremity were significantly higher than control group on FP (69.29±34.46 vs 44.17±21.89; 0.03) and BP (3.93±1.61 vs 2.82±1.06; 0.03) images. Counts of late plantar and lateral tarsal, lateral metatarsal and distal tibia of affected extremity were prominently high than control group(p< 0.05). **Table 1.** Mean net cts/ pixel values on late static images of affected and normal extremities

	Affected Extremity	Normal Extremity	p value
I. Phalanx	10.65 ± 6.28	35.95 ± 4.72	0.008
Metatarsal bones	11.76 ± 7.48	9.73 ± 5.73	0.008
Tarsal bones	26.58 ± 17.57	19.99 ± 13.14	0.006
Calcaneus	38.06 ± 27.54	29.01 ± 18.76	0.023
Distal Tibia	22.95 ± 16.55	16.14 ± 9.30	0.003
Lateral metatarsal	21.37 ± 17.30	15.65 ± 9.56	0.006
Lateral tarsal	36.80 ± 24.93	27.07 ± 20.01	0.013
Lateral calcaneus	31.22 ± 26.51	21.78 ± 15.41	0.038
Lateral distal tibia	28.52 ± 18.45	19.24 ± 13.43	0.0001

CONCLUSION: Quantitative bone analyses of TPBS images provide the early diagnosis of CRPS type I. SPECT study has an important role in the differential diagnosis of fracture from CRPS.

OP459

Utility of ^{18}F-FDG PET/CT in the evaluation of bisphosphonate related osteonecrosis of the jaw.

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Aims: Long-term bisphosphonate therapy, especially with the higher doses given intravenously for multiple myeloma or malignancy, is associated with bisphosphonate related osteonecrosis of the jaw (BRONJ). The latter is a diagnostic challenge as clinical exam and plain films (Panorex) can be equivocal. Additionally, treatment is often complicated by overlying osteomyelitis (OM). ^{99m}Tc-MDP bone scintigraphy has been shown to be very sensitive for ON as well as OM, but not specific. The combined metabolic and anatomic information in ^{18}F-FDG PET/CT may provide a sensitive method to help differentiate and diagnose ON and OM of the jaw, as well as assess treatment response. The utility of ^{18}F-FDG PET/CT for this indication is evaluated further. **Methods**: This is a retrospective study of 13 patients (pts) with ON ± OM of the jaw evaluated with ^{18}F-FDG PET/CT. The pts included 9 women and 4 men, ranging from 47 to 86 years-old (mean: 72). The average duration of bisphosphonate therapy upon initial presentation was 4.2 ± 2.7 years. In addition to the initial scan, 5 pts also had a follow-up PET/CT after completion of therapy. The PET/CT findings were marked as either positive or negative, and compared to the pts' clinical and histological results. **Results**: Table 1 summarizes the patient demographic and imaging findings. In all but 1 case (9/10 pts) the pre-therapy PET/CT scan was positive in patients with OM (the majority of whom also had ON). Three of four patients who had negative pre-therapy PET/CT scans did not have pathology proven OM, though 2 did have ON. As such, only 1 patient with biopsy proven OM had a negative PET/CT scan initially. After therapy, in all but 1 case (4/5 pts), the PET/CT findings either resolved or improved in comparison to the initial scan. Clinically, all 5 pts improved after therapy. **Conclusions**: The findings suggest that ^{18}F-FDG PET/CT will be positive with OM, but not with ON alone. In conjunction with a ^{99m}Tc-MDP bone scan, then, patients with suspected BRONJ can be categorized into different treatment groups depending upon whether they have ON alone, or ON plus OM. Additionally, PET/CT can be used to assess treatment response as it shows decreased or absent uptake after effective therapy. These preliminary results suggest a favorable role for PET/CT in the diagnosis and management of BRONJ. Table 1. Patient demographic and imaging findings.

Patient	Age (years)	Sex	Bisphosphonate	Location of lesion	Histology	Pre-Tx PET/CT	Post-Tx PET/CT
1	47	F	Zolendronate	Maxilla		-	
2	81	F	Alendronate	Mandible	ON,OM	+	
3	64	M	Pamindronate	Maxilla	ON,OM	+	
4	68	F	Zolendronate	Mandible	ON,OM	+	-
5	59	M	Zolendronate	Mandible	ON,OM	+	-
6	81	F	Zolendronate	Mandible	ON,OM	+	+
7	83	F	Alendronate	Mandible	OM	+	
8	67	F	Zolendronate	Mandible	ON	-	
9	86	F	Alendronate	Maxilla	ON	+	↓

10	76	M	Alendronate	Mandible	ON(OM)	-	
11	83	F	Alendronate	Mandible	ON(OM)	+	
12	65	M	Alendronate	Mandible	ON,OM	+	-
13	79	F	Alendronate	Maxilla	ON,OM	-	

Key: ON = osteonecrosis; OM = osteomyelitis; Tx = therapy; ↓ = improved but not absent; ( ) = clinical suspicion but not biopsy proven.

OP460

Recent Mechanical Low Back Pain in Young Patients: Results of Bone SPECT Application

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INTRODUCTION: Low back pain is a common reason for visiting a physician. Imaging strategy varies according to the background of acute or persistent low back pain. The use of lumbar spine radiography and either CT or MRI is well established, whilst bone scan is not included in the diagnostic work-up. However, bone SPECT seems to be a valuable tool in the assessment of inflammatory back pain and in the detection of active sacroilitis. The aim of this study was to evaluate bone SPECT findings in patients referred to our department with mechanical low back pain of recent origin. MATERIALS AND METHODS: Thirty-eight patients (thirty males, eight females, mean age 28 yrs) underwent SPECT of lumbar spine-sacroiliacs. All had pain for less than a month, associated with conditions of physical stress (military or athletic training). None had findings from the x-rays exams. SPECT study was performed 3 hours after IV administration of 20 mCi Tc-99m HDP by a single-head gamma-camera (SPECT data: patient at prone position, 180^{o} rotation, 32 projections of 60 seconds, matrix 64x64, iterated reconstruction method). RESULTS: Thirty-nine totally lesions were found in 28/38 patients. Bone SPECT revealed findings justifying the pain in 13 patients (pars defects, spondylolysis, fractures, facet joint arthritis, and transitional vertebrae with increased radiopharmaceutical uptake). Fifteen patients had findings that needed further evaluation from the practitioner (vertebrae body stress, enthesopathy of the pelvis and spinous procecess) and 10 patients had no findings at all. The most common lesion detected was stress of the vertebrae body (in 14 patients) followed by pars defect (in 6 patients). CONCLUSION: Bone SPECT imaging revealed the etiology of recent mechanical low back pain in a great percentage of patients and can thus provide useful additional data to the enquiry of pain. Its application on conventional planar bone scan, an economic and widely available diagnostic technique, appears to be a valuable aid for the referring physician.

OP461

Molecular radionuclide imaging with human polyclonal immunoglobulin (^{99m}Tc-HIG) and bone scan in patients with ankylosing spondylarthritis and peripheral serum-negative arthropathy.

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Ankylosing spondylarthritis (AS) is a chronic syndrome associated with the presence of the human leucocyte antigen (HLA)-B27. A 25% of these patients develop serum-negative peripheral arthropathy (SNPA) in which actively inflamed joints coexist with others being in remission. By definition, these patients are serum negative in the antigen associated with rheumatoid arthritis. Compatible bone scan (BS) reveals joints with increased activity due to degenerative alterations, whilst scanning with human polyclonal immunoglobulin (HIG) is capable to show which of the joints present active inflammation of the synovial membrane. The aim of the study is to investigate the utility of molecular imaging with HIG in patients suffering from AS with coexisting SNPA. Sixteen patients suffering from SNPA, with a mean age 35.3±7 years and duration of disease 15.3±4.5 months, who were recruited from a total of 70 patients with AS, are enrolled in the study. All these patients were positive in the human leucocyte antigen (HLA)-B27 and negative in the antigen associated with rheumatoid arthritis. All patients were submitted to x-rays and ultrasound examination (US) in joints of interest, plus whole body BS with ^{99m}Tc-MDP and finally scan with ^{99m}Tc-HIG. A total of 640 joints were evaluated. In 4 of the patients (160 joints), molecular imaging with HIG was within normal limits, whilst in compatible bone scan degenerative alterations have been mentioned in 22 of the joints. In all these patients disease was evaluated as inactive. In the remaining 12 patients (480 joints), increased accumulation of HIG was mentioned in 163 joints, whilst BS revealed degenerative changes in 265 joints. Increased uptake of HIG was found in 134/165 swollen and painful joints yielding thus a sensitivity of 81.1%, plus in 29 joints without any clinical evidence of inflammation. Matched findings between these two methods were mentioned in 155 out of 163 joints with an abnormal scan with HIG. Abnormal x-rays and US findings were mentioned in 67 of the joints. According to the above mentioned, BS in SNPA reveals joints being actively inflamed or not, whilst radionuclide study with HIG is the proper one and the method of choice to distinguish actively inflamed joints from inactive ones, presents an acceptable level of sensitivity when compared to clinical appearance of inflamed joints, and finally, it reveals synovial inflammation in a greater extent than anatomical imaging modalities.

OP462

99mTc-Labelled ECDG in the Evaluation of Disease Activity in Rheumatic Conditions

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Background Disease activity of rheumatic conditions is notoriously difficult to monitor with the presently available clinical armamentarium. Active disease is often under appreciated with resultant delays in implementation of therapy. Conversely, the indiscriminate use of therapeutic agents can, and does, result in otherwise preventable morbidity. Aim The aims of this project were to investigate: i) the ability of 99m-technetium-labeled glucosamine (^{99m}Tc-ECDG) to localize in joints and other inflamed tissues in patients suffering from Rheumatoid Arthritis (RA) or Systemic Sclerosis (SS), and, ii) whether uptake of this agent correlated with disease activity. Methods Patients suffering from RA or SS, and with varying disease severity, but not taking glucosamine, were recruited to the study. Patients without documented inflammatory disease (with particular emphasis on peripheral joint, lung and muscle involvement) were used as negative controls. All patients were fasted for 4 hours and injected intravenously with ^{99m}Tc-ECDG (600MBq). Planar (spot and whole body) and SPECT scans were acquired at fifteen minutes, two hours and three-four hours post-injection using a *Siemens e-Cam* gamma camera. Results Thirty patients (18 with RA, 12 with SS) were recruited. Tracer accumulated in joints with clinically active disease, and the degree of uptake correlated with disease activity. Subclinical disease (as determined on follow-up of these patients over the ensuing 6 months) was also detected. No appreciable uptake was seen in joints with quiescent disease. In larger joints sufficient imaging resolution enabled distinction between an inflammatory process involving primarily the synovium and one involving the cartilaginous structures. In patients with SS, ^{99m}Tc-ECDG accumulated only in lungs with active inflammation. Tracer uptake correlated well with pulmonary function tests and was a better discriminator of active disease than computed tomography scans of the lung. Diffusely increased tracer uptake was also noted in the muscles of patients with active myositis. Uptake correlated well with symptoms, and was more sensitive than biochemical markers, such as creatine kinase levels. Conclusion ^{99m}Tc-ECDG accumulates at sites of active inflammation in affected peripheral joints, muscles and lungs in patients suffering from RA or SS. Uptake correlates well with clinical findings. Furthermore, subclinical disease can also be detected.

1401 - Tuesday, October 13, 2009, 14:30 – 16:00, Hall 211/212

CME 11: BONE (Interactive): The Role of Nuclear Medicine in Exploring Pathology of the Skeleton: Infection, Complications of Joint Prostheses, Primary Bone Tumours

OP463

Clinical Cases I

N. Prandini (IT)

OP464

Clinical Cases II

F. Paycha (FR)

OP465

Clinical Cases III

J.N. Talbot (FR)

1402 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 112

Symposium 12: Targeted radionuclide therapy (COST BM0607)

OP466

Radionuclides for targeted radionuclide therapy: expectations and limitations

F. Rösch (GE)

OP467

Dosimetry of radionuclide therapy studies in small animals

M. Konijnenberg; Mallinckrodt Medical BV, Petten, NETHERLANDS.

With the development of small animal SPECT/CT and PET/CT scanners it is now possible to have high resolution quantitative data on activity distributions in mice and rats. The pharmacokinetics of a targeted radionuclide therapy agent can now be followed almost in real time and also its pharmacodynamics can be easily studied by giving concomitant drugs to alter e.g. its renal uptake pattern. Ideally the quantitative data should be valuable for estimating the radiation dosimetry of a compound instead of using several animals per time-point as done traditionally. This can reduce not only the number of animals needed but also the total time per experiment considerably. Several aspects of small animal dosimetry based on imaging data will be presented and discussed. Various stylized phantom models for normal sized rats and mice have been developed, that enable "ready made" dose calculations with S-values for source and target organs, using the MIRD formalism[1,2,3,4]. Animal specific dosimetry using the actual anatomy from the CT-data and voxel-based dose models suggest higher accuracy[5]. Determination of the compound's pharmacokinetics, however, may form a more critical parameter than anatomical accuracy. Especially the slower excretion pattern may be problematic to quantify, or would necessitate very high injected activities. The dose by these high activities might cause effects in radiation sensitive organs like the kidneys, thus influencing the normal PK of the compound[6,7]. What can be learned from performing dosimetry in small animals? The kinetic profile of the compound and especially the uptake pattern in organs and tumours is usually the main aim of such studies. Dosimetry can be used to establish dose-effect models for damage in dose-limiting organs and for efficacy in tumor control. Allometric transformation of animal-based dosimetry to

human equivalent dosimetry depends on all aspects discussed: not only the difference in the anatomy, but also the dose models for radiation transport, the pharmacokinetics and the dose effect relationships.

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OP468

Preclinical and clinical therapy studies with new targeted radiopharmaceuticals

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Targeted radionuclide therapy is a rapidly growing field in nuclear medicine. Previously only radioiodine was available for targeted radionuclide therapy of benign and malignant thyroid diseases. Nowadays there is a number of approved radiopharmaceuticals (e.g. MIBG, phosphonates, anti-CD-20-antibodies). Beside these commercially available radiopharmaceuticals numerous newer compounds are under preclinical and clinical investigation. Radiopeptides are of particular interest for radionuclide therapy as they feature highly suitable pharmacokinetics (rapid targeting, high diffusibility and fast clearance). Most experience was acquired with radiolabeled somatostatin analogues. The somatostatin analogues are exemplary for the development of a radiopharmaceutical with its way from a non radioactive drug to an imaging agent and further to a therapeutic drug. Efforts are made to improve this therapy further as e.g. reduction of toxicity. An overview of the current status and approaches for improvements will be given. A number of other radiopeptides such as gastrin-, bombesin-, and substance P-derivatives are in clinical studies. These studies as well as the specific limitations of these peptides will be discussed. As many radiopeptides are conjugated with DOTA, they could potentially be labelled with an alpha emitting radionuclide. However, the generally short physical half life of the alpha emitters is a drawback. The direct intratumoral application might be a strategy to circumvent this problem. The results of a phase I/II study with ^{213}Bi-DOTA-Substance P for the intratumoral therapy of malignant glioma will be reported. Antibodies are much larger than peptides and their biodistribution is much slower. However, antibodies are relatively simple to be engineered and can be directed against a selected antigen. Two anti-CD-20 antibodies for the treatment of malignant lymphoma are currently FDA approved and commercially available. However, their clinical acceptance from medical oncologists is still limited. It remains unclear at which time point in the course of the disease radioimmunotherapy should be used. With regard to the most recent studies this question will be addressed. As the most suitable radionuclide is not defined as yet the newly developed ^{177}Lu labelled antibody ^{177}Lu-DOTA-Rituximab will be discussed as well. Certain small radiolabelled molecules such as radiofolates are currently tested in preclinical studies. Selected results will be presented. Additionally specific advantages and drawbacks will be discussed and their pharmacodynamic properties compared with other radiopharmaceuticals for targeted radionuclide therapy. Finally an outlook for the further developments in targeted radionuclide therapy will be given.

1403 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 111

Featured: cardiac PET

OP469

Invited Talk

A. Cuocolo (IT)

OP470

Hyperemic myocardial blood flow assessment of the right and left ventricle by supine exercise in PET

Y. Wong, P. Raijmakers, M. Lubberink, N. Westerhof, A. Vonk-Noordegraaf; Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, Amsterdam, NETHERLANDS.

Background The use of vasodilatory pharmaceuticals is a generally accepted way to assess hyperemic myocardial perfusion using PET and $H_2{}^{15}O$, but may cause hypotension and pulmonary afterload reduction in patients with pulmonary arterial hypertension (PAH). Assessment of myocardial perfusion during exercise circumvents these adverse effects and reflects a physiological response of the heart to physical activity. Here, we aim to study the feasibility of using a recumbent bike during dynamic PET to induce stress myocardial blood flow (MBF) of both the left and right ventricle in PAH patients. **Methods** 6 PAH patients (NYHA II and III) underwent consecutive $H_2{}^{15}O$-PET scans at rest and during supine exercise, at 40% of maximal obtained load on cardiopulmonary exercising test. Supine cycling started 2 minutes prior to administration of 1100 MBq $H_2{}^{15}O$. Cycling load was increased to 40% of patients maximal load; ranging from 13 to 40 W. Patients continued this steady state exercise during the 10-min $H_2{}^{15}O$ PET scan. Using parametric perfusable tissue fraction images of the $H_2{}^{15}O$ scans, left and right ventricular free walls (LV and RVFW) were delineated and MBF was computed. Flow reserve was defined as the ratio of MBF during stress to rest. During right heart catheterization performed within a month prior to PET, pulmonary arterial pressure (PAP) was measured at rest and during 40% of maximal cycling load. Heart rate and systemic blood pressure (BP) were monitored during rest and exercise. Rate pressure product (RPP) was calculated as the product of heart rate during PET and systolic BP or PAP. **Results** Mean MBF of the LVFW at rest was 0.89 (SD±0.14) and increased to 1.41 (±0.40) ml/min/g during exercise (paired t-test $p < 0.01$); LVFW flow reserve was 1.56 (±0.28); LV RPP was 7859 (SD±1289) and 14000 (±1812) beats-mmHg/min, respectively. Mean RVFW MBF at rest was 0.61 (±0.14) and increased to 1.25 (±0.35) ml/min/g during exercise (paired t-test $p < 0.01$); RVFW flow reserve was 2.11 (±0.57). RV RPP was 5645 (± 1313) and 11574 (±2546) beats-mmHg/min, respectively. For both LV and RV free walls, there was a positive correlation between MBF and RPP: r=0.50 and r=0.77, respectively. **Conclusions** Performing submaximal exercise on a recumbent bike during $H_2{}^{15}O$-PET is feasible to assess hyperemic MBF in PAH patients. MBF in both the LV and RV increased significantly during exercise. Furthermore, there was a positive correlation between MBF and the RPP in both the the LV and RV.

OP471

PET-measured hyperemic, longitudinal myocardial flow gradient in cardiovascular risk individuals with or without coronary artery calcification

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Aims: We investigated possible differences of a longitudinal myocardial flow gradient during pharmacologically-induced hyperemia, reflecting a non-invasive probe of epicardial vasomotor dysfunction, in cardiovascular risk individuals with or without coronary artery calcification (CAC). **Materials and Methods:** Myocardial blood flow (MBF) was measured with ^{13}N-ammonia and PET/CT in ml/g/min at rest, and during pharmacologic vasodilation with dipyridamole in healthy controls (CON, n=10) and in individuals with cardiovascular risk factors such as arterial hypertension, smoking, diabetes mellitus, hypercholeterolemia and obesity but without CAC (group 1; n=15) or with CAC (group 2, n= 13). MBF was assessed globally as mean MBF, and in the mid and mid-distal myocardium of the left ventricle (LV). A decrease in MBF from mid to mid-distal LV myocardium was defined as longitudinal MBF gradient. **Results:** Compared with CON, the global hyperemic MBF progressively declined in group 1 and group 2 (2.10±0.60 vs. 1.65±0.30 and 1.45±0.48 ml/g/min, respectively; $p<0.001$), while it did not differ significantly between group 1 and group 2. Absolute MBFs during pharmacologic vasodilation were significantly lower in the mid-distal than in the mid LV myocardium in group 1 and group 2 (1.45±0.25 vs 1.78±0.23 ml/g/min, and 1.35±0.47 vs 1.58±0.52 ml/g/min, $p<0.0001$), resulting in a MBF gradient that was significantly higher in group1 than in group 2 (0.32±0.15 vs. 0.23±0.11 ml/g/min, $p<0.0001$), not observed in CON (0.006±0.05 ml/g/min, p=NS). Notably, the MBF gradient in group 1-2 correlated significantly with the mid LV MBF during pharmacologic vasodilation ($r=0.42$, $p<0.05$), implicating the velocity of coronary blood flow as an important determinant of the MBF gradient. **Conclusion:** As it was observed, the hyperemic MBF gradient was more pronounced in coronary risk individuals without CAC than in those with CAC, while it dependent the velocity of coronary blood flow. These preliminary results further emphasize functional and/or structural alterations of the epicardial vessel as prevalent cause for the longitudinal MBF gradient.

OP472

Validation of 11C-acetate tracer kinetic models for the assessment of myocardial blood flow in normal adults and in patients with hypertrophic cardiomyopathy.

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Background: The clearance rate of carbon-11-labeled acetate (11C-acetate) is generally used for the non-invasive assessment of myocardial oxygen consumption with positron emission tomography (PET). Initial myocardial uptake of 11C-acetate, however, is related to myocardial blood flow (MBF). Several tracer kinetic models have been proposed to quantify MBF with 11C-acetate. Our objective was to validate and compare different models for the determination of MBF with 11C-acetate. Methods: Eighteen healthy subjects and 18 patients with hypertrophic cardiomyopathy (HCM) were studied under baseline conditions with 11C-acetate and 15O-water. Four previously validated methodologies were employed to calculate model parameter K1 based on the 11C-acetate studies. Subsequent MBF values were obtained by use of previously obtained relationships between K1 and MBF as reported in each of the validation studies. Flow values were then compared to 15O-water values. Results: For all models, correlates between 11C-acetate and 15O-water obtained MBF ranged from 0.67 to 0.86 (all $p < 0.005$) in the control group and 0.73 to 0.85 (all $p < 0.001$) in the HCM group. Two out of four models underestimated actual perfusion with 11C-acetate, the third model resulted in overestimation of MBF, whereas the fourth model, based on a simple single compartment model with spillover, partial volume and recirculating metabolite corrections, demonstrated a regression equation with a slope of near unity and a Y-intercept of almost zero (controls, $K1 = 0.74[MBF] + 0.09$, $r = 0.86$, $p < 0.001$ and HCM, $K1 = 0.89[MBF] + 0.03$, $r = 0.85$, $p < 0.001$). Conclusion: 11C-acetate enables quantification of MBF in fairly good agreement with actual MBF in both healthy individuals and patients with HCM. The use of a single compartment model with a standardized recirculating metabolite, as well as partial volume and spillover corrections most accurately reflects MBF.

OP473

Extra-Cardiac Uptake on Rubidium-82 Cardiac PET-CT Scan

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Aim: To collect preliminary results regarding avidity of malignant and benign processes for Rubidium-82 (Rb). **Material and Methods:** 255 subsequent Rb cardiac PET-CT scans performed at our institution were assessed for uptake in malignant and benign processes that were included in the field of view. Definitive etiology (histology or definitive imaging findings) was used as gold standard. A nuclear medicine physician graded the uptake of these processes qualitatively as -1 (< surrounding normal tissue), 0 (= surrounding normal tissue) or +1, +2, +3 or +4 (minimally, mildly, moderately and markedly > surrounding normal tissue, respectively). Qualitative analysis was not performed due to uncertainties regarding the time-activity curve of Rb in malignant

tumors and exact Rb dose and injection time. **Results:** Nine scans fulfilled the inclusion criteria. There were five patients with malignant and four patients with benign processes. Rb uptake in all malignant processes was higher than in the benign processes. There was no overlap between the degree of uptake in the malignant and benign processes, suggesting that a cutoff of +2 for malignancy could perhaps be used to distinguish these two types of processes on Rb PET. No formal statistical analysis was performed due to the low number of cases.

Case #	Gender	Age (y)	Size (cm)	Uptake	Etiology
1	M	67	3.5	+4	Malignant Neuroendocrine Tumor
2	M	81	4.2	+3	Diff Large B-Cell Lymphoma
3	M	78	5.4	+4	Lung Cancer
4	M	62	2.8	+3	Renal Cell Cancer
5	F	76	1.8	+3	Breast Cancer
6	M	75	10.3	-1	Lung Abscess
7	F	63	2.0	0	Breast Benign Fibrocystic Changes
8	M	75	3.1	+1	Benign Lung Scarring
9	F	60	5.1	+1	Pneumonia

Conclusion: Rb appears to be taken up more avidly by malignant processes than by benign processes and has the potential to be used in cancer imaging. Additionally, incidentally noted increased Rb uptake on cardiac PET CT scan should probably be further evaluated for malignancy. This new area of potential PET utilization warrants further investigation. Our preliminary results represent a first step in that direction.

OP474

ECG-gated [18F]FDG-PET/CT hybrid imaging in the evaluation of patients with unsatisfactory response to CRT pacemaker implantation: initial clinical results

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Objectives: Cardiac-resynchronization-therapy (CRT) is increasingly exerted in patients with advanced ischemic coronary artery disease (CAD) and reduced left ventricular function. However, 30-40% of patients do not adequately respond to this costly and time-demanding therapy, even if the implantation surgery was successful and the pacemaker-system is working correctly. The present study aimed to analyse a cohort of CRT non-responders using gated [18F]FDG-PET/CT (PET/CT). We hypothesized, that PET/CT is able to detect possible reasons for the non-response like position of the pacemaker electrodes within areas of non-viable myocardium or persistent left-ventricular dyssynchrony. Methods: Non-response to CRT was defined as the combination of unchanged clinical conditions (same NYHA stage and/or ongoing chestpain) and a minimum of two out of three unchanged clinical parameters consisting of LVEF improvement < 5%, decrease of Brain Natriuretic Peptide (BNP) < 10% and decrease of Left Ventricular End Diastolic Diameter (LVEDD) < 10%). Six patients (5m, 1f; mean age 61±10.1 years) met these criertia and underwent PET/CT 30±19months after CRT implantation. CT display of the pacemaker electrodes was fused with the PET scar map three dimensionally and left ventricular wall motion and synchrony was analyzed. Results: LVEF, BNP and LVEDD in the six non-responders were 27±9 %, 427±99 pg/ml and 71±1mm before and 28±6 %, 324±172 pg/ml and 67±5mm after CRT. All patients got optimized medical treatment according to german guidelines. In 4/6 Patients the lateral pacemaker electrode was assigned to an area with significant reduced myocardial glucose metabolism and reduced wall thickening. Additionally, persistent septal/lateral dyssynchrony of more than 300 ms was found in 3/6 patients. Conclusions: In 4 of 6 patients with unsatisfactory response to CRT implantation 3D-fusion of PET and CT images identified allocation of the pacemaker electrodes within non-viable myocardial areas. These results supporting the theory, that pre-existing myocardial scars could worsen the transfer of pacemaker signals and therefore diminish the grade of resynchronisation leading to persisting clinical discomfort. This hybrid diagnostical approach should be evaluated in a lager cohort of patients before CRT implantation to optimize therapy results by locating the optimal coronary vein for electrode positioning.

OP475

The Role of 18F-FDG PET/CT and Myocardial Perfusion Scintigraphy in the Evaluation of Cardiac Damage After Radiotherapy

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Introduction Radiotherapy has an important role in cancer treatment. Mediastinal radiotherapy is commonly performed for lymphomas, lung, breast and esophagus carcinomas. Radiotherapy zones can involve some regions of myocardium within the irradiation of mediastinal structures. Since 18F-FDG PET/CT is a noninvasive examination for the diagnosis and follow up of these malignancies, we aimed to evaluate the risk of myocardial damage by observing the biological distribution of FDG in patients who has undergone mediastinal radiotherapy. Materials and Methods The list of the patients who has undergone 18F-FDG PET/CT examination in our hospital, and the list of the patients who has undergone mediastinal radiotherapy were matched. 18F-FDG PET/CT examination was performed in 38 patients at least four months after the completion of radiotherapy. ROI's were drawn over the irradiated and nonirradiated myocardial regions on the PET/CT images. In the database check, it was found that eight of these patients have also undergone myocardial perfusion scintigraphy, and visual analysis of these images was performed. Results In the visual analysis, five patients had diffuse myocardial 18F-FDG uptake (13%), five patients had no significant 18F-FDG uptake (13%) and 28 patients had regional 18F-FDG uptake (74%). The SUV calculations of these 28 patients were significantly higher in the irradiated regions in comparison to other myocardial regions (p<0.001). Six of the eight patients that has undergone myocardial perfusion scintigraphy showed fixed hypoperfusion in the irradiated myocardial regions in consistent with the regions that increased 18F-FDG PET/CT uptake was seen. There was no correlation between the radiotherapy doses and the SUV measurements in the myocardial regions. Conclusion Since the patients had no myocardial infarction or diabetes and these myocardial regions were not consistent with the vascular territory of coronary arteries, the findings might were thought to indicate radiation induced myocardial damage. The patients with mediastinal radiotherapy history that showed increased 18F-FDG uptake, especially in the basal myocardium, should be followed cautiously for the early diagnosis and treatment of cardiac events.

1404 - Tuesday, October 13, 2009, 14:30 – 16:00, Hall 117

CTE 5: Clinical Audit

OP476a

Introduction to Clinical Audit

B. Moran (IE)

OP476b

Practical Examples of Clinical Audit in Nuclear Medicine

C. Murtagh (IE)

OP476c

Practical Examples of Clinical Audit in PET/CT

C. Walsh (IE)

1405 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 113

Molecular Imaging: Oncology

OP476d

Development of bevacizumab-conjugated ferromagnetic nanoparticles for non-invasive angiogenesis detection

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Introduction: The development of radioimmunoconjugates as diagnostic tools, which enable the acquisition of important data on tumor localization, is an exciting area of research. Bevacizumab (Avastin®, Roche) is a humanized monoclonal antibody which binds all VEGF-A isoforms. In recent studies it has been shown that radiolabeled bevacizumab accumulates in VEGF-expressing tumors with high specificity. Our efforts are focused on targeting VEGF-A with Bevacizumab-conjugated Ferromagnetic Nanoparticles (bc-FNs), thus leading to a highly-specific targeted contrast agent that could be utilized in Magnetic Resonance Imaging (MRI) applications. Materials and Methods: Magnetite Fe_3O_4 was employed as the FN constituent mainly due to its almost ideal biocompatibility. DMSA was used as the conjugation moiety for the targeting ligand since it forms a stable coating on the Fe_3O_4 FNs, while its remaining free thiol groups are used for the attachment of the target-specific antibody. The DMSA-FNs were conjugated to bevacizumab, which was adequately modified by use of either sulfo-SMCC, SATA or 2-mercaptoethanol. Conjugation between the FNs and the targeting antibody was proven by means of UV-vis spectrophotometry. In addition, the modification of the magnetic properties of the formed Bc-FNs was investigated by means of a Superconducting Quantum Interference Device (SQUID) magnetometer. Finally, the binding efficiency of Bc-FNs was investigated by means of standard immunostaining tests with FITC-goat anti-human IgG in MDA MB231 human breast cancer cells, as well as in their VEGF-165 transfectants M165, since the former has a moderate expression of VEGF, while the latter overexpresses the cell-associated 165 isoform of VEGF. Results: UV-vis data for the supernatant of the Fe_3O_4-bevacizumab conjugates showed no indication of the characteristic absorption of the antibody at 280 nm, indicating the absence of bevacizumab in the supernatant. Immunostaining test with FITC-goat anti-human IgG revealed no green fluorescence activity from cells treated with a control conjugate, but bright green fluorescence from cells treated with the FN-bevacizumab conjugate. Furthermore, a notable difference in fluorescence activity was observed in the two cell lines with different VEGF expression levels. Conclusions: Our results give strong evidence for the efficient formation of Bc-FNs that (i) retain good magnetic properties, (ii) possess high binding affinity and, (iii) good specificity to relevant cancer cell lines. Since the Bc-FNs examined in this work fulfill these three cornerstone prerequisites that should be met for the effective utilization of any contrast agent in MRI we believe that the need of further *in vitro* and *in vivo* investigations is fairly documented.

OP477

Evaluation of early therapy response by [18F]FDG-PET/CT in a transgenic gastric cancer mouse model

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Purpose: Initial evaluation of the transgenic gastric cancer mouse model CEA424/SV 40T for response monitoring of chemotherapy-induced changes in tumor glucose metabolism with [18F]fluorodeoxyglucose-PET/CT ([18F]FDG). Methods: CEA424/SV40 antigen-transgenic mice develop gastric cancers around day 30. Pretherapeutic imaging was performed in 11 mice aged day 40-45 by [18F]FDG-PET using a dedicated small animal PET/CT system (Inveon, SIEMENS

Preclinical Solutions, Knoxville, TN). 6 mice received cisplatin chemotherapy (0.1 mg/g body weight i.p.) on day 1, 5 and 9 after the first PET/CT scan, whereas the control mice (n=5) received PBS injections (100µl i. p.). PET/CT scans were repeated on day 4 and 14 after initial imaging. Static image acquisition was performed 60 min after injection of 5-10 MBq [18F]FDG. Mice were sacrificed for histopathological analysis on day 15. Tumour-to-background ratios (TBR) were calculated from the 50% isocontour 3D regions of interest of the FDG uptake in the tumor. The spinal muscle served as background. Results: In the control group (n=5), pretherapeutic TBR was 1.94±0.78 which increased over the time course to values of 3.40±1.03 and 3.69±0.96 at day 4 and 14, respectively. In the mice undergoing cisplatin chemotherapy, the initial TBR (3.20±0.92) remained stable over the time course (3.75±0.34, and 3.07±0.62, at day 4 and 14). Analysis of variance for repeated measurements revealed a statistically significant difference in TBR changes between control and treatment group (p=0.027). For the late time point, the within-subject growth was higher for the control group compared to the treatment group (1.74±1.43 vs. -0.12±0.91; partial eta squared: 0.649 vs. 0.022; corresponding p-values: 0.053 and 0.753). Correlation to histopathology is currently under investigation. Conclusion: Therapy monitoring of an transgenic gastric cancer mouse model with [18F]FDG-PET/CT is feasible. TBR remained stable in mice undergoing cisplatin chemotherapy, whereas the control group revealed a significant increase in tumoral glucose metabolism. The difference in tumoral FDG-uptake has to be correlated with the histopathological findings currently under investigation. [18F]FDG-PET/CT has a high potential for detecting early response to treatment in transgenic gastric cancer.

OP478

Ga-68 DOTATATE PET Imaging Of AAV Mediated Somatostatin Receptor 2 Gene Transfer

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Montoring of gene expression through external imaging may be a useful tool for following gene therapy procedures. In particular, the use of PET may allow quantitative evaluation in these situations. Given the relatively low endogenous expression of the Somatostatin Receptor 2 (SSTR2) and the availability of very efficient positron emitter labeled radiotracers capable of binding this receptor such as 68Ga-DOTA-Tyr(3)-Thr(8)-octreotate (68Ga-DOTATATE), we have evaluated the use of this combination of reporter gene/reporter compound for quantitative, non invasive monitoring of gene transfer. Adeno Associated Virus (AAV) vectors encoding the human SSTR2 gene or green fluorescent protein (GFP) as control, under the cytomegalovirus (CMV) or the thyroxin binding globulin (TBG) promoters were constructed. Different sets of C57/BL6 mice received intravenous (IV) AAV-TBG-SSTR2, intramuscular (IM) or inhaled AAV-CMV-SSTR2. Control animals received both IV AAV-TBG-GFP and IM AAV-CMV-GFP. PET imaging was carried out over a 6 month period following the AAV administration in treated and control animals with 1-5 MBq of 68Ga-DOTATATE using a clinical PET scanner. Images were acquired 15-20 min after injection and region of interest analysis was utilized to determine SUV values for the tracer in different tissues. IV AAV-TBG-SSTR2 transduced animals showed markedly increased uptake in the liver,that was several-fold above control levels. IM AAV-CMV-SSTR2 transduced animals showed a 3 to 4 fold increase in muscle uptake compared to controls. In both instances, the increase in 68Ga-DOTATATE uptake was dependent on the amount of administered AAV. Liver transduced animals showed a tendency for a decrease in liver uptake over time whereas transduction in muscle showed a steady increased uptake over the 6 month observation period. Inhaled AAV-CMV-SSTR2 did not yield significant increase in 68Ga-DOTATATE uptake in the lungs. The figure below shows images obtained 1 month after transduction. Panel A shows a control mouse who received intramuscular (IM) and intravenous (IV) control AAV. Uptake is seen mainly in the kidneys and the bladder (route of excretion). Panel B shows remarkable liver uptake of the tracer in a mouse treated with IV AAV-TBG-SSTR2. Panel C shows specific increased uptake of tracer in the thigh of a mouse treated with IM AAV-CMV-SSTR2. Use of the SSTR2 as reporter gene and repetitive imaging with 68Ga-DOTATATE demonstrates that monitoring is feasible and high uptake levels are maintained for long periods of time. This approach may be useful for quantitative monitoring of gene therapy in animal models.

OP479

Differential Expression of the Na+/I- Symporter in Estrogen Receptor Positive and Negative Invasive Breast Carcinomas

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Purpose: The Na+/I- symporter (NIS) is a key plasma membrane protein that mediates active iodide (I-) transport in the thyroid cells. Breast cancer (BC) is the only other cancer demonstrating endogenous functional NIS expression and NIS activity was proven in BC metastases. The aim of the present study is to explore and compare the NIS expression in Hormone Receptor (HR) negative and HR-positive BC. Materials and methods: NIS expression was evaluated by immunohistochemistry in two groups of tumor samples (untreated ductal carcinomas), 49 ER-PR- and 41 ER+PR+. Slides were analyzed by light microscopy by two pathologists (NS, DL) and the percentages of cells exhibiting NIS immunostaining at the level of their cytoplasm (cNIS) and/or of their membranes (mNIS) were reported. Each tumor was scored for mNIS from 0 (no cell stained), 1+ (1 to 5%), 2+ (6 to 9%) to 3+ (>10% positive cells) and for cNIS from 0 (no cell stained), 1+ (1 to 10% positive), 2+ (10 to 30%) to 3+ (30% and more positive) Results: mNIS (1+ to 3+) as well as cNIS stainings were more frequently observed in HR-negative BC (45% mNIS and 67% cNIS) than in HR-positive ones (7% mNIS and 20% cNIS) (both P < 0.01). However, no difference between HR+ and HR/-/ could be detected in the percentage of cells cNIS stained (median : 30% versus 20%, P=0.93). On the another hand, half of the patients scored cNIS 3+ (9/18) had 50 to 80% of the cells stained. cNIS staining was present in 24 out of the 25 cases with mNIS staining. In 22 of the 49 HR/-/ cases classified as mNIS positive, on average only 9% of the cells were stained. However, 4 (31%) of the 13 patients scored mNIS 3+ had 20 to 30% of the cells stained. Results obtained on BC over expressing HER2/Neu suggest that NIS expression is rather related to ER negativity (6 NIS positive out of eight Neu+) than to ER positivity (one out of eight Neu+). No statistically significant difference in rate of NIS staining between Neu amplified and Neu non amplified tumors was found. Conclusions: Our results demonstrate that NIS is more frequently expressed in ER-negative BC than in ER-positive ones. It could make these aggressive ER negative BC the group to be targeted with iodine therapy after the demonstration of their NIS expression and of the in vivo functionality of the symporter.

OP480

Preclinical evaluation of new radioligands of cholecystokinin/gastrin receptors

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Aim: Whereas somatostatin receptor scintigraphy has been proven a valuable tool for staging endocrine tumors, its sensitivity and accuracy in other cancers, such as metastatic medullary thyroid cancer (MTC) or small cell lung cancer (SCLC), is limited by the poor and inconstant expression of these receptors. The cholecystokinin (CCK)/gastrin receptor (CCK2R) is overexpressed in up to 90% of MTC and 60% of SCLC but not in the corresponding healthy tissues. The CCK2R represents a ideal target for the diagnosis and internal radiotherapy of these tumors. Although previously studies had demonstrated the feasibility of radiolabeled CCK/gastrin ligands to target MTC in animals and patients, different adverse effects were reported indicating that tumor uptake, biodistribution and renal toxicity must be improved for clinical application. The aim of this study was to synthesize and assess the effectiveness of new radioligands with optimized properties to target the CCK2R. Materials and Methods: We have used a tri-dimensional molecular model of the CCK2R occupied by CCK that we have previously built to design "*in silico*" modified CCK derivatives covalently coupled to a chelating agent. Two original CCK derivatives have been synthesized, coupled to chelating agent DTPA and to an original chelating multimodality imaging agent before labelling with ^{111}Indium. The stability and affinity of these CCK derivatives were studied *in vitro.* Nude mice, bearing NIH-3T3 tumors expressing a constitutively active mutant of the CCK2R, were intravenously injected with these radiolabelled CCK derivatives. *In vivo* scintigraphy was performed 24 h post injection and compared with the control ^{111}In-DTPA-CCK8 previously used in the published studies. A dynamic acquisition of planar images was performed. Images analysis was done on a Xeleris workstation. Thereafter biodistribution studies (% ID/g tissue) were done. Results: The conditions of radiolabeling were optimalised to lead to a radiochemical purity > 95%. *In vitro* studies confirmed that the two CCK compounds displayed nanomolar affinities for the CCK2R and greater stabilities. Scintigraphic and biodistribution studies showed significant improvement of tumor targeting and renal toxicity compared to the control ^{111}In-DTPA-CCK8: in particular, for the ^{111}In- multi-modality chelator-CCK derivative, we have a 4-fold higher tumor uptake with a tumor to kidneys ratio higher than 7. Conclusion: A more suitable biodistribution and less renal fixation were obtained for these two new radioligands. In particular, the original multi-modality radiolabeled CCK derivative appears to be a promising candidate for molecular imaging and internal radiotherapy for tumors overexpressing the CCK2R.

OP481

Changes of carcino embryonic antigen (CEA) mediated uptake of a CEA-specific pretargeting system in colorectal cancer in vitro after external irradiation

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Aim: In clinical routine, the early determination of response of colorectal cancer (CC) to neoadjuvant radio-chemotherapy is highly relevant. In most of colorectal tumors CEA is expressed. Pretargeting systems allow radioimmuno-mediated SPET and PET investigations. Both techniques are based on the high affinity of antibodies to tumors and the quick kinetics of radiolabelled peptides. TF2 is a humanized bispecific trivalent monoclonal antibody (mAb). This mAb is directed against CEA expressed by tumors and, additionally, to the sequence histamine-succinyl-glycine (HSG). The HSG peptide IMP288 is DOTA-linked and should bind to TF2 with high affinity. The aim of our study was to investigate the kinetics of the pretargeting system in vitro, the influence of CEA expression levels as well as changes in uptake after external irradiation in vitro prior to patient investigations. Materials & methods: TF2 (0.5-1 mg, Immunomedics) was labelled with 50-100 MBq ^{131}I. IMP288 (6 µg, Immunomedics) was labelled with $^{111}InCl_3$. Three CC cell lines (HT29, SW480, T84, all ATCC) with different CEA expression were incubated (4-72 h) with ^{131}I-TF2 and ^{111}In-IMP288 alone or after preincubation with "cold" TF2. Additionally, parallel cultures were previously irradiated with 2-10 Gy high energy photons. The uptake/10^6 cells as well as the proliferation were investigated. Statistical analyses were performed using non-parametric tests. Results: The specific uptake of ^{131}I-labelled antibodies reached a maximum after 24-48 h was and depended on the CEA expression of the different cell lines (0.2, 3 and 10 %). The incubation of cells with ^{111}In-IMP288 alone resulted in a low unspecific binding. Cultures after 48 h of preincubation with "cold" mAb showed an uptake of ^{111}In-IMP as high as the radiolabelled antibody, but more rapid kinetics. An external irradiation increased the specific uptake of ^{131}I-mAb as well as of ^{111}In-peptide after preincubation with "cold" mAb significantly up to 4-fold ($p<0.05$), dose-dependently. Conclusions: The investigated pretargeting system allows not only to analyze semi-quantitatively CEA expression of colorectal cancer cells but also to evaluate changes of antibody uptake after external irradiation. In clinical studies the early increased uptake after irradiation has to be considered. The molecular biology basis of these findings is under further investigation.

OP482

Imaging of EGFR expression in murine xenografts using site-specifically labelled anti-EGFR ^{111}In-DOTA- $Z_{EGFR:2377}$ Affibody molecule: aspect of the amount of injected tracer.

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Aim. Overexpression of epidermal growth factor receptor (EGFR) has a prognostic value in many carcinomas. Radionuclide molecular imaging of EGFR expression may provide important

diagnostic information. A number of radiolabelled tracers for imaging of EGFR have been developed. However, the expression of EGFR in normal tissues might complicate imaging. The aim of this study was to evaluate if optimization of the injected tracer dose can improve imaging of EGFR expression in murine xenografts using a novel targeting protein, the ^{111}In-DOTA- $Z_{EGFR:2377}$ Affibody molecule. **Materials and methods.** An anti-EGFR Affibody molecule, $Z_{EGFR:2377}$, was selected for this study because it has equal affinity (K_D) to human [0.9 nM] and murine [0.8 nM] EGFR $Z_{EGFR:2377}$ was labelled with ^{111}In via DOTA site-specifically conjugated to the C-terminal. The specificity of ^{111}In-DOTA- $Z_{EGFR:2377}$ for EGFR-expressing cells was confirmed in vitro. The biodistribution of radiolabeled Affibody molecules after injection of different tracer amount was compared in mice bearing EGFR-expressing A431 xenografts. **Results.** The conjugate accumulated specifically in xenografts and in EGFR-expressing tissues. Injection of small amount of tracer (high specific radioactivity) resulted in uptake in normal EGFR-expressing organs (e.g. liver and salivary glands) and provided suboptimal tumour-to-organ ratios. Increasing the amount of injected tracer up to 50 µg (ca. 7 nmol) saturated EGFR in healthy tissues, but not in xenografts. Further increase of the injected amount resulted in decreased tumour uptake. In murine xenografts, the optimal tumour to organ ratios were obtained after injection of 30-50 µg ^{111}In-DOTA- $Z_{EGFR:2377}$. The results of the biodistribution study were confirmed by γ-camera imaging. Table. Tumour-to-organ ratios 4 h after injection of alternative doses of ^{111}In-DOTA- $Z_{EGFR:2377}$ Affibody molecule.

	0.1 µg	5 µg	30 µg	50 µg	100µg
blood	0.7±0.2	1.5±0.9	4.5±2.9	7.0±0.6	6.4±1.0
salivary gland	1.2±0.3	1.8±0.8	6.4±1.8	9.3±2.5	7.0±0.2
liver	0.25 ±0.04	0.38±0.13	0.42±0.19	0.46±0.03	0.34±0.10
muscle	10±5	10±5	32±13	27±8	22±2

Conclusion. Careful optimization of a tracer dose is required for high-contrast imaging of EGFR expression in vivo.

OP483

Study on in vivo imaging of ^{99}Tc^{m}-hTERT mRNA as antisense molecular probe in breast cancer tumor-bearing nude mice

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Objective Antisense imaging is one of the important modalities in the domain of molecular nuclear medicine. The purpose of this study was to design, synthesize antisense oligonucleotide molecular probe of human telomerase reverse transcriptase (hTERT) mRNA, and validate the potential application value using animal model experimental study to early diagnose the tumor. **Methods** Antisense and sense molecular probes targeting hTERT mRNA were radiolabeled with technetium-99m through bifunctional chelator N-hydroxysuccinimidyl derivative of S-acetylmercaptoacetyltriglycine (S-Acetyl NHS-MAG_3). The BALB/c *nu/nu* nude mice were inoculated with MCF-7 mammary tumor cells in the right upper limbs. ^{99}Tc^{m}-hTERT mRNA ASON and ^{99}Tc^{m}-hTERT mRNA SON with or without mediated by liposome was injected intravenously in mammary tumor-bearing BALB/c nude mice, respectively. Imaging in vivo was performed periodically. All data were analyzed by the statistic software of SPSS12.0. **Results** The in vitro study showed that the labeling efficiencies of ^{99}Tc^{m}-hTERT mRNA ASON reached 76%±5%, with the radiochemical purity of more than 96% and the specific activity of 1850 kBq/µg. The stability of ^{99}Tc^{m}-hTERT mRNA ASON in room temperature and serum incubation after 24 h was still above 93%. The in vivo study showed that tumor uptake of ^{99}Tc^{m}-hTERT mRNA ASON was high from 4 h to 8 h after injection. On the contrary, there was little ^{99}Tc^{m}-hTERT mRNA SON accumulated in tumor within 8 h. The radioactivity ratio of. tumor-to-nontumor (T/NT) of antisense probe group mediated by liposome or not was 8.02±0.03 and 7.55±0.12,respectively(P>0.05), and that of sense probe group mediated by liposome or not was 1.23±0.06 and 1.33±0.15,respectively (P>0.05). However, there was significant difference between antisense and sense probe groups mediated by liposome or not (P<0.001). **Conclusion** This in vivo study provided evidence that antisense oligonucleotide molecular probe targeting hTERT mRNA labeled with technetium-99m could be used as a potential candidate for visualization of hTERT expression in breast cancer MCF-7 tumor tissues. **Key words** Breast neoplasma;RNA, messenger; human telomerase reverse transcriptase (hTERT), antisense oligonucleotides; Mouse, nude

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Oncology PET: lymphoma 2

OP484

Concordance between four European Centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma

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Aim: Standardised reporting criteria are required in multicentre trials to ensure consistency in image interpretation. The aim of this study was to determine if reporting criteria developed for the Response Adapted Treatment in Hodgkin Lymphoma (RATHL) trial were sufficiently robust to enable satisfactory agreement to be reached between centres acting as 'core labs' reporting scans in different countries. **Methods**: Four European centres viewed the same 100 FDG PET scans from 50 patients with HL, acquired before chemotherapy and after 2 cycles of ABVD. Datasets were anonymised and saved in DICOM format. Each centre used their standard reporting software. A five point scale was used to score uptake in regions involved by lymphoma at staging : 1) no increased uptake 2) uptake less than or equal to mediastinum 3) uptake greater than mediastinum but less than or equal to liver 4) moderately increased uptake compared to liver 5) markedly increased uptake compared to liver. Centres read scans independently then discussed scans where there was disagreement to determine if consensus could be reached. For the RATHL study a score of 1, 2 or 3 is regarded as 'negative' and a score of 4 or 5 is regarded as 'positive' for lymphoma. A positive scan results in escalation of chemotherapy to BEACOPP or escalated BEACOPP. **Results**: There was agreement that the response scan was 'positive' or 'negative' for lymphoma in 44/50 patients when scans were read independently at four centres. Consensus was reached in 46/50 patients after discussion. Kappa for negative (score 1,2,3) vs positive (score 4,5) was 0.85 (95% CI 0.74-0.96) for the independent read (very good agreement) and 0.90 (95% CI 0.79 - 1.00) for the consensus read (very good agreement). The data were reanalyzed, considering score 3 as a separate category that was 'equivocal' for disease. There was agreement in 40/50 scans on independent reading and 44/50 scans with consensus reading. Kappa for negative (score 1,2) vs equivocal (score3) vs positive (score 4,5) was 0.76 (95%CI 0.66-0.85) (good agreement) and 0.85 (95%CI 0.75-0.95) (very good agreement) for independent and consensus reading respectively. **Conclusion**: The criteria developed for interpretation of PET scans in the RATHL study are sufficiently robust to be used in a multicentre setting. Continued audit will be required to ensure consistency in reporting is maintained. The criteria could be adapted to change the threshold for 'positivity' according to the clinical or research context.

OP485

Interim PET in Hodgkin lymphoma: comparison of the different criteria to evaluate chemotherapy response

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Aim: Interim FDG-PET (iPET) is strongly correlated with progression-free survival in Hodgkin lymphoma (HD). However the criteria to define negative or positive iPET are not yet clearly defined. In this study we compared the accuracy of different qualitative methods to evaluate therapy response with iPET. Moreover, we explored the incremental prognostic power of a semiquantitative analysis using SUVmax. **Material and methods**: We retrospectively analyzed 58 HD patients with a baseline and iPET performed after two cycle of ABVD treatment. Images were evaluated visually comparing the uptake in the residual to a reference using the following criteria: iPET positive if: 1) uptake > liver; 2) uptake > liver and dimension >= 2 cm or uptake = liver and dimension < 2 cm; 3) uptake > mediastinal blood pool structure (MBPS); 4) uptake > MBPS and dimension >= 2 cm or uptake = MBPS and dimension < 2 cm.. The 4 criteria were then revised in patients with uptake between MBPS and liver; iPET was set positive if SUVmax was > than threshold. Results of iPET were compared with the clinical status at follow-up (range 138-1783 days). **Results:** during post-treatment follow-up 6 pts had a progression disease (3 died) and 52 were in complete regression. A cut-off value of 3.5, determined using ROC analysis, was utilized to distinguish negative from positive results in iPET. In the table are reported the results obtained using the four criteria of interpretation. In bold are evidenced the results obtained using SUVmax as an additional parameter.

Method:	TP (**withSUV**)	FP (**withSUV**)	FN (**withSUV**)	TN(**withSUV**)	Accuracy(**withSUV**)
1	2 (**4**)	5 (**2**)	4 (**2**)	47 (**50**)	84 **(93)**
2	4 (**4**)	7 (**4**)	2 (**2**)	45 (**48**)	84 **(90)**
3	4 (**4**)	8 (**4**)	2 (**2**)	44 (**48**)	83 **(90)**
4	4 (**4**)	17 (**4**)	2 (**2**)	35 (**48**)	67 **(90)**

The number of TP and FN patients is the same using the different criteria except for criteria 1) that has a relative lower TP rate and higher FN rate while the different criteria significantly affects the FP rate. A SUVmax.>3.5 applied to a qualitative interpretation of iPET increases the accuracy and reduces the FP rate the best results being observed using criteria 1. **Conclusions:** in iPET the number of FP results is influenced by the criteria utilized for defining a study positive or negative. The number of FP is higher using MBPS as a reference than liver. The dimension criteria linked to a qualitative scoring system increase the number of FP. The SUVmax linked to a qualitative analysis increases always the accuracy.

OP486

Assessment of Early Treatment Response after 4 Cycles of Chemotherapy using FDG-PET in Patients with Advanced-Stage Hodgkin Lymphoma

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Background: As positron emission tomography (PET) seems to be a powerful prognostic marker in the treatment of Hodgkin lymphoma (HL), we analysed the prognostic value of PET after 4

Tuesday

cycles of BEACOPP in patients with advanced-stage HL. **Patients and methods:** Between January 2004 and March 2007, 50 adult patients with newly diagnosed HL in clinical stages IIB with large mediastinal mass or extranodal disease, III and IV were treated according to the HD15 protocol of the German Hodgkin Study Group (GHSG) with 6-8 cycles of BEACOPP variants. All patients received an intermediate PET scan after 4 cycles of BEACOPP (PET-4). **Results:** Of the overall group, 14/50 patients had a positive PET-4 while 36 had a negative PET-4. At a median observation time of 25 months, 2 of the 14 patients with a positive PET-4 had progressed or relapsed, while there was no progression or relapse in PET-4 negative patients. **Conclusion:** Our results indicate a very good negative predictive value of intermediate PET-4 in advanced-stage HL patients treated with BEACOPP.

OP487

Prognostic value of SUV reduction in early 18F-FDG PET in patients with diffuse large B-Cell lymphoma:Comparison with visual analysis

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Aim: To evaluate, in patients with diffuse large B-Cell lymphoma (DLBCL) the prognostic value of reduction in FDG uptake after two cycles of chemotherapy. **Methods**: Forty seven patients with newly diagnosed DLBCL underwent ^{18}F-FDG PET at baseline (PET0) and after 2 cycles of induction treatment (PET2). According to Juweid criteria, the images were interpreted visually as negative (complete response) or positive (partial response or progressive disease). For quantitative analysis, the tumor uptake of FDG was evaluated by the maximal standardized uptake value (SUVmax) corrected to body weight. The response of chemotherapy was evaluated using the SUV reduction between PET0 and PET2 (ΔSUVmax). The threshold used was 65% according to ITTI's publication (*J Nucl Med 2007,48:1626*). Survival curves were estimated using Kaplan-Meier analysis and compared using log-rank test. **Results:** With a median follow-up of 21 months, 6 of 47 patients progressed or died. According to the visual analysis, PET2 was interpreted as negative in 18 patients and positive in the 29 remaining patients. The quantitative analysis showed a ΔSUVmax < 65% in 9 patients and ΔSUVmax >= 65% in 38 patients. Among the 29 patients reaching a PR according to Juweid criteria, 21 (72%) had a SUVmax reduction higher than 65%. The 2-years estimate for progression-free survival was 94% in patients with a ΔSUVmax higher than 65%, versus 63% in those with reduction less than 65% (P=0.0046). The visual analysis had no statistical impact on progression-free survival. **Conclusion:** The SUV-based assessment of glucose metabolic changes after two courses of chemotherapy is more reliable to patient outcome than visual analysis estimated by Juweid criteria. The SUVmax reduction is an early prognostic factor that may help to reduce false positive interpretations, and provides a more reproducible assessment of early PET study, in order to guide risk-adapted therapies.

OP488

Standard criteria and standardized uptake value (SUV) in the post treatment PET/CT evaluation of patients with malignant B-cell lymphoma.

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Introduction: According to the Swedish National guidelines PET is recommended as follow-up after treatment of malignant B-cell lymphoma. However, recently the method has been questioned because of too many false positive (FP) results. One reason could be over diagnosis due to only visual analysis of the PET scan. **Material and methods:** We have re-evaluated our first 40 consecutive B-lymphoma patients and compared our interpretation with a 6 month clinical follow-up. All patients had a PET/CT about one month post treatment with R-CHOP-14 x 6 in combination with rituximab. 4 MBq/kg body weight F18-FDG was given one hour (51-68 min) before PET acquisition using a Siemens Biograph PET/CT. All patients had intravenous X-ray contrast injected 60 s before the full dose CT investigation. The hottest PET lesions in mediastinal, abdominal and peripheral locations were chosen for SUV analysis. SUV ware calculated as max values/kg bodyweight in a spherical VOI created by the Siemens software TrueD. To obtain background SUV levels of mediastinal blood pool a circular ROI was applied to the 3 mm transaxial slice containing aorta + truncus pulmonalis. A positive PET was defined according to the standard criteria recommended by Juweid et al.(J Clin Oncol 2007;25:571-578), which are focal or diffuse uptake above background incompatible with normal anatomy or physiology. A defined exception is mild and diffusely increased FDG uptake in residual masses >2 cm, with intensity lower than or equal to that of mediastinal blood pool structures. **Results:** There was six true and four false positive results in our material by visual assessment alone. All FP lesions had no doubt uptake higher than surrounding background or mediastinal blood pool, but the lesions were small (largest CT- diameter 9, 11, 12 and 26 mm respectively), and with comparatively low SUVs (2,6, 2,8, 2,8 and 3,6). One lesion was mediastinal, one abdominal and two peripheral. The reproducibility of SUV determinations was high. The mediastinal blood pool background varied between SUVmax 2,1-3,6, probably due to individual variations in blood concentration of given x-ray contrast agent affecting the attenuation correction. **Conclusion:** Using the standard criteria and visual analysis alone there was a 10% FP rate in our material. Our preliminary data indicate that the number of FP residual lymphoma would be significantly reduced using a SUVmax around 3,0 as cut-off in addition to the visual assessment in the post treatment evaluation of B-lymphoma patients. F:\PETCT\Abstract till EANM Barcelona 2009.doc

OP489

Prognostic value of 18F-FDG-PET after first-line therapy in patients with Diffuse Large B-cell Lymphoma

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AIM: The purpose of this study was to assess the prognostic value of ^{18}F-FDG-PET in patients with diffuse large B-cell lymphoma (DLBCL) after completion of first-line therapy. MATERIALS AND METHODS Thirty-two patients (14 women/18 men) with a mean age of 54.86±15.09 years old (range: 22-84) with newly diagnosed and histologically proven DLBCL underwent 18F-FDG-PET before and after first-line therapy. The image data was collected and retrospectively analyzed and correlated with outcome data. Patients were staged according to Ann Arbor classification (stages I:15.6%, II:21.9%, III:18.8% and IV:43.8%) and had a minimum follow-up of 2 years (mean: 27.19±17.76 months). Maximum SUV (SUVmax) was computed by normalizing the most intense uptake area to the patient's body weight. The SUVs max and their changes over time were compared for predicting overall survival and survival curves using the Kaplan-Meier analysis. RESULTS All patients had a positive baseline PET scan, with an average SUVmax of 11.51±5.20. 22/32 patients showed complete response (CR) after completion of first-line therapy, 8 showed partial response (PR) and continued progression of disease (PD) occurred in 2 patients (EORTC criteria). The average SUVmax on PET images after completion of treatment was 3.10±3.85 (p<0.001). There was a statistically significant difference of SUVmax on PET images after first-line therapy between patients group with and without relapse disease (p<0.006). 9 of 32 patients relapsed (28.12%). Of the patients who demonstrated residual disease on their post-treatment PET scan, 40% relapsed and 60% remained in remission. Comparatively, only 22.7% of patients who demonstrated CR relapsed and 77.3% remained in remission. The 2-year overall survival was 81.2%.The percentage of mortality in patients with CR was 13.6% (3/19) compared to 30% (3/10) in patients with treatment failure. (Table 1). CONCLUSION ^{18}F-FDG-PET imaging after completion of first-line therapy has a good prognostic value in patients with DLCBCL. There was a statistically significant difference between SUVmax of PET images after completion of treatment and the relapse ratio. This imaging modality is able to predict those patients who are at high risk for disease relapse or mortality and may play an essential role in managing patients with DLCBCL.

		MORTALITY NO	MORTALITY YES
^{18}F-FDG-PET AFTER FIRST-LINE THERAPY	CR	19 (86.4%)	3 (13.6%)
	Treatment failure(PR+PD)	7 (70%)	3 (30%)
	TOTAL	26 (81.3%)	6 (18.8%)

OP490

Validation of FDG-PET/CT in evaluation of early remission in patients with refractory lymphoma after treatment with high dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT)

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Objectives**:** The aim of this study was to evaluate the predictive value of sequential PET before and after HDT and ASCT in Hodgkin (HL) and Non Hodgkin lymphoma (NHL). Methods**:** We studied 20 lymphoma patients,9 patients with NHL and 11 patients with HL. There were 10 male and 10 female patients aged between 12 and 65 years (mean 34.58). A pretreatment PET/CT was performed for all patients (PET0, CT0). Follow-up scans were performed on 30th (PET1, CT1), 60th (PET2, T2), 100th days (PET3, CT3). The mean follow-up period was 12 months (range 6-18 months). PET and CT scans were retrospectively blindly evaluated by a nuclear medicine and radiology physicians. Results**:** PET and CT scans were positive for all patients before HDT/ASCT. PET1 and PET2 scans were positive for 8 patients, PET3 scans were positive for 6 patients. 30th, 60th and 100th day CT scans were positive for 10, 8 and 5 patients, respectively. At the end of 1st year 4 patients died whose PET scans were positive. 12 patients of 20 had negative PET scans confirming CR while 8 patients had negative CT scans. Six patients had still positive CT scans. Two of these 6 patients had positive scan and relapsed. After one year, overall survival and progression free survivals were 100% and 91%, respectively. All results were correlated with clinics and follow up. Conclusions**:** Our study suggested PET had a higher prognostic value than CT in refractory lymphoma and should be performed as a more valid alternative for post-treatment evaluation.

OP491

FDG PET/CT as a Response Surrogate in Patients with Multiple Myeloma.

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Determination of response in multiple myeloma (MM) is challenging and requires uniform criteria. The response criteria recommended are primarily derived from the International Myeloma Working Group (IMWG). Early evaluation of response with FDG-PET/CT (PET/CT) may be used as a response surrogate in MM and it may improve the response classification. Our objective was to correlate PET/CT findings obtained early after treatment with progression free survival (PFS) and the IMWG response criteria in MM patients who are undergoing therapy after relapse. **Methods:** Seventeen patients with relapsing MM had a whole body PET/CT imaging 2-3 months after initiation of therapy. Therapy consisted of various combination treatments, mainly based on dexamethasone with thalidomide or equivalent regimens. All patients had a 12-month follow up. PET/CT was evaluated using liver as the reference organ. The laboratory data involving serum and urine M component using immunofixation, serum free light assay and bone marrow biopsy were available in all patients to determine response by IMWG criteria. The therapy

response based on PET/CT and IMWG was correlated with PFS at 12 months. **Results:** Of 17 patients, PFS was not reached in 9 (53%) patients at 12 months while 8 (47%) patients relapsed with a median PFS of 9 months. By IMWG, 7 (41%) patients had CR, 6 had PR, 1 had very good partial response (VGPR), 3 had no response. The patient with VGPR was lumped with the CR group. By PET/CT, 11 (65%) patients had CR and 6 (35%) patients had no response. There were 2 false negative PET/CT studies when IMWG results were true positive. There was no false positive PET/CT results. There were 4 false positive IMWG results when PET/CT was true negative in all. There were 3 false negative IMWG results when PET/CT was true positive in all. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for PET/CT and IMWG to predict 12-month PFS were 75%, 100%, 100%, 82% and 100%, 55.5%, 67%, 100%, respectively. **Conclusion:** In the prediction of 12-month PFS, PET/CT obtained at 2-3 months after therapy appears to have a superior specificity and PPV while IMWG criteria yield higher sensitivity and NPV. The combination of these two methods may increase the accuracy of response classification. Although these data are limited by sample size and short follow up period, these results lay groundwork for further studies to determine the predictive value of PET/CT as a response surrogate.

1407 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 115

Oncology SPECT: thyroid cancer

OP492

99mTc-MIBI imaging in presurgical characterization of thyroid follicular neoplasm: qualitative and semiquantitative analysis

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Aim. Discrepant results have been reported about the usefulness of ^{99m}Tc-sestaMIBI-thyroid scintiscan in identifying thyroid malignancies, particularly in mitochondrial-rich oncocytic lesions. The aim of this study was to investigate the usefulness of visual and semiquantitative analysis of ^{99m}Tc-MIBI scintiscan in an attempt to improve the diagnostic accuracy in follicular oncocytic and non-oncocytic neoplasms. **Materials and methods.** We prospectively enrolled 51 consecutive patients with ^{99m}Tc-pertechnetate "cold" thyroid nodule cytologically diagnosed as non-oncocytic (36/51) and oncocytic (15/51) follicular neoplasm. Static images of the neck were acquired at 10 minutes (early image) and 120 minutes (late image) after intravenous injection of 400 MBq of ^{99m}Tc-sestaMIBI. Images were visually assessed using a scoring system: pattern 0 -no increased nodular uptake in both early and delayed images; pattern 1 -increased nodular uptake in early image without retention in the delayed image; pattern 2 -increased nodular uptake in early images with retention in the delayed image; pattern 3 -no increased uptake of the nodule in the early image and increased uptake in the delayed image. For the semiquantitative analysis, regions of interest (ROI) were drawn in ^{99m}Tc-pertechnetate image in correspondence of the "cold" nodule and transferred on the early and delayed MIBI images. A ROI in the MIBI background was also drawn. Then, early ratio (ER) and delayed ratio (DR) were calculated and the retention index (RI) was then found using the formula: RI=(DR-ER)*100/ER. Histological diagnoses of the nodules were used as gold standard. **Results.** The table reports the Sensitivity, Specificity, Positive and Negative Predictive Value, and Accuracy levels in differentiating benign from malignant non-oncocytic tumours for both visual and semiquantitative analysis. No significant difference was observed in the ER values between malignant and benign non-oncocytic lesions, whereas significant differences were found for both DR and RI values (P<0.05 and P<0.001, respectively) in the same group.

Analysys	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Visual	73	81	73	81	78
Semiquantitative	100	90	88	100	94

Conclusions. In summary, our findings indicate that ^{99mTc}MIBI scintigraphy is an effective diagnostic method in patients with non-oncocytic thyroid lesions, improving the accuracy of the conventional cytology if properly selected by FNAB cytomorphology, and allowing a better selection of patients requiring surgery. Semiquantitative 99mTc-MIBI scan resulted to be more sensitive and specific than the visual one for this purpose.

OP493

Automated triple fusion of Na-I SPECT/CT and MDP SPECT image triples for thyroid carcinoma localizations

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Aim Thyroid carcinoma detection is mostly performed on Na-I SPECT/CT image pairs, although the perfect localization is often very difficult due to the poor details of Na-I images. In questionable cases an MDP bone SPECT is acquired to decide if the carcinoma is in the bones or outside of other tissue. Our goal was to automatically perform a triple fusion of the separately acquired MDP SPECT to its corresponding Na-I SPECT/CT image pairs based on our higher dimensional mutual information based registration method. Materials and methods. 34 Na-I SPECT/CT and MDP SPECT image triples were collected. Since the Na-I image had poor details, it was excluded from the registration step. In order to gain a third image, the CT was copied and post processed. A master MDP SPECT representing a normal stage of the bones was chosen. Both actual MDP SPECT and the copy of the CT were normalized by histogram matching to the master MDP SPECT. This way the bone segmentation of the CT could be gained and the anatomical information of the MDP SPECT could be increased. Registration of the MDP SPECT to the CT and the segmented bone CT was performed by a higher dimensional normalized mutual information similarity measurement. For comparison the widely used dual NMI - and four extended MI similarity measurements were performed to superimpose the image triples. After superimposing the MDP SPECT, it was fused with the Na-I SPECT and the CT image in a triple fusion window. Validation of the registration was done by a medical physician based on the triple fusion. The modification of the automated transformation parameters as well as the number of iterations to converge to the optimum was recorded for all similarity measurements. Results Our extended NMI similarity measurement has provided the best registration parameters to superimpose the image triples (approx. 1mm mean registration error) and it needed the least iterations to converge to the optimum. Previously proposed extended measurements generated high misalignments in axial directions that were associated with high voxel sizes in the CT images. Triple fusion of the images significantly increased the localization accuracy of the thyroid carcinoma. Conclusion We have presented a method to superimpose thyroid Na-I SPECT/MDP SPECT/CT images. Our future work will focus on the evaluation of the usefulness of our triple fusion visualization environment. Comparisons with the classic dual fusion environment will be performed.

OP494

Exacerbated Aggressiveness of Multifocal Papillary Thyroid Carcinioma in Association with Hashimoto's Thyroiditis after Possible Radiation Exposure: Assessment by Means of Nuclear Medicine

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Aim: Papillary thyroid carcinoma (PTC) is the most frequent endocrine cancer and it is the most common thyroid cancer (85-95%). Multiple potential risk factors for the incidence of the PTC include radiation exposure, iodine deficiency, and family history. The association between PTC and chronic lymphocytic thyroiditis (CLT) has been reported too. The aim of study was to examine this association leading to neoplastic aggressiveness shift at risk cohort of ethnic Germans from Nord Kasakhstan after possible radiation exposure. Methods: We prospectively studied 42 first-grade relatives (f30; m12; 59 +/-14 y.o.) of patiets with CLT/PTC (Gr.A) and 21 pts with PTC without CLT (Gr.B). 41 of 42 studied patients from Gr.A (99%) were residents of North-Eastern Kazakhstan near to NuclearTestingGround, prior to their repatriation to Germany. Initial investigation included clinical examination, thyroid sonography/99mTc-scitigraphy, thyroid hormone (fT4, fT3, TSH) and anti-TPO/anti-Tg antibodies levels estimation, FNAC. Every case of PTC was confirmed by patho-histological examination. Age, sex, tumour features (dimensions, angioinvasion, capsular infiltration, multifocality and lymphnode metastases, nuclear medicine examination data and therapy history, geographic anamnesis) were analysed. Results: Statistically significant difference in tumour size was founded in two Groups: the average diameter was found to be 1.721+/-0.5812 and 1.145+/-0.871 cm in Gr.A and in Gr.B, respectively (P=0.001). Capsular infiltration was present only in Gr.A in 3 cases. The angioinvasion was found in 8 cases of Gr.A and 1 cases in Gr.B (P=0.310). Multifocality was found in 19 patients in Gr.A and in 2 in Gr.B (P=0.0009). There were no statistical differences in sex (P=0.423) and age (P=0.330). All pts in Gr.A had CLT with high levels of thyroid Abs (TgAb/TPOAb). 17 of 33 (51.5%) autoantibody positive pts with US suspicious multifocal non-uniform thyroid goiter revealed scintigraphic cold lesion, in Gr.B 60% nodes were undetectable in scans. Conclusions Statistically proven high prevalence (100%) of CLT and multifocal PTC in Gr.A compared to Gr.B in our study might be related to the fact, that a majority of pts were previously residents of North-Eastern regions of Kazakhstan (probability of extensive radiation exposure). Indeed, there is a high incidence of CLT/PTC in the regions, adjacent to Semipalatinsk NuclearTestingGround. The external radiation, concomitant HT must be taken into account and assume more aggressive tumours. Our results justify a neccessity of screening for PTC in this population group. A more significant attention of the clinical examination, US guided FNAC and thyroid scan, Doppler will guarantee a precise diagnosis.

OP495

Is diagnostic whole body scan useful in the follow-up of differentiated thyroid cancer patients who have negative serum Tg and neck ultrasonography?

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Purpose: The aim of this study was to evaluate the diagnostic relevance of diagnostic whole body scan(DxWBS) for management of patients with differentiated thyroid cancer(DTC). Subjects and methods: The study subjects consisted of 93 patients (M/F 20/73, mean age; 47yr) who had a high-dose radioiodine therapy after total thyroidectomy for DTC. DxWBS, serum Tg and neck USG were all performed within 2 months. Serum Tg≥2ng/mL(off) or Tg≥1ng/mL(on) and abnormal focal uptake of DxWBS were considered positive. Results: DxWBS was positive in 25(26.9%), serum Tg in 71(76.3%), and neck US in 68(73.1%) patients. DxWBS did not detect lesions but neck USG & serum Tg was positive in 39(41.9%) patients, neck USG did not detect but DxWBS & serum Tg was positive in 10(10.8%) patients, serum Tg was negative but neck DxWBS & neck USG was positive in 2(2.2%) patients. 10 patients(10.8%) were positive for all of DxWBS, serum Tg and neck USG. DxWBS was only positive in 3 patients, while Tg and neck USG were negative. 2 patients had lung metastasis and 1 patient remnant thyroid tissue. In comparison, serum Tg or neck USG was positive in 90 patients(96.8%). Conclusion: The result of our study suggest serum thyroglobulin combined with neck ultrasonography could detect most recurrence or metastatic lesions in patients with DTC. DxWBS does not seem to be efficient method in the detection of recurrence or metastatic lesion in DTC patients.

OP496

Post-I-131 ablation SPECT-CT has an additional diagnostic value to post-ablation planar scintigraphy and cervical ultrasound

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Objective: To assess the additional value of SPECT-CT scanning over planar imaging and ultrasound only for the detection of cervical lymph node metastases around I-131 ablation. **Methods:** A planar whole-body imaging study with detailed images of the cervical region was acquired and a SPECT-low-dose-CT scan was recorded from the mandibula to below the sternoclavicular joints in 55 patients. **Results:** Overall, 27/55 (49%) patients were judged to be negative for the presence of cervical lymph node metastases, 22/55 (40%) positive and 6 patients (11%) indeterminate for the presence of lymph node metastases based on planar imaging. After SPECT-CT imaging these numbers were 35/55 (64%), 20/55 (36%) and 0/55, respectively. 4 patients who were negative on planar imaging were positive SPECT-CT, and positive 6 patients were negative in SPECT-CT. In all, SPECT-CT was of clinical benefit in 27/55 (49%) patients. In ultrasound 19 patients showed enlarged lymph nodes on ultrasound of the neck; in only one of these patients the enlarged lymph nodes were classified as likely to be malignant. Only 7 of these patients showed lymph node metastases on SPECT-CT, additionally 9 other patients that did not show enlarged lymph nodes on ultrasound were found to have cervical lymph node metastases by SPECT-CT. **Conclusion:** SPECT-CT allows a greater rate of detection of lymph node metastasis, more precise determination of lesion dignity as well as more precise localisation of lymph node metastases than planar imaging and / or ultrasound. It is of clinical benefit in half the patients undergoing ablation.

OP497

Anato-Functional Documentation of Patho-Physiological ^{131}I Uptake Patterns with SPECT/CT in Differentiated Thyroid Cancers

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Objectives: To document anato-functional patho-physiological ^{131}I uptake patterns with SPECT/CT in differentiated thyroid cancer (DTC). **Methods:** We reviewed 29 cases of DTC patients from the Canadian thyroid cancer database who underwent a planar whole-body scan (PWB) followed by a SPECT/CT study after administration of a diagnostic (n=5) or a therapeutic (n=24) ^{131}I dose. DTC patients were imaged on an integrated SPECT/low-dose CT scanner (Infinia™ Hawkeye™ -1/-4, GE Healthcare). SPECT/CT data were compared to PWB, and correlated to clinical data, Tg levels, high-resolution neck US, diagnostic CT, brain MRI, barium swallow oesophagus, dacryoscintigraphy, ^{18}FDG PET/CT, and pathological results. **Results:** Following the PWB, SPECT/CT allowed definition of various patho-physiological ^{131}I uptake patterns: **1)** *physiological patterns* in the neck corresponding to the lacrimal sac, naso-lacrimal duct, nasal fossa, oro-pharynx, parotid glands, sub-mandibular glands, thyroglossal tract, thyroid bed, scalp and hair contamination; **2)** *physiological patterns* in the thorax corresponding to the thymus, oesophagus, stomach, and breasts; **3)** *physiological patterns* in the abdomen corresponding to the transverse colon, ascending and descending colon; **4)** *physiological patterns* in the pelvis corresponding to the uterus, sigmoid colon and rectum, the bladder, and urinary contamination; **5)** *pathological patterns* corresponding to DTC metastases were precisely localized in the brain, lungs, liver, the skeleton, and lymph nodes; **6)** *pathological patterns* related to benign diseases including dental work, lacrimal duct obstruction, mastoiditis, an atypical mycobacterium lung tuberculosis, an ovarian teratoma with struma ovarii, a breast cystic mass, a salivary gland cyst, a gastro-oesophageal reflux, and a diaphragmatic hernia; **Conclusions:** In DTC patients, SPECT/low-dose CT allowed clarification of equivocal planar ^{131}I-WBS for better anato-functional definition of patho-physiological uptake patterns.

OP498

I-131 SPECT/CT in therapy and follow-up of thyroid cancer

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Aim: The introduction of SPECT/CT into clinical routine reveals new diagnostic aspects in detecting the exact morphologic analogue of increased tracer uptake in different scintigraphic findings. Considering patients under I-131 surveillance or primary detection of unkown metastases in I-131 ablation, the question arises to what extent SPECT/CT improves the interpretation of diagnostic scans. *Materials and Methods:* 28 SPECT/CT examinations were performed in 25 patients (13 men and 12 women, aged 18 - 83 years) suffering from malignant thyroid diseases (11 papillary cancers, 8 follicular cancers, 1 both papillary and follicular cancer, 1 mixed medullary and papillary cancer, 2 occult thyroid cancers (1 Graves' disease with previously unknown lung metastases, 1 multifocal autonomous thyroid disease (MFA) with a previously unknown focal bone metastasis). Two patients had ectopic thyroid parenchyma according to pathological findings in I-131 whole body scans. Anterior and posterior images as well as spot views of the neck were performed 72 hours after oral application of 0,4 - 6,0 GBq I-131; a dual-headed whole-body ECAM camera (Siemens, Germany) was used : high energy collimator, scan time 10 cm/min, 256x1024 matrix, zoom 1. SPECT/CT followed using a Symbia dual-headed whole-body gamma camera (Siemens, Germany): SPECT 128x128 matrix, zoom 1, rotation 180° and 36 steps/head, scan time mainly 40 sec/view. Subsequently a low dose CT in the same acquisition position was carried out. An iterative SPECT reconstruction was applied as well as a CT recontruction for bone and soft tissue. *Results:* Planar scintigraphy showed 50 tumour suspicious foci with increased I-131 uptake but SPECT even 57 foci whereas CT presented 55 foci with a corresponding morphological structure. In 17 patients (46 foci) tumour recurrence or metastases were detected in this way. In 6 patients (9 foci) metastases could be excluded. In 2 patients (2 foci) CT demonstrated no morphological analogy. In comparison to planar scintigraphy the additive use of SPECT-CT considerably increased the sensitivity and illustrated the corresponding morphological structures. In this context it should be kept in mind that image fusion of I-131 SPECT with CT or NMR (acquired before or after I-131 scan) is difficult due to the absence of special landmarks for precise fusion and due to obstacles during reproducible patient positioning. *Conclusion:* I-131 SPECT/CT in patients with thyroid cancer offers an improved tumour localisation involving a higher diagnostic sensitivity.

OP499

Effect of scan duration in the assessment of optimum reconstruction parameters of I-131 post-therapy Thyroid SPECT scans

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Aim: To find optimum reconstruction parameters for I-131 post therapy SPECT and assess the use of resolution recovery in the context of acquired counts. **Materials and methods:** Preliminary assessment was based on 15 parameters applied to phantom data, for objective and subjective analysis. Three parameters were discarded and remaining applied to two patient datasets for qualitative evaluation by two clinicians. Data analysis narrowed these parameters to six, two Filtered Backprojection (FBP) and four Astonish (Ast):

Name	Filter	Subsets	Cutoff	Order	Iterations
FBP1	Butterworth		0.4	4	N/A
FBP2	Butterworth		0.6	4	N/A
Ast1	No filter	8			2
Ast2	No filter	8			4
Ast4	Hanning	8	0.9	1	5
Ast5	Hanning	8	0.9	1	10

The above were applied to both 10 and 20 second projection scans of 14 patients. Each anonymised scan was graded by the named two clinicians from 1-5 according to quality, 5 being the highest. **Results: Fullscan duration**- On comparing both reconstruction methods using General Linear Model a p value of <0.0001 denoted a least square mean difference of 0.929 for Observer1 and -0.143 for Observer2, with a p value <0.0001. Mixed Analysis of Variance showed that Observer1 scores on average 1.214 more than Observer2 with a 95% confidence interval (CI) of 0.724-1.704; pvalue <0.0001. Astonish scores on average 0.393 more than FBP with a CI of 0.168-0.617 and the pvalue=0.0023. **Halfscan duration**- Observer1 seemed to prefer the Astonish methods to FBP1 as denoted by the statistically significant t-test values for both parameteric and nonparametric tests. **Full vs. halfscan duration** - on comparison of both, there was no difference in scoring with the exception of Ast2 (favoured) which had statistically significant results for Observer1, 0.040 (paired t-test), 0.046 (Wilcoxon's). On analysis of cumulative scoring between Ast and FBP for both scan durations, the difference in mean value was small, 0.10 $_{(2d.p.)}$ in Observer1 and 0.16 in Observer2 $_{(2d.p.)}$. **Conclusion:** Results from Observer1 showed the Ast methods did better than FBP1 in particular. For Observer2, defining an optimum reconstruction pattern was more difficult, highlighting subjectivity in grading image quality. The results seem to imply that the difference between 10 and 20 second projections are not as large as would be expected. Further research could help establish this observation and may have implications with regards to patient comfort and image quality in post-therapy I-131 SPECT studies.

1408 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 116

Neurology/psychiatry: receptor/transporter imaging

OP500

In Vivo Dopamine Release in the Extrastriatal Reward Circuit during a Monetary Reward Task : a [^{18}F]fallypride PET study

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Aim: Reward capacity, or the ability to respond to positive reinforcers, is an important feature of human behaviour and protects an individual against different psychiatric illnesses. Mesocorticolimbic dopamine (DA) neurotransmission, particularly in the extrastriatal part of the reward circuit, plays a role in the ability to experience pleasure (liking the reward), but also in behaviours like motivation and drive (wanting the reward and learning). The aim of this study was to measure presynaptic DA release in particular the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), using the DA D_2/D_3 receptor ligand [^{18}F]fallypride in healthy subjects while performing a monetary reward task. **Methods:** 10 female volunteers (33.4 ± 8.1 years) underwent a single dynamic PET scanning session [1] with 178±16 MBq [^{18}F]fallypride. A probabilistic monetary reward task [2] was initiated after 100 minutes. Voxel-wise analysis of PET data was carried out on each subject using the linearized simplified reference region model (LSRRM), which accounts for *in vivo* time-dependent changes in [^{18}F]fallypride displacement. This kinetic model was used to generate individual parametric maps of all parameters. Voxel-wise *t*-statistic maps of the gamma parameter [1], reflecting specific D_2/D_3 binding changes, were computed to localize areas with increased ligand displacement after the task initiation hence DA release. These *t*-maps were correlated with behavioural measures for reward responsiveness and feedback-related behaviour to probabilistic reward (learning and reward anticipation) (SPM2; p_{height}<0.001). **Results:** Voxel-based analysis revealed a significant inverse correlation between reward capacity and DA release in the ventral medial PFC (Brodmann Area (BA) 10), orbitofrontal PFC (BA 11) and ACC (BA 32). Furthermore, the ACC and thalamic DA displacement shows a significant positive correlation with feedback-related negativity to probabilistic rewards. **Conclusion:** These findings support the hypothesis that several extrastriatal brain areas are involved in reward capacity. Individuals with lower reward responsiveness show a higher DA release in prefrontal areas and the ACC during a reward challenge. This is consistent with previous literature and implicates greater attendance to the reward context of potential rewarding stimuli in less reward sensitive individuals. Furthermore, integration of reinforcement history over time inversely correlates with thalamic and ACC DA release, but not with DA release

in the PFC, supporting the hypothesis that the ACC and thalamus play a role in learning and reward anticipation, in contrast to the PFC which probably mediates consumption of reward. **References:** [1] Christian BT. *Neuroimage*: 31(1): 139-152, 2006. [2] Pizzagalli DA. *Biol Psychiatry:* 57(4): 319-27, 2005.

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[18F]-Labelled Benzamides as Probes for MicroPET Studies of Amphetamine-evoked Dopamine Release in Mouse Brain

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Aim: The competitive binding of benzamide radioligands at dopamine D2-receptors has been employed to great effect for molecular imaging studies of dopamine release in living human brain. However, PET ligands labelled with C-11 are only available at sites with cyclotron-radiochemistry facilities, whereas SPECT suffers from limited spatial resolution. Therefore, we tested the fitness of the high affinity ligand [18F]fallypride (FP) and its lower affinity congener [18F]desmethoxyfallypride (DMFP) for revealing endogenous competition in mouse brain. The small size of mouse striatum relative to the resolution of microPET results in substantial vulnerability to bias. Therefore, accuracy of the microPET methods was assessed in comparison with "gold-standard" results obtained by brain dissection. Materials and Methods: Groups of awake mice were pretreated with saline, amphetamine (10 mg/kg) or reserpine (5 mg/kg), followed by i.v. tracer injections. Mice were killed at 2.5 to 90 min (DMFP) or 2.5 to 210 min (FP). Brains were dissected and radioactivity measured by gamma counting. Constructed time-radioactivity curves were used to calculate binding potentials (BPND) using cerebellum as reference region. Other groups of mice were anesthetized for FP or DMFP microPET recordings, in which four mice were scanned simultaneously. Maps of BPND were calculated by conventional methods and transformed into a standard coordinate system for mouse brain. Results: The DMFP BPND in striatum was 2.2 according to the gold standard method, and 2.1 according to microPET. In contrast, the FP BPND in striatum was 24 according to the gold standard method and only 9 by microPET; the bias seemed to arise from progressive spill-in of bone radioactivity to the cerebellum. DMFP proved to be highly vulnerable to amphetamine challenge, declining by as much as 60% in the microPET studies, and increasing by 30% after reserpine treatment. FP binding in striatum was likewise vulnerable to amphetamine treatment (-30%). Reserpine treatment did not increase FP binding in striatum, but nearly doubled the binding in the olfactory bulbs, as revealed by the gold standard dissection method. Conclusions: FP microPET results were biased due to spill-over from striatum and spill-in of bone signal to cerebellum. In contrast, DMFP microPET results were seemingly unbiased. Striatal binding of both ligands was highly vulnerable to altered competition from endogenous dopamine; we detected an unexpectedly high basal occupancy by dopamine at receptors in the olfactory bulb. The [18F]-labelled benzamides should make the amphetamine challenge paradigm accessible to PET centres lacking a cyclotron unit.

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[11C]NNC112: A Selective PET ligand for in-vivo Imaging of Dopamine D_1 Receptors? A Human Study with Ketanserin Challenge

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Aim: The 100-fold reported in vitro selectivity of the PET ligand [11C]NNC112 for the D1 receptor (K_D=0.18) over the 5-HT2A receptor (K_D=18) (1) indicates that the [11C]NNC112 signal in the frontal cortex should reflect D1 receptor concentration only. Recent studies in primates and humans, using MDL100907 and risperidone (2,3), reveal that 5-HT2A binding contributes 20-30% of [11C]NNC112 signal in this region. We examined the suitability of intravenously administered ketanserin to pre-block cortical 5-HT2A binding of [11C]NNC112, allowing an accurate estimation of D1 receptor status in humans in vivo. **Methods:** Seven healthy male volunteers (25±2 yrs.) underwent two [11C]NNC112 PET scans, at baseline and 15 min. after ketanserin 0.15mg/kg i.v. Time-activity curves for the frontal cortex and the striatum were extracted after applying a template of regions of interest (ROIs) to the MRI-coregistered PET images. Total distribution volume (V_T) for each ROI was estimated by fitting the data to a two tissue compartmental model with metabolite corrected arterial input for prefrontal cortex, striatum, and cerebellum (CER). Binding potential was calculated as BP_{ND}=(V_T,ROI/V_T,CER)-1. The percentage of BP_{ND} change between the post-ketanserin and baseline scans was then calculated. **Results:** The mean BP_{ND} in the prefrontal cortex decreased from 0.43±0.06 at baseline, to 0.28±0.07 post-ketanserin (mean change = -35.1±11.1%, 95% CI: -46.73%, -23.39%). There was no significant effect of ketanserin in the striatum (baseline BP_{ND} 2.27±0.25, post-ketanserin BP_{ND} 2.08±0.22, mean change= -7.5%, 95% CI: -20.84%, 5.87%). **Conclusion:** These data are consistent with previous in-vivo data (2,3) indicating around 30% contribution of the 5-HT2A to the cortical [11C]NNC BP_{ND}, and claiming for caution in the interpretation of previously published findings on cortical D1 receptor status in humans using [11C]NNC112. Given the negligible amount of 5HT2A compared to D1 receptors in striatum, the lack of significant effect of ketanserin on striatal [11C]NNC BP_{ND} supports the utility of this paradigm in defining D1 receptor binding. **References:** Andersen et al, *Eur J Pharmacol* 1992; 219:45-52; Eckelund et al, *Mol Imaging Biol* 2007; 9:117-125; Slifstein et al, *J Cereb Blood Flow Metab* 2007; 27:1733-1741

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The phase III clinical trial to evaluate the efficacy and safety of F-18 FP-CIT PET/CT in Parkinson's disease and Essential tremor patients

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F-18 FP-CIT is one of the promising radiopharmaceuticals for dopamine transporter imaging. To evaluate the efficacy and safety of F-18 FP-CIT in the diagnosis of Parkinson's disease, we performed F-18 FP-CIT PET/CT in 39 patients (59±9 yrs, M/F=19/20) with Parkinsom's disease (PD), 39 controls (63±8 yrs, M/F=20/19) consisted of 29 essential tremor (ET) and 10 healthy controls (HC). Both blinded visual interpretation and region of interest (ROI) analysis using striatal specific to occipital uptake ratio (SOR) were performed on static PET/CT images obtained at 90 min after the injection of 185 MBq of F-18 FP-CIT. Acute adverse reaction of F-18 FP-CIT injection was also evaluated. All of 39 PD and one of ET showed asymmetrical reduction of striatal uptake on visual analysis. Therefore, visual interpretation demonstrated a sensitivity of 100% and specificity of 97% comparing PD versus controls (ET+HV). Striatal SORs of PD (1.0-2.0) were significantly lower than those of controls (2.83-3.03). SORs of ipsilateral striatum were significantly correlated with H&Y stage (r=0.45, p<0.01). There was one minor adverse reaction (chilling sensation) related to F-18 FP-CIT injection. F-18 FP-CIT PET/CT imaging effectively and safely distinguish between subjects with PD and without PD (ET+HC).

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Amyotrophic lateral sclerosis: a [^{123}I]FP-CIT SPECT study

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Aim. The involvement of dopaminergic system in amyotrophic lateral sclerosis (ALS) is controversial. According to some authors, there is an involvement of the nigro-striatal dopamine transporter (DAT), such as to assume a similar pathogenesis with Parkinson's disease (PD). Aim of this study is detecting DAT levels of the striatum by ^{123}I-FP-CIT single photon emission tomography (SPECT) imaging in ALS pts. Materials and methods. Five patients (pts), age range 58.2 ± 5.3 years, suffering from 4.4 ± 1.3 months from ALS, defined, clinically or with laboratory support probable (in agreement with electrophysiological data), according to EI Escorial criteria (World Federation of Neurology) were enrolled in this study. We excluded: pts with other neuropsychiatric disorders, particularly excluding forms of ASL with fronto-temporal dementia associated; pts with imaging findings indicative of infarction in basal ganglia region and pts with different possible causes of neuropsychiatric symptoms (history of alcohol or drug abuse, previous diagnosis of schizophrenia) were excluded. SPECT was performed after i.v. injection of 111 MBq of [^{123}I]FP-CIT, using a double head gamma camera. Statistical parametric mapping 5 (SPM5) was then used to localize striatal binding in ALS and to compute the absolute change relative to 5 age-matched healty control (H) and 5 age-matched PD pts. Results. In ALS pts the overall uptake in basal ganglia was significantly greater than H group ($P < 0.01$) and PD groups ($P < 0.0001$). SPM5 comparison of ^{123}I-FP-CIT uptake in the ALS and control groups revealed the presence of a significant increase in both putamen and caudate ($P < 0.01$; two-tailed Student's *t*-test). Similar findings were obtained considering separately right and left caudate and putamen. Conclusions. Our results confirm data of some studies in which functional MRI has revealed the hyperfunction of cortical and subcortical extramotor systems (basal ganglia and cerebellum) in patients with ALS, probable expression of a compensatory mechanism due to phenomena of neuronal plasticity and functional reorganization in motors and sensors circuits controlling the movement. A confirmation of this hyperfunction, a preliminary data on an assessment of the ways of pain in patients with ALS, have suggested the hypothesis of central pain with a likely "compensatory hyperactivity of cortical sensory areas.

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[^{123}I]ADAM binds selectively to serotonin transporters in healthy young adults: a double-blind, placebo-controlled study

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Introduction: Disturbances in the central serotonergic system are thought to play a major role in psychiatric disorders, such as anxiety or major depression. Serotonin transporters (SERTs) are located in the membrane of serotonergic neurons and play an important role in the regulation of the serotonin content in the synaptic cleft. Additionally, SERTs are believed to be the primary target for antidepressants, such as selective serotonin reuptake inhibitors. Recently, ^{123}I-2-([2-({dimethoxylamino}methyl)phenyl]thio)-5-iodophenylamine ([^{123}I]ADAM) has been developed as a selective SPECT tracer for the SERT. Although the results of in-vitro as well as animal studies have shown that this tracer binds selectively to SERTs, such evidence is lacking for humans. *Aim:* The aim of this study was therefore to evaluate whether [^{123}I]ADAM binds selectively in humans. *Materials and Methods:* Using a double-blind study design, 12 healthy young male adults (age 18-30 years) were pre-treated orally with a selective serotonin transporter blocker (20 mg of the selective serotonin reuptake inhibitor paroxetine), a dopamine/norepinephrine transporter blocker (20 mg of the dopamine/norepinephrine reuptake inhibitor methylphenidate) or placebo. Then each subject was injected intravenously with a bolus of 140-180 MBq ADAM (produced by Schering, Finland; radiochemical purity > 95%). SPECT images were acquired 5 hrs p.i. using a brain-dedicated SPECT system (Neurofocus; a 12-detector single slice scanner). All images were corrected for attenuation and reconstructed in 3D mode. For analysis purposes, the SPECT images were co-registrated with individual MRI scans (obtained on a 3T machine). ROIs were drawn manually on the co-registrated MRI scans in SERT-rich brain areas (midbrain), and ADAM binding in the cerebellar cortex was used to assess non-specific binding. Specific to non-specific binding ratios were calculated and used as the outcome measure. *Results:* Binding ratios were statistically significantly lower in the paroxetine pre-treated group as compared to the placebo as well as to the methylphenidate pre-treated group (non-parametric tests). Binding ratios in the methylphenidate pre-treated group were not significantly different from such ratios obtained in the placebo pre-treated group. *Conclusion:* The results of our preliminary double-blind, placebo-controlled study may indicate that [^{123}I]ADAM binds selectively in healthy young humans.

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A Comparative PET Study of the Two Norepinephrine Transporter Radioligands (*S,S*)-[^{18}F]FMeNER-D$_2$ and (*S,S*)-[^{11}C]MeNER Using the Reference Tissue Model in the Rhesus Monkey

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The norepinephrine transporter (NET) is considered to play an important role in various aspects of neuropsychiatric diseases such as depression and attention-deficient hyperactivity disorder. After a long struggle in PET radioligand development for NET, (*S,S*)-[^{11}C]MeNER was successfully prepared by several groups. (*S,S*)-[^{18}F]FMeNER-D$_2$ has been developed after the fluorine-18 was introduced within the 11C methyl group together with the introduction of deuterium. Although these two NET radioligands have been reported to have different characteristics, there has not been a direct comparative study *in vivo*. In this study, we compared the brain distribution and outcome measures from reference tissue models in the same rhesus monkeys of these two NET radioligands. **Methods:** Two rhesus monkeys underwent three PET measurements each, one with (*S,S*)-[^{18}F]FMeNER-D$_2$ (156MBq) and two with different amounts of radioactivity of (*S,S*)-[^{11}C]MeNER (175MBq and 360MBq). PET measurements were conducted using the High Resolution Research Tomograph (HRRT). The regions of interest (the whole brain, the thalamus, brainstem, the anterior cingulate cortex, the temporal cortex, and the caudate) were delineated on the coregistered MRI/PET images. The regional brain uptakes and BP$_{ND}$ values from reference tissue models (simplified reference tissue model and multilinear reference tissue model) with different time lengths were compared. **Results:** The peak whole brain uptake was higher for (*S,S*)-[^{18}F]FMeNER-D$_2$ (5.3 %) than for (*S,S*)-[^{11}C]MeNER (3.4%) while the washout after the peak were slower for (*S,S*)-[^{11}C] MeNER (approximately 64% of the peak uptake at 120 min) than for (*S,S*)-[^{18}F]FMeNER-D$_2$ (approximately 50% of the peak uptake at 120 min). The regional uptakes in the thalamus and the brainstem with [^{11}C]MeNER did not always reach the peak during 123-min measurements while those with (*S,S*)-[^{18}F]FMeNER-D$_2$ did reach the peak before 30 min. The specific binding (regional uptake-the caudate) for (*S,S*)-[^{11}C]MeNER did not reach the peak during 123 min measurements whereas (*S,S*)-[^{18}F]FMeNER-D$_2$ did reach the peak before 80 min except for the temporal cortex. The ratios of the region to the caudate increased in (*S,S*)-[^{11}C]MeNER during 123 min while those in (*S,S*)-[^{18}F]FMeNER-D$_2$ reached the plateau. In both SRTM and MRTM analysis, the regional BP$_{ND}$ of (*S,S*)-[^{18}F]FMeNER-D$_2$ were stable after 150 min while those of (*S,S*)-[^{11}C]MeNER were not stable during 123 min measurement. The outcome measures of (*S,S*)-[^{11}C]MeNER were not obviously improved with higher radioactivity. **Conclusions**: (*S,S*)-[^{18}F]FMeNER-D$_2$ was demonstrated to be superior for the quantitative analysis with reference tissue models in the rhesus monkey. This study should be helpful to select the appropriate radioligand for human NET studies.

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Whole-Body Biodistribution and Estimation of Radiation-Absorbed Doses of the Glycine Transporter 1 Radioligand ^{11}C-GSK931145 in Humans.

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Aim: ^{11}C-GSK931145 has been reported to be a new suitable radioligand to image Glycine transporter 1 (GlyT1) in brain [1]. The aim of this study was to characterize the biodistribuition and estimate the human radiation doses of ^{11}C-GSK931145, based on dynamic whole-body PET in healthy volunteers. **Materials and methods**: Eight subjects (4M/4F) (37.25±16.28 yrs, range: 19-62 yrs) underwent whole-body PET/CT scans after the bolus injection of 11C-GSK931145 (304±113 MBq). Emission scans included 9 passes acquired up to 2h. Regions of interest were drawn on 3D PET images on subsamples of the organs, when needed the CT image was used to identify organs. The regions of interest were drawn on the kidneys, liver, urinary bladder, lungs, heart, gallbladder, brain, stomach, large intestine (ascending colon), small intestine (duodenum), cortical bone (skull and femur) and red marrow (femur). Residence times for each organ were calculated from the area under the time-activity curves divided by injected activity. Area under the time-activity curve for each region was determined by trapezoidal integration plus physical decay for the tail of the curve after the last acquired time point. Radiation dose estimates were calculated from organ residence times using the OLINDA software and the 70-kg male phantom [2]. **Results**: Early scans presented high activity in the liver, and moderate activity in the kidneys and heart content. Progressive increase in the activity of the stomach and small intestine was also observed. The principal route of clearance was intestinal and no urinary excretion was observed. The limiting organ with the highest radiation-absorbed dose was the liver (9.96±0.02 µSv/MBq) and the mean effective dose was 3.79±0.34 µSv/MBq **Conclusion:** The liver is the critical organ for ^{11}C-GSK931145 in humans. Derivation of total and organ radiation burden of ^{11}C-GSK931145 will enable predictions of radiation exposure to subjects engaged in multiple PET examinations with this ligands, for studies such as occupancy studies supporting the development of GlyT inhibitors candidate drugs. 1. Murthy NV, Passchier J, Gunn RN, et al. [^{11}C]GSK931145: A new pet ligand for glycine transporter 1. NeuroImage 2008; 41(2): T21 2. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: The second-generation personal computer software for internal dose assessment in nuclear medicine. Journal of Nuclear Medicine 2005;46:1023-7.

1409 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 120/121

Featured: dosimetry in therapy

OP508

Invited Talk

G. Flux (UK)

OP509

3D dosimetry with standard and voxel MIRD methods on Intraoperative Avidinination for Radionuclide Therapy (IART®) to evaluate absorbed dose and radiobiological effects

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Aim: The new procedure named IART® has been applied in early breast cancer patients immediately after surgery to irradiate the residual mammary gland. This approach consists of tumour bed targeting using the avidin-biotin system. The therapeutical rationale was to deliver - immediately after surgery, by the injection of ^{90}Y-biotin- a Biologically Effective Dose(BED) of 21 Gy as a boost anticipating external beam radiotherapy(EBRT). The aim of this study was to compare dosimetric evaluations derived from standard (MIRD 16) vs. voxel (MIRD 17) methods. The BED and Equivalent Uniform biological effective Dose (EUD) were evaluated in order to assess the possible effect, including dose distribution heterogeneity. **Methods**: Fifteen patients were evaluated. The tumour bed was avidinated (100 mg) during surgery, after tumour removal, and targeted by systemic injection of 3.7 GBq of ^{90}Y-biotin (+^{111}In-biotin,185 MBq, for imaging) one day later. The therapeutical target was considered to be the region in which the uptake was >50% of the maximum in the breast. Average self-dose in the target was calculated with standard MIRD method, assuming spherical shape and deriving patient-specific biokinetic data from sequential images (planar+SPECT). For voxel dose calculation, a dedicated software was developed (Matlab® support, Mathworks). Input data were: SPECT images (activity distribution), biokinetic data (planar images) and S-voxel factors for ^{90}Y and 4.4 mm voxels, specifically calculated for by Monte Carlo simulation (PENELOPE code). BED distribution was also evaluated with radiobiological parameters derived from literature (α/β=10, μ_{repair}=0.5 h^{-1}). Dose-volume and BED-volume histograms were generated, and the corresponding average BED (BED$_{voxel}$) obtained. EUD was estimated considering the surviving fraction of the target (α=0.3 Gy^{-1}). **Results:** Absorbed doses (average±SD) from standard vs. voxel dosimetry were (19.5±4.0) vs (22.2±3.0) Gy (difference: 12±3%). As regards the mean BED values: (21.2±4.3) vs. (24.4±3.2) Gy. The BED-volume histograms showed that 68±25% of voxels received a BED>21 Gy. All voxels received a BED>14 Gy. The EUD/BED$_{voxel}$ ratio was 0.9, indicative of slight heterogeneous dose distribution. **Conclusions**: Radiobiological evaluations indicated that IART® allows delivering tumoural bed an anticipated boost comparable to a EBRT boost. The absorbed doses evaluated with standard method were systematically lower than those calculated with voxel method (differences up to 16%). The EUD/BED$_{voxel}$ ratio in the target indicated biological efficacy comparable or close to that of uniform dose distribution, thus the hypothesis of uniform activity distribution is not misleading. The voxel method is recommended for improving accuracy on activity distribution in the breast tissue.

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Tumor Dosimetry In The Treatment Of Liver Metastases With SIRTEX Does Not Correlate With Therapeutic Response

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Use of 90Y-microspheres for Selective Internal Radiotherapy (SIR) of primary or metastatic liver cancer is increasing. Treatment with SIR-microspheres is based on the notion that arterial blood supply in tumor metastases is higher than portal hepatic flow, therefore microspheres delivered by hepatic artery will be deposited at higher concentration in tumor areas, decaying by beta emission. The heterogeneity of liver activity distribution observed in the pre-treatment breakthrough scan with 99mTc-MAA appear to confirm this hypothesis. Although tumor doses estimated with the MIRD approach from pre-treatment static images are considerably high (~100Gy), we observed a great variability in treatment responses. The correlation between areas of increased microsphere concentration in SPECT images and tumor active areas visible on PET images, was investigated. In detail, we evaluated the relationship between response, based on average SUV variations of lesions between pre- and post- therapy PET studies, and TLR (tumor to liver ratio) of the same lesions in SPECT images. Eight patients with 31 liver metastases from different primary tumors (breast, melanoma, colo-rectal cancer) were analyzed. Each patient underwent static (256x256 pixels, 140 keV±15% peak) and SPECT (128x128, 64 views) scans, after 99mTc-MAA injection (185 MBq) 1-3 weeks prior to treatment. 18F-FDG wholebody PET was performed before and 6-8 weeks after 90Y-SIRspheres therapy. Injected activity was defined using the Body Surface Area Method and MIRD equations were utilized to measure lung and normal (un-involved) liver absorbed doses, which should be below 20 Gy and 80 Gy respectively. Applying the MIRD equations we estimated the mean dose delivered to normal liver was: 30±7 Gy (20±6 Gy/GBq) while for lungs: 3.6±3Gy (2.1±1.7Gy/GBq). The wide range in lung is caused by highly variable shunting fractions among patients. On the basis of our experience no patients exceeded dose limits in organs at risk. PET images before and after treatment were registered and compared to define SUV variations for all lesions. The same areas were selected on SPECT images to determine TLR. Regions showing uptake in SPECT colocalized with uptake areas observed in pre-treatment PET. Lesion absorbed doses based on the results obtained in pre-treatment simulation do not correlate with the degree of response, suggesting that treatment efficacy is highly dependent on individual biological features of the tumor deposits.

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DNA repair focus formation in blood cells after thyroid cancer therapy with I-131

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Objectives: The aim of the study was to investigate the DNA damage response in blood lymphocytes as measured by the induction, persistence and the decay behaviour of γ-H2AX and 53BP1 DNA damage-induced foci in patients with differentiated thyroid carcinoma (DTC) treated with I-131. γ-H2AX forms foci surrounding radiation-induced double strand breaks (DSBs) while 53BP1 binds to and signals damaged chromatin (histone H3-K79) at the DSB site and is thereafter retained by γ-H2AX. Nuclear foci containing the two markers thus represent DSBs. Methods: We investigated 25 patients (7m, 18f, age 42±13) diagnosed with DTC during their first treatment with I-131. Sequential peripheral blood samples and data on the external dose rate were obtained between 2h and 144h after the administration of 3.5±0.6 GBq I-131. The physical dosimetry procedures were performed according to the EANM SOPs for pre-therapeutic dosimetry in DTC therapy (1). The average frequencies of the radiation induced γ-H2AX and 53BP1 foci/nucleus were derived from mononuclear peripheral blood lymphocyte samples taken prior to therapy and concurrently to dosimetric blood sampling. White blood cells were recovered by CPT (BD Biosciences) column centrifugation and immunostained as described in (2). **Results**: The mean absorbed dose to the blood was 0.39±0.40 Gy (Min: 0.17 Gy, Max: 2.2 Gy) which is in the range of previous investigations (1). Dose rate is highest in the first hours after the administration. After 24h the daily mean dose increment was less than 0.05 Gy. The mean number of radiation-induced excess foci per nucleus (γ-H2AX and 53BP1) reached, after 2h, a maximum of 0.294±0.188 (γ-H2AX, 20 patients; baseline value: 0.004±0.003) and 0.267±0.189 (53BP1, 18 patients; baseline value: 0.008±0.007). Slightly but significantly elevated numbers of excess γ-H2AX and 53BP1 foci per cell were still present 120-144h after therapy. Both tests, γ-H2AX and the DNA damage transducer protein 53BP1, showed a time-dependent significant (2h vs. later time points) decrease of induced foci with little change between 48h and 96h after therapy. A direct correlation between absorbed dose (rate) and the number of excess foci, however, could not be established, which suggests a large inter-individual variability. **Conclusions**: We consider both DNA damage-induced focus detection methods to be well suited for the investigation of exposure from incorporated radionuclides, even when the absorbed dose to the blood is less than 20 mGy. **References**: 1. Lassmann M et al. Eur J Nucl Med Mol Imaging. 2008 35:1405 2. Scherthan et al. Rad Res 2007; 167:615-23

OP512

Iodine-124 and PET-CT imaging for the evaluation of patients with thyroid carcinoma submitted to re-differentiation therapy

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Objectives: 13-cis retinoic acid was demonstrated in past studies to be able to re-differentiate thyroid carcinoma (TC) that had lost their ability to take up iodine. However, these observations were obtained after the systematic administration of Iodine-131 therapeutic activities (TA) in all patients. Our aim was to evaluate PET-CT imagings with Iodine-124 as a way to define the responders to such re-differentiation therapy (RDT). Material and methods: 2 men and 2 women with metastatic TC who showed on previous 131-I treatments very faint (even no) or decreasing iodine uptake (IUpt) in their lesions have been up to now enrolled in this phase II clinical trial. Using a dedicated full-ring PET/CT scanner (GE medical systems, Discovery LS), PET-CT imagings were obtained under Thyrogen stimulation 24, 48 and 120 hours after the IV injection of 1 mCi of Iodine-124, before and after 8 to 10 weeks of daily intake of 1 mg/kg of 13-cis retinoic acid. Standard clinical software available on the Advance scanner has been used. 3D raw data were rearranged in a 2D-raw data sinogram by Fourier rebinning. All scans were normalized and corrected for randoms, scatter, attenuation, and decay. The images (matrix 128x128) were reconstructed using attenuation and normalization weighted OSEM algorithm followed by post-smoothing of the reconstructed image using a 8-mm FWHM Gaussian filter. Reconstructions without attenuation correction were done as well. Results: One first (male) patient with no uptake in his lesions showed no further uptake after RDT (he was not treated and died 4 months later). The second (female) patient had very faint uptake in her lesions before treatment and the mean IUpt was increased by a factor 3 after treatment. The third (female) patient with no IUpt showed no change after 2 months of RDT but well in a single pulmonary metastases after 5 months. The fourth (male) patient also showed a three-fold increase of IUpt in some lesions. In these patients with multiple lesions, change in IUpt appeared to be heterogeneous. The last 3 patients received thereafter TA (7400 MBq) of 131-Iodine (the last patient the 13/03/2009). The second patient showed a radiolysis due to 131-I treatment and a transient biological response lasting two months before re-evolution. The third patient is stable 4 months after treatment. Conclusion: PET-CT imaging with iodine-124 can show subtle changes IUpt after RDT and be used to select the patients to be treated with iodine-131.

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SPECT-CT imaging quantification and S-voxel method to study the dose distribution in Indium-111 and Yttrium-90 phantoms: a 3-D dosimetric model for targeted isotope-based therapy.

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Aim: The goal of this work was to study the S-Voxel method on 90Y Bremsstrahlung and 111In imaging to assess a dosimetric model suitable for therapeutic applications. **Materials & Methods:** An anthropomorphic thorso phantom, with radioactive inserts of different dimensions, was used to obtain the activity quantification by SPECT-CT imaging. The acquisitions were achieved by a hybrid system and parameters set as follows: energy windows between 36 and 204 keV for 90Y, at 247 (±15%) and 172 keV (±15%) for 111In (with three scatter windows); medium energy collimators; acquisition matrix 128x128; 64 projections (40s/step). A concomitant low-dose CT was obtained for attenuation correction and the OSEM 3D-Fast algorithm was used for the reconstruction of images. An algorithm for MATLAB® software was developed to convert a 3D-voxel cumulated activity map into the correspondent dose distribution while considering the 90Y-S values implemented. The dose volume histograms (DVHs) calculated by the above described method were then compared with the ones obtained by calculation of the local energy absorption. **Results:** A large variability of calibration factors (CFs) for 90Y was observed for source volumes ranging from 8 to 150 cc, due to the partial volume effect. A minor variability of CFs was reported by employing 111In sources. The full width at half maximum (FWHM), in air by a static acquisition and in a plexiglas phantom by tomographic acquisition resulted 19 mm and 30 mm for the 90Y and 14 mm and 19 mm for 111In. The thresholds for source identification (in absence of background activity) were ranging from 35 to 55% for 90Y and from 20 to 35% for 111In. By introducing the CFs, the 90Y- and 111In-related overall variation for clinical application was within 20%. The DVHs obtained by S-Voxel method were consistent with the DVHs resulted from the local absorption of energy. Moreover, for 90Y we tested the coherence between the absorbed dose calculated in the phantoms by conventional MIRD method and the mean dose values obtained by the S-Voxel method (difference< 10%).**Conclusions:** The results of the studies showed a good accuracy of 3-D quantification for 90Y and 111In and a coherence between the S-Voxel and MIRD methods. Anyhow, the S-Voxel method, represents, in our opinion, a more accurate dosimetric procedure (in terms of equivalent uniform dose EUD) to take into account for a tailored radiotargeted therapy.

OP514

Monte Carlo dosimetric and radiobiological evaluations for ^{131}I-, ^{90}Y- and ^{177}Lu- locoregional treatments of high grade gliomas

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Aim: After surgery and external-beam-radiotherapy, progression of high grade gliomas is reported mostly in the 2cm thick Brain Adjacent Tissue (BAT_{2cm}) surrounding the original site. Injection of radio-pharmaceuticals in the surgical cavity releases high doses to BAT_{2cm}. Good clinical outcomes (tumour response, not frequent radionecrosis causing neurotoxicity) were observed with ^{131}I-MoAbs delivering 44Gy average dose to BAT_{2cm}. In this study, the injected-activities (IA) of ^{131}I, ^{90}Y and ^{177}Lu able to give this average dose were calculated for cavities of different size, with the aim of evaluating biological efficacy differences of isotopes in BAT_{2cm}. To this purpose Tumour Control Probability (TCP), tumour Biological Effective Dose (BED) and Equivalent Uniform BED (EUD) were compared. **Materials & Methods:** With PENELOPE Monte Carlo code, 5 spheres (radius R=6,8,15,21,36mm) uniformly filled with ^{90}Y, ^{177}Lu and ^{131}I were simulated. Dose distribution was tallied inside spheres and up to 3cm outside. IA required to deliver 44 Gy to BAT_{2cm} were calculated considering 0% and 30% washout (IA leaving the cavity). TCP was calculated at different distances from the sphere edge; BED and EUD were evaluated in BAT_{2cm} and its subshells (0-0.2cm, 0.2-0.5cm, 0.5-1cm, 1-2cm). Radiobiological parameters were derived from literature: α/β=7Gy, α=0.24Gy^{-1}, μ_{repair}=0.5h^{-1}, ρ=clonogenic cell density=10^7cells/cm^3. **Results:** Representative results are reported for R=21mm sphere. IA are: 2.2(3.1), 2.7(3.8), 24(34) GBq for ^{90}Y, ^{131}I, ^{177}Lu with 0%(30%) wash-out. With equal average dose (44Gy), dose profiles differ remarkably. 100% TCP is guaranteed up to 1mm from the edge with ^{177}Lu, while ^{90}Y and ^{131}I give 100% control up to 4-5mm. At the outer BAT_{2cm} limit, a dose of 19.5Gy, 0.05Gy, 8.1Gy is absorbed with ^{131}I, ^{90}Y and ^{177}Lu, respectively. **Conclusion** ^{177}Lu delivers the highest BED within the 0-2mm sub-shell, ^{90}Y in the 2-5mm sub-shell, and ^{131}I beyond 0.5mm. ^{90}Y gives more homogeneous irradiation in the 0-2mm shell, ^{131}I in all the other sub-regions. As regards normal tissue irradiation inside BAT_{2cm}, ^{177}Lu and ^{90}Y give higher doses than ^{131}I in the 0.2cm and 0.5cm shells respectively, with possible drawback of increasing necrosis incidence with respect to ^{131}I. On the contrary, ^{131}I delivers higher doses outside BAT_{2cm}. These evaluations offer quantitative information guiding towards the most convenient balance in patient-specific treatment planning.

		0-0.2cm	0.2-0.5cm	0.5-1cm	1-2cm
Average BED (Gy_7)	^{131}I	368	70	**47**	**26**
	^{90}Y	2203	**180**	5	0.1
	^{177}Lu	**2917**	27	18	10
EU-BED (Gy_7)	^{131}I	91	65	44	24
	^{90}Y	601	45	2	0.1
	^{177}Lu	38	26	18	10

1410 - Tuesday, October 13, 2009, 14:30 - 16:00, Hall 122/123

Radiopharmacy/radiochemistry: antibodies-proteins/peptides 2

OP515

PEGylation of Bombesin analogues to increase their potential as tumor targeting radiopharmaceuticals

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Aim: The potential of bombesin(BN)-based radiopharmaceuticals for imaging and therapy of tumors that overexpress gastrin-releasing peptide (GRP) or BN-2 receptors may be hindered by a poor *in vivo* stability and an unfavorable hepatobiliary excretion. PEGylation would shield from enzymatic degradation, prolonging the *in vivo* half-life of the peptide analogues. PEGylation would also increase their hydrophylicity and contribute to favor a renal excretion. Moreover, the

higher molecular weight may improve the systemic exposure and enhance permeation and retention (EPR effect) in the tumor tissue. New PEGylated BN analogues have been synthesized and tested as potential radiotracers. **Material and methods:** N^{α}His-KAA-BN and DOTA-KAA-BN were synthesized by solid-phase peptide synthesis. The PEGylated analogues were obtained by reaction of the Lys of the spacer with the N-hydroxysuccinimidyl ester of PEG-NHS. The N^{α}His-analogues were labeled with ^{99m}Tc and the DOTA-analogues with ^{111}In. The radiolabeled analogues were then tested *in vitro* in human prostate carcinoma PC-3 cells and *in vivo* in nude mice with PC-3 xenografts. SPECT/CT was used to image the tumors. **Results:** Labeling yields were higher than 95% for both ^{99m}Tc and ^{111}In. Binding to GRP receptors in PC-3 cells was very specific for all the labeled derivatives although the PEGylated analogues showed slower binding kinetics than the non-PEGylated ones. However, PEGylation increased stability and residence time in the tumor cells *in vitro*. PEGylation of N^{α}His-KAA-BN resulted in improved biodistribution. ^{99m}Tc-N^{α}His-PEG-KAA-BN showed preferential renal excretion, much lower liver accumulation and a 3-fold decrease in colon uptake. Tumor uptake was slightly higher to that of ^{99m}Tc-N^{α}His-KAA-BN (3.9 vs. 2.4 %ID/g at 1h p.i.) and the visualization of the tumors by SPECT/CT was clearer. ^{111}In-DOTA-PEG-KAA-BN also showed a more favorable biodistribution than ^{111}In-DOTA-KAA-BN, with a 5-fold lower uptake in the receptor-positive organs pancreas and colon, and reduced kidney uptake (3.9 vs. 5.0 %ID/g, 1 h p.i.). Tumor uptake was similar for both analogues but ^{111}In-DOTA-PEG-KAA-BN showed improved SPECT/CT imaging. **Conclusion:** PEGylation of BN analogues resulted in favorable biodistribution, which led to higher signal-to-noise ratios and improved *in vivo* imaging. The PEGylated analogues showed preferential renal clearance and lower accumulation in the gastrointestinal tract. This would translate into lower whole-body radiation exposure and be advantageous to increase their therapeutic potential.

OP516

[^{111}In]Sargastrin 1, a Gastrin I-based radioligand targeting CCK2-R-positive tumors *in vivo*

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Aim: Radiolabeled minigastrin and CCK analogs have been proposed for application in the diagnostic imaging and radionuclide therapy of CCK2-R-positive human tumors, like medullary thyroid cancer (MTC). The Gastrin I heptadecapeptide is a most interesting candidate for this purpose; [^{131}I]Gastrin I already exhibited promising properties in animal models and in man. With the aim to obtain human Gastrin I analogs for labeling with a wide spectrum of clinically useful metallic radionuclides we have coupled the universal chelator DOTA to the N-terminal amine of [Gln[1],Nle[15]]Gastrin I. First biological data of the ^{111}In-labeled analog ([^{111}In]Sargastrin 1) is reported herein. **Materials and Methods**: The [Gln[1],Nle[15]]Gastrin I sequence was assembled on the solid support and DOTA was coupled to its N-terminus. After deprotection-release from the resin and HPLC purification Sargastrin 1 was retrieved. Labeling with ^{111}In was completed at pH 4.7 by heating for 40 min at 90°C; quality control was performed by HPLC analysis. AR4-2J cells were inoculated in the flanks of female SCID mice and well palpable tumors were grown at the inoculation site in 10 days. Biodistribution was conducted after injection of a 100 μL bolus of [^{111}In]Sargastrin 1 (2 μCi, 17 pmol) via the tail vein. Animals were sacrificed at 4 h and 24 h pi; for in vivo blockade 100 μg Demogastrin 2 was coinjected with the radioligand. **Results**: Sargastrin 1 was efficiently labeled with ^{111}In in >95% yield and radiochemical purity, as shown by analytical HPLC. After injection in SCID mice bearing CCK2-R-positive AR4-2J tumors, [^{111}In]Sargastrin 1 localized in the tumor (5.7 ± 1.6 %ID/g at 4 h pi and 2.7 ± 0.5 %ID/g at 24 h pi) and in the stomach (3.6 ± 0.5 %ID/g at 4 h pi and 2.3 ± 0.2 %ID/g at 24 h pi). Uptake in the blocked animal group was significantly reduced (0.3%ID/g and 0.1%ID/g, respectively, at 4 h pi) implying a CCK-2-R mediated process. Kidney uptake was significant at 4 h pi (>100%ID/g) and remained at high levels even at 24 h pi (75%ID/g). **Conclusions**: This work has shown that Gastrin I-based radioligands can target CCK2-R-positive tissues in vivo equally well or better than their minigastrin-based counterparts. Although the observed high kidney uptake and retention may represent a species-related finding not reproduced in human, work is currently in progress to reduce renal values by kidney protection regimens (e.g. administration of poly-glutamates, gelofusine, or other agents and combinations thereof).

OP517

Substitution of (L)Trp[8] by (D)Trp[8] in [(^{111}In-DOTA)Ala[1]]SS-14 enables targeting of sst_2-expressing tissues in animal models

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Aim: Radiolabeled somatostatin analogs exhibiting expanded sst_{1-5} affinity profiles, the so-called pansomatostatin-like radioligands, may prove to be useful for broader clinical indications than for sst_2-expressing tumors only. For this purpose, we have coupled the universal chelator DOTA at the N-terminal Ala of either native SS-14 or [(D)Trp[8]]SS-14. In this way, labeling with the diagnostic radionuclide ^{111}In or other bi- and trivalent metallic radionuclides, interesting for diagnostic (PET/SPET) or therapeutic applications, is feasible. Radiochemistry and preliminary biological results for these two radiotracers are reported herein. **Materials and Methods**: The linear tetradecapeptides Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp/(D)Trp-Lys-Thr-Phe-Thr-Ser-Cys were assembled on the solid support and 3-^{t}Bu-DOTA was coupled to Ala[1]. After deprotection and cleavage from the resin the analogs were cyclized by I_2-oxidation and [(DOTA)Ala[1],Trp/(D)Trp[8]]SS-14 were isolated by HPLC. Labeling with ^{111}In was conducted in acidic conditions. Radiopeptide internalization was studied by incubation at 37°C in sst_2-expressing AR4-2J cells in the absence or presence of 1 μM Tate ([Tyr[3],Thr[8]]octreotide). Biodistribution was studied in healthy male Swiss albino mice and, selectively for [(^{111}In-DOTA)Ala[1],(D)Trp[8]]SS-14, in AR4-2J tumor-bearing SCID mice. Radiopeptides were injected as a 100 μL bolus (2 μCi, 10 pmol total peptide) via the tail vein; for in vivo blockade animals additionally received 50 μg Tate. **Results**: [(DOTA)Ala[1],Trp/(D)Trp[8]]SS-14 were synthesized in good yields and high purity adopting SPPS-techniques, as confirmed by ES-MS and HPLC analysis. Radiolabeling with ^{111}In afforded [(^{111}In-DOTA)Ala[1],Trp/(D)Trp[8]]SS-14 in >95% yield and radiochemical purity, as verified by analytical HPLC. Both radiopeptides internalized specifically into AR4-2J with the (D)Trp[8]-substituted analog internalizing more rapidly. In healthy mice, only [(^{111}In-DOTA)Ala[1],(D)Trp[8]]SS-14 succeeded to specifically target somatostatin-binding sites in vivo, such as the pancreas (2.9 ± 1.5%ID/g vs. 0.5 ± 0.2%ID/g (Trp[8]-analog) at 4 h pi, vs. 0.2 ± 0.1%ID/g in the blocked animals), presumably due to its enhanced stability. The same analog was successful to specifically target the implanted tumor in SCID mice (3.1 ± 0.5%ID/g at 1 h pi and 1.8 ± 0.4%ID/g at 4 h pi, vs. 0.2 ± 0.2%ID/g at 4 h pi in the blocked animals). **Conclusions**: The present study has shown that in vitro and in vivo targeting with radiolabeled analogs of native SS-14 is in principle feasible. Substitution of Trp[8] by (D)Trp[8] appears to be crucial for effective in vivo targeting, most probably by preventing rapid enzymatic cleavage of this site by endogenous peptidases. Further studies are in progress to reveal the applicability of [(^{111}In-DOTA)Ala[1],(D)Trp[8]]SS-14 as a pansomatostatin-like radiotracer.

OP518

Selection best bombesin-analogue for use in phase I trail imaging prostate cancer with SPECT

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Introduction PSA-based screening of prostate cancer (PC) has dramatically increased early diagnosis. Current imaging techniques are not optimal to stage early PC adequately. A promising alternative for PC imaging is radiolabelled peptide based scintigraphy using radiolabelled bombesin (BN)-analogues that bind to Gastrin-Releasing Peptide Receptors (GRPR) being overexpressed in PC. **Purpose** Determining GRPR-expression in patient samples of different PC stages and to select the best BN-analogue for GRPR based PC-imaging using xenografts. **Methods** Using RT-PCR and BN-autoradiography GRPR-expression was determined in patient PC samples from our frozen tissue bank. We compared promising BN-analogues in human PC3, PC295 and VCAP xenografts under standardized conditions. The ^{111}In-labelled BN agonists Pesin, AMBA, MP2346 and MP2653 and the ^{99m}Tc-labelled antagonist Demobesin-1 (DB1) were evaluated for in vivo stability, biodistribution and visualisation by SPECT/CT and autoradiography. **Results** GRPR mRNA levels showed variable but significant expression in all stages of PC. This was confirmed by BN-based autoradiography in early and late stage PC. PC-3 tumour uptake at 1 hour was comparable for DB1, AMBA, Pesin and MP2346 (2.99±0.44, 2.69±0.48, 2.31±0.54 and 2.08±0.93%ID/g, respectively), but very low for MP2653 (0.91±0.24%ID/g). In addition, MP2346 showed undesirable high uptake in the kidneys (7.85±1.94%ID/g) being much less for the other analogues. AMBA, MP2346 and Pesin revealed favourable increases in tumour to blood ratios over time while changes in tumour-to kidney and pancreas ratios for DB1 1 to 24h after injection were significantly better than for the other analogues (see table I). All analogues visualised PC tumours by SPECT-CT and autoradiography. HPLC analysis showed intact DB1 at 5 and 15min after injection (64.1%±1.6 and 41.0%±01, respectively) being much less for the other compounds. AMBA, the second most stable analogue, showed 36.1%±2.7 and 9.8%±1.1 intact peptide after 5 and 15min. **Conclusion** GRPR expression was high, but variable, in the majority of PC samples with no clear distinction between various stages. In our study DB1 was the best performing analogue showing best in vivo stability, high tumour-uptake and retention while pancreatic clearance was rapid. Pesin and AMBA were the best GRP-agonists with high tumour-uptake and retention. DB1 has been selected for use in a phase I trial. Pharmacologically, being an antagonist, this analogue is expected to cause few side effects. Initially, 10 patients with histologically proven PC will be included for DB1-SPECT prior to scheduled radical prostatectomy to evaluate accuracy of PC detection. SPECT images will be verified using histopathology as the "golden standard".

OP519

Comparison of 177-Lutetium and 161-Terbium labeled monoclonal antibody chCE7 for radioimmunotherapy

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Aim: The aim of this study is to compare the therapeutical effects of the low-energy β[-]-emitters ^{177}Lu and ^{161}Tb coupled to the the tumor-targeting monoclonal antibody chCE7. The radiolanthanides ^{177}Lu and ^{161}Tb have very similar decay properties, but ^{161}Tb in addition emits several conversion- and Auger-electrons. Due to their very short range in tissue, Auger-electrons may have a beneficial effect in radioimmunotherapy, for example in the treatment of micrometastases and the eradication of individual tumor cells. Recently, antibody therapy directed against the L1-cell adhesion molecule (L1-CAM) has emerged as a new option for targeting ovarian cancer metastases. mAb chCE7 binds to L1-CAM with high affinity and specificity, and radioimmunoconjugates based on this antibody have been shown to have a significant therapeutical benefit in preclinical tumor models (1). Materials and Methods: mAb chCE7 was labeled with ^{161}Tb and ^{177}Lu via the macrocyclic ligand DOTA. The immunoconjugates were functionalized by a nuclear localizing sequence (NLS) to direct the internalized antibody to the nucleus. The properties of the radioimmunoconjugates were compared both *in vitro* on L1-CAM expressing tumor cells and *in vivo* in a mouse model of intraperitoneally disseminated ovarian cancer. This previously established mouse model will then be used to address therapeutic efficacy *in vivo*. Results: Both ^{177}Lu-DOTA-chCE7 and ^{161}Tb-DOTA-chCE7 bind to L1-CAM expressing tumor cells and internalize rapidly. The radioimmunoconjugates have excellent targeting properties *in vivo* with high accumulation at the tumor site and low activity in non-targeted organs. First results on the comparative therapeutic efficacy will be presented. Discussion: We here evaluate ^{161}Tb as a promising alternative to the clinically established low energy β[-]-emitters ^{77}Lu for targeting of micrometastases or single cancer cells. 1. Knogler et al., 2007; Clin. Cancer Res. 13:603-611

OP520

First experience with an ^{111}In-labeled bombesin antagonist designed to mimic [^{99m}Tc]Demobesin 1

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