Moving

Annual report 2016

Department of Nuclear Medicine & PET-Centre, Aarhus University Hospital

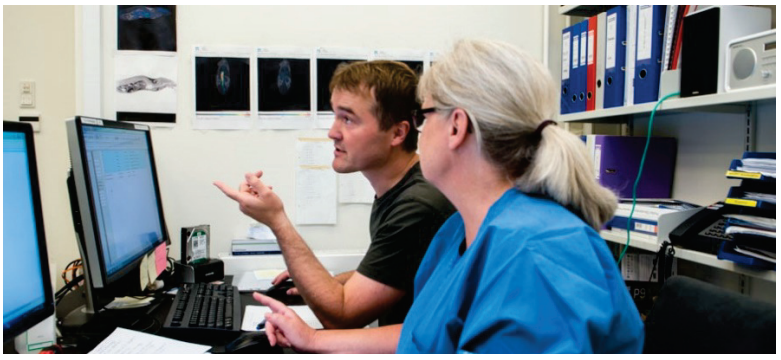
AARHUS UNIVERSITY

Aarhus University Hospital

Department of Nuclear Medicine & PET-Centre

2016

Building 3, Nørrebrogade



Building 10, Nørrebrogade

Skejby

Table of contents

TABLE OF CONTENTS

Preface

In 2011, the Department of Nuclear Medicine and the PET-Centre merged into one major department for molecular imaging at Aarhus University Hospital. The department has been through a long journey since then and has of 2016 transformed into a department where we value diagnosis, research and development, and education as the output of the dedicated work from our highly skilled staff.

The Department of Nuclear Medicine & PET Centre is based on the very strong platforms provided by the infrastructure of the former PET-Centre and Departments of Nuclear Medicine at the former "Aarhus Sygehus" and "Skejby", respectively. Since the merge in 2011, this infrastructure has expanded and thanks to a highly dedicated staff and with the outstanding support from the management of the Head and Heart Centre the department has strongly moved forward. We are proud to note that despite the thorough organisational changes and increasing clinical activities, major achievements were reached during the past couple of years. With the patient in focus, we expanded our activities introducing new patient examinations and clinical research projects demonstrating that the merged organisation creates synergy!

We have become a strong team with high ambitions and a multitude of skills. We constantly strive to provide state-of-the-art and up-front diagnostic tests focusing on delivering the best investigation to each individual patient in time for diagnosis and treatment without delay. This is only possible through close cooperation with referring physicians and all staff members. The close cooperation is constantly evolving by the department's active participation in a large number of frequent multidisciplinary conferences.

An important focus is the continuous training and education of each staff member combined with sharing of knowledge to obtain the highest standard. This together with continuous efforts to optimize procedures and work flows ensures the most efficient use of equipment and staff resources.

These efforts have been of fundamental significance in the increasing importance and demand for clinical PET/CT. The vast majority of PET/CT studies continues to be 18F-FDG-scans for staging and follow up of cancer patients included in the diagnostic work-up defined by The Danish National Board of Health. We perform close to 7500 clinical PET/CT scans in patients with malignant disease and the number and demand continues to increase. A special attention is given to the use of PET/CT in radiation therapy planning, and we look forward to being a close partner when we implement particle therapy in 2018 at the Danish Centre for Particle Therapy located at Aarhus University Hospital.

In parallel, PET/CT studies belong to our strategic core areas nuclear cardiology, neuroimaging, and hepatology using existing and novel tracers. New tracers are constantly being developed and implemented at our department and our experience in such matters is high. Examples are cardiac PET with 82Rubidium and 15O-water, oncological PET with Ga-PSMA, neuroimaging with 18F-DOPA, 11C-donepezil and 11C-methionin, and imaging of hepatic function with 11C-CSar. Furthermore, a large number of tracers for preclinical and clinical research are available and more are in the pipeline. This is enabled by our large radiochemistry unit, which belongs to the top international league. Because it is staffed with highly qualified chemists and technologists and equipped with two cyclotrons and state-of-the-art GCP facilities for radiopharmaceutical production, we are able to produce and develop new radiotracers for clinical and research supply to Aarhus University Hospital and other hospitals as well as collaborating institutions.

We constantly focus on excellence in research and we have a strong profile in the core research fields of expertise including neurology, oncology, cardiology, hepatology and radiochemistry. Thanks to a dedicated staff, we are an important partner in numerous cross-disciplinary research projects.

The Department of Nuclear Medicine & PET Centre provides a unique core facility within the University Hospital and Aarhus University. The department is

PREFACE

aware of the special obligations and responsibility that follows from this and we are constantly improving our research facilities to secure that they have the highest international standards. In particular, we also focus on recruitment of top-scientists to our department and collaborating research groups.

There is no doubt, that the creation of our strong merged department combined with the expansion of a large local, national and international network of collaborating researchers and clinicians has created a platform for achieving our ambition of being among the international leading nuclear medicine institutions. The department has special focus on our core areas in the fields of oncology, cardiology, neurology, hepatology, endocrinology and radiochemistry where we work on long-term strategies including staff recruitment and education, funding of equipment and scanners, collaboration and networking and establishment of up front clinical and research activities and projects. This work was initiated in 2012 and continuous to this day.

We therefore warmly thank our staff and colleagues from collaborating departments for their great effort. The collaboration with colleagues at Aarhus University is fundamental for the excellent research achievements and we are grateful for the support from Aarhus University. We also wish to thank the management of the Head and Heart Centre and the hospital management for their extensive support.

Jørgen Frøkiær
Professor, Head of Department, MD, DMSc

Michael Werenberg Mikkelsen
Head Biomedical Laboratory Scientist

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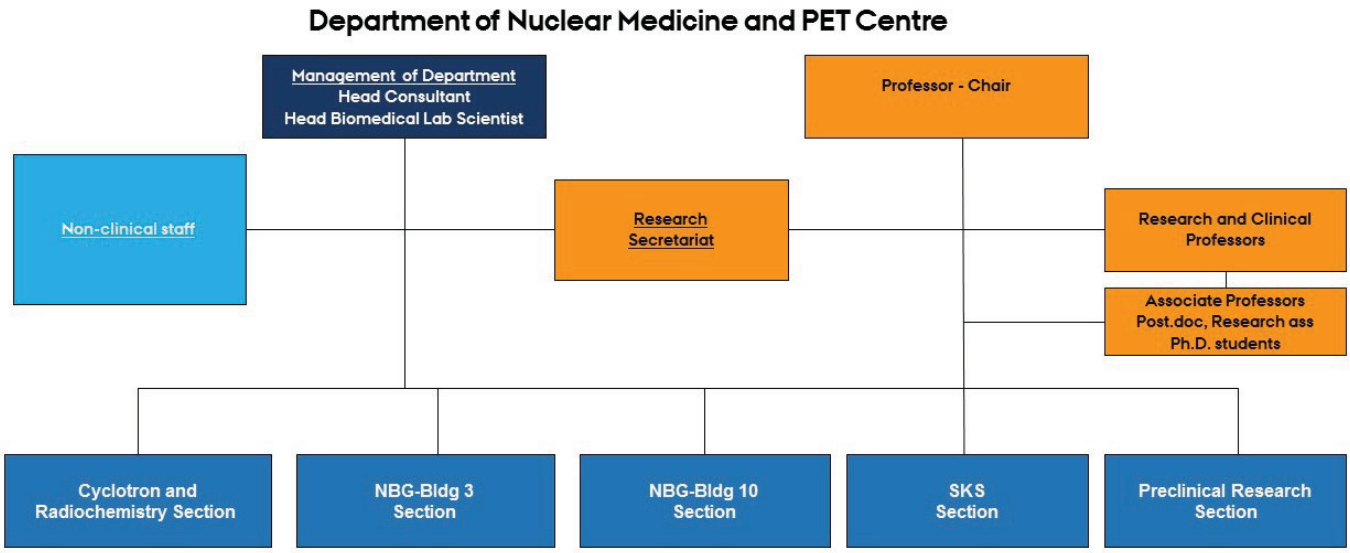
Organisation chart



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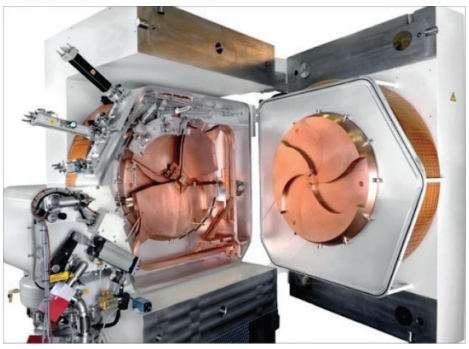
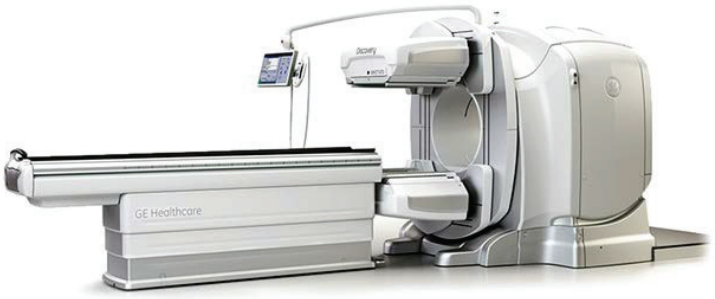
Equipment

Equipment type	Model	Year of purchase
Gamma camera	Mediso TH-45	2005
	Mediso TH-45	2015
	DDD Nephrocam	2016
SPECT cameras	Picker Axis	2000
	Philips CardioMD	2007
SPECT/CT scanners	GE Discovery NM/CT 670	2011
	Siemens Symbia T-16	2011
	Siemens Symbia T-16	2012
PET brain scanner	Siemens HRRT	2005
PET/CT scanners	Siemens Biograph 40 True Point	2007
	Siemens Biograph 64 True Point	2009
	Siemens Biograph 64 True Point	2009
	GE Discovery 690	2009
Cyclotrons	GE PETtrace	1993/2010
	IBA Cyclone 18/18	2009

Pre-clinical equipment		
Phosphor imager	FujiFilm BAS-5000	2002
SPECT camera	Philips BrightView	2009
MicroPET/MRI	Mediso Nanoscan	2014



GE PETtrace cyclotron



GE Discovery NM/CT 670

Excellence – from molecule to man

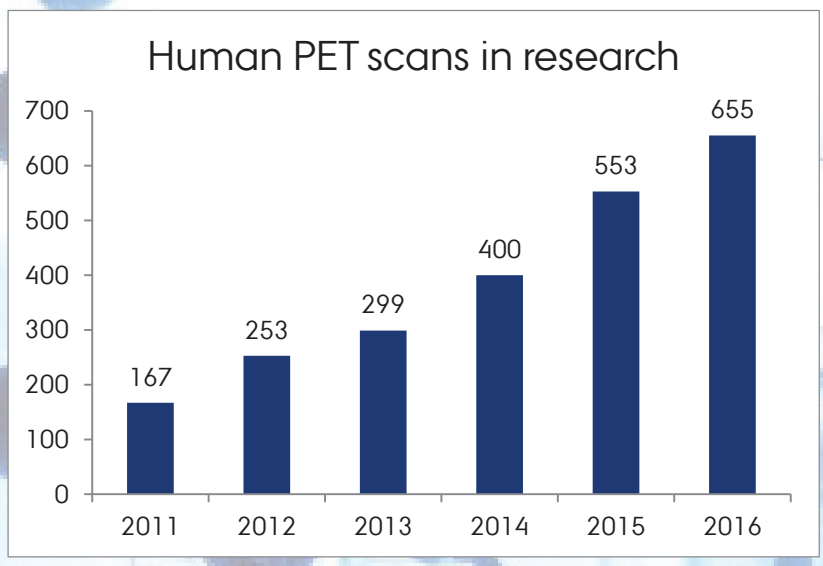
Jørgen Frøkiær, Professor, Head of Department, MD, DMSc

Molecular imaging is a fast developing discipline. From the beginning of the nuclear medicine era more than 50 years ago the principles for refining diagnostic examinations using radiopharmaceutical have been characterized by targeting specific cellular (and molecular) processes in tissue. Although knowledge of molecular pathways and processes within cells and tissues were much more limited in the beginning of this era, the principles remain the same. Radioactive labeling of precursor makes the tracer, which ideally targets exclusively the process which is in focus all the way from the very simple to the much more complex level (e.g. iodine (I-) uptake in the thyroid and [11C] donepezil targeting acetylcholinesterase in the synaptic cleft of cholinergic nerve terminals). Regardless of the referring question, our aim is always to provide the very best answer to our clinical partners and the patients.

By addressing highly relevant medical scientific challenges, our department strive to be in the top-league of developing novel imaging methods to the benefit of patients with both common or highly complex diseases. As a large core facility at Aarhus University Hospital and an academic department the goal is to provide cutting-edge science, which will transform into novel paradigms for diagnosing clinical problems. We work from molecule to man and we aim for the highest quality in every step we take to full fill our goals. Quantitatively, it is satisfying to notice that the effort and strategy we have for research based development in our department is documented by a steady increase (more than 400% since 2011) in the number of clinical based research PET-CT scans.

In this annual report, we present a palette of exciting examples of areas characterized by highly original projects within a variety of areas where The Department of Nuclear Medicine and PET-Centre have highly unique expertise. This expertise includes the capacity to generate excellent ideas combined by the man power, the infrastructure, our radiochemistry and skillful ability to collaborate internally and externally with local and international colleagues.

Visibility is also part of scientific excellence and we are proud to publish many of our studies in the very best journals. This year we have decided to list the scientific production from the past 3 years demonstrating a constant increase in scientific activity and productivity.



Radiochemistry

Radiochemistry - PET

Dirk Andreas Bender, Chief Radiochemist, PhD

2015 and 2016 were busy years for PET radiochemistry. Additional tasks were assigned to the group with respect to the construction of the new facility at DNU. Construction work started in 2015 and besides consultant task for the constructors the EU tender process for the purchase of a new cyclotron and GMP hotlab was initiated in 2016. Many hours were spent on definition on user specific demands. The tender was published in September 2016. Site visits, tender evaluation and tender award are scheduled for early 2017.

In terms of tracer productions in 2015 and 2016, PET tracers were supplied every working day. The centers 6 PET radiochemists, 3 PET radiochemistry technologists and 4 other technologists taking care of the FDG morning production performed more than 3000 PET tracer productions, dedicated for use in patients and healthy control subjects. The radiotracer portfolio of tracers produced within delivery permits or marketing authorization was 42 for 2016 and 41 for 2015. From this radiotracer portfolio were 27 different tracers used in 2015 and 24 in 2016. All productions resulted in almost 27000 single doses (2016: 13846; 2015:13019). Number of productions and doses were almost constant in 2015 and 2016, even so a slight increase was observed in 2016. In terms of doses, FDG was with 9178 doses (2015, 70.5%) and respectively 10055 (2016, 72.6%) the dominating PET tracer. Besides the generator based Rb-82 with approximately 1800 doses both in 2015 and 2016, all other tracer productions varied from few produced doses to several 100. An interesting trend was observed for the C-11 labelled radiotracers. Whereas in 2015 355 productions were distributed on 13 different C-11 tracers, in 2016 328 productions were distributed only on 9 different tracers and here mainly focused on C-11 PIB and C-11 PK11195 productions.

The most remarkable new introduction of a new tracer was the Ga-68 labelled PSMA, which is used for examinations of patients with prostatic cancers. PSMA was introduced in March 2016 and already by end of 2016, more than 290 patients were examined with this tracer. The formerly used F-18 fluorocholin was discontinued almost immediately. The demand for PSMA examinations is still increasing and efforts must be taken in 2017 to increase production capacity to cover the demand.

In 2015 and 2016 several tracers with considerable potential within research projects were validated and applied.. Here especially the tau tracer F-18 AV1451, the calcium channels ligand F-18 GE179 and the biguanid C-11 metformin.

Likewise, in 2016 the PET-Centre started to work with Cu-64 a radio metal with 12 hours half-life. As the use is currently limited to one research project, Copper-64 is not produced in house, but purchased from several European producers.

Both in 2015 and 2016 the department continued to supply radiotracers out- of house deliveries to up to eight different user sides. The total number of radiotracer deliveries was 974 (2015) and respectively 1031 (2016). The main out of house users sites were both in 2015 and 2016 Aalborg University Hospital, Aarhus University Hospital Department for Nuclear Medicine at Skejby, Aarhus University Hospital Department for Oncology at Skejby and the Regional Hospital in Herning with each more than 200 deliveries per year. The total number of delivered doses was in 2015: 6809 and in 2016: 8129.

Both in 2015 and 2016 the most remarkable out of house delivery in terms of logistics were the deliveries of F-18 FDOPA to Oslo. Despite the comparable short shelf life and limited production yields, the combination of emergency ground and air taxi transport ensured sufficient amounts of FDOPA in Oslo to perform several patient examinations per delivery.

Challenges for 2017 and 2018 are primary related to the establishment of the department's new facilities within the New Aarhus University Hospital,

which is currently under construction in Skejby. Early in 2017 delivery contracts for a new cyclotron and new GMP production facility ("hotcells") will be entered. The building will be ready for installation of the new equipment early 2018. It is expected that installation and finishing of the building will take place in April/May 2018. Laboratories and equipment are planned to be qualified and validated by July 2018, followed by an inspection by the Danish Medicines Agency in August 2018. In case no delays occur, it is aimed to have a new production licence in place by September 2018. After the new facilities are operational, the existing two cyclotrons will be moved and likewise hotcell equipment. By end of 2019, the facility should be 100% operational.

In terms of research activities, the PET-Centre's radiochemistry continues it program for the development of new labelling techniques and tracer development. These research activities are both performed in department internal collaborations, AUH internal collaborations, joint projects with Aarhus University departments and other universities in both Denmark and Europe, here besides other partners in EU FP 7 initiative targeting tracers for alpha synuclein aggregates. Besides scientific collaborations, collaborations with industry (currently Novo Nordisk, Lundbeck, Ferring and Octreopham) continued as well in 2015 and 2016.

Within teaching obligations a new PhD course, "Introduction to GMP", was established in 2016. Due to its success, this course will be continued in 2017.

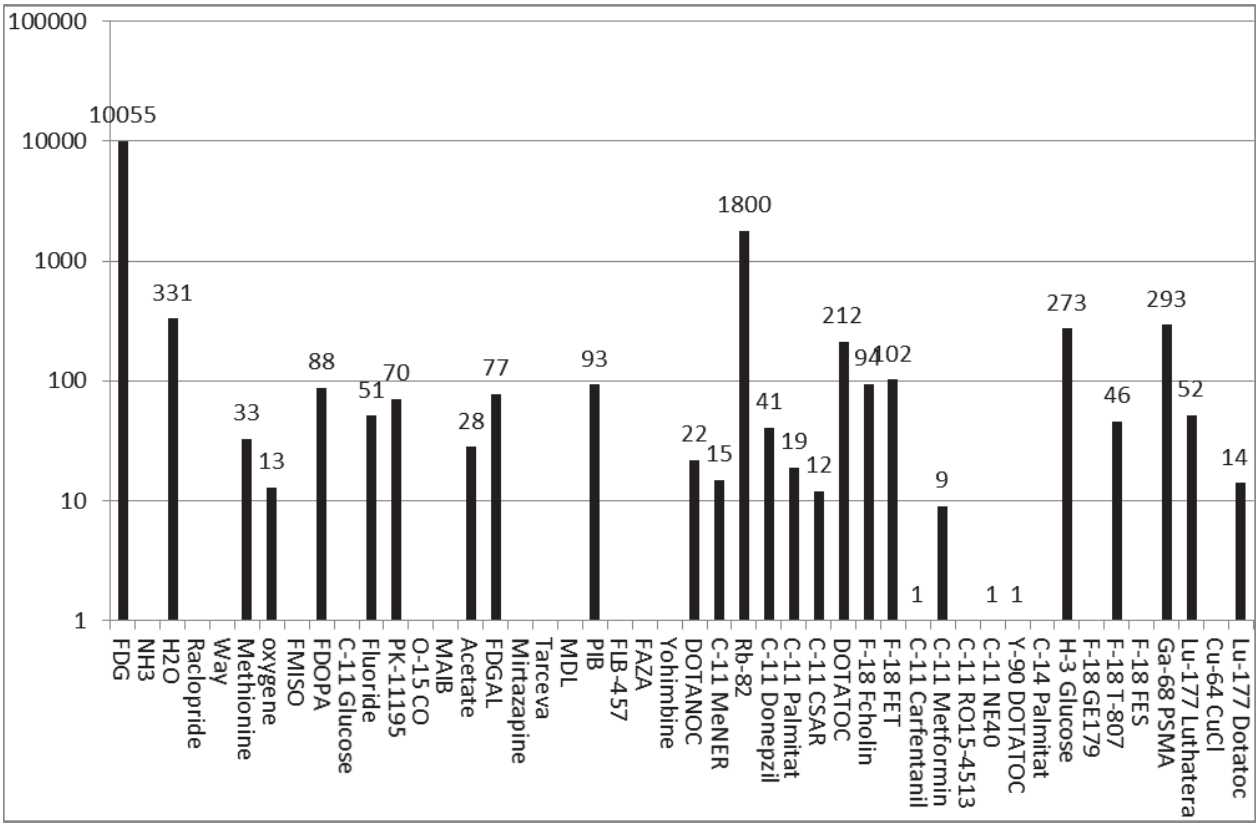


Figure 1. Portfolio of radiotracers produced for human use, both under marketing authorization and within compassionate delivery permits (GMP tracers) in 2016 including number of doses.

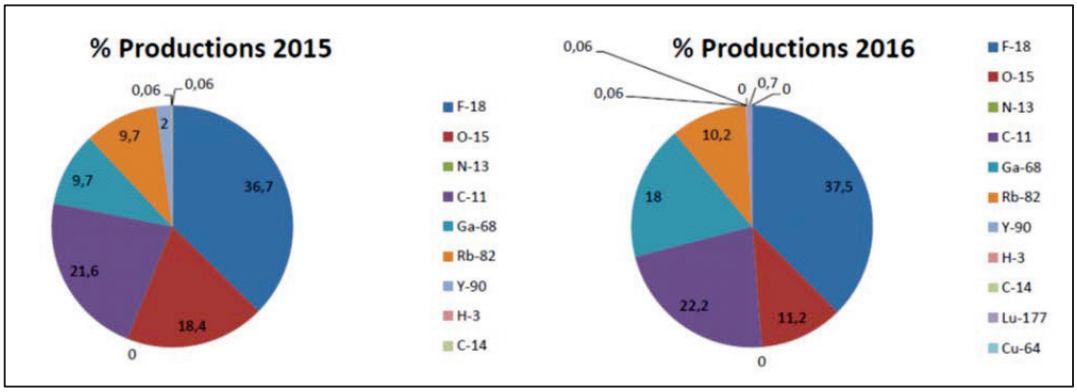


Figure 2. GMP productions: Distribution per radioisotope for 2015 and 2016

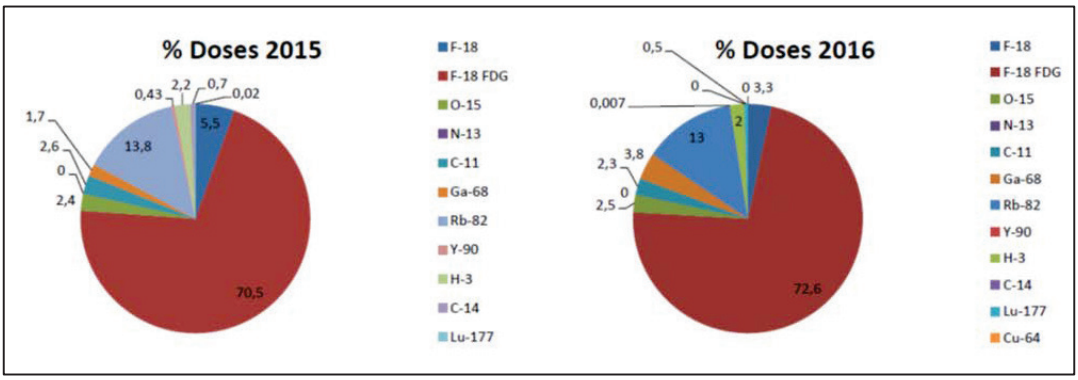


Figure 3. GMP produced doses: Distribution per radioisotope for 2015 and 2016

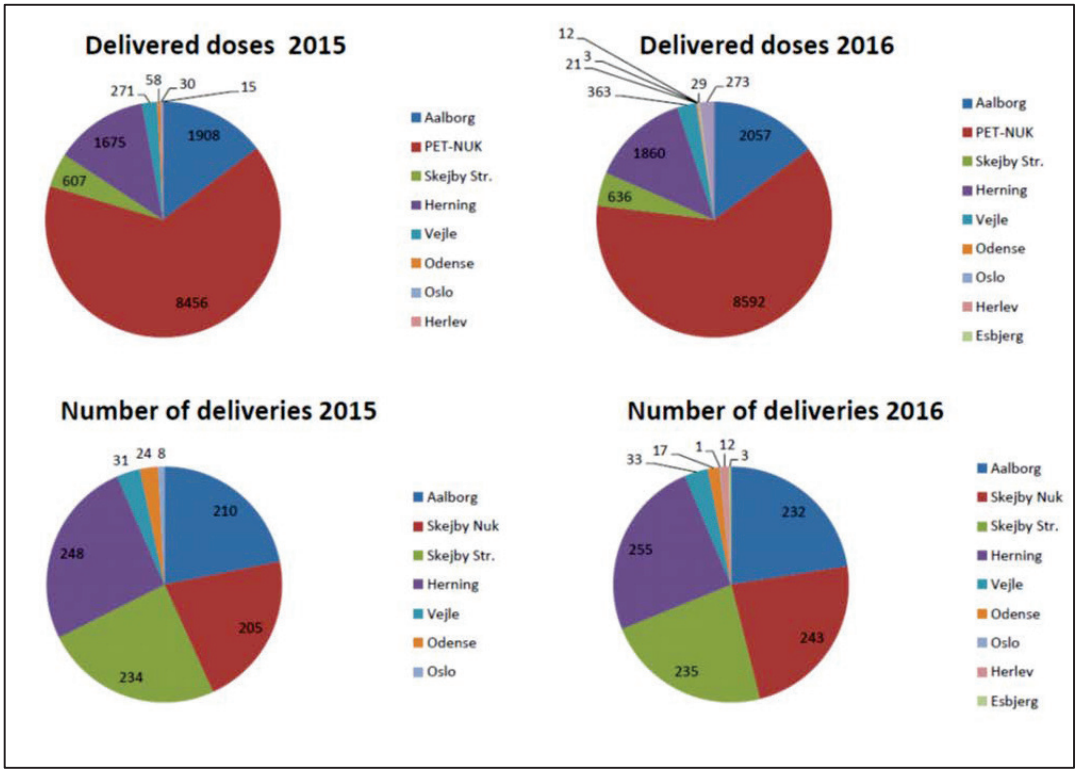


Figure 4. Doses delivered and number of deliveries for out of house users for 2015 and 2016

Radiochemistry – Nuclear medicine

Anders Floor Frellsen, Chemist, PhD

The years 2015 and 2016 have been spent under the sign of therapy at the Department of Nuclear medicine. Most prominently targeted internal radiotherapy for the treatment of neuroendocrine tumors has seen its fair share of development. At the beginning of 2015 local production of Y-90 DOTATOC was a weekly recurring event – a total of 57 patient doses were administered in 2015. But in the fall of 2015 a decline in demand was observed, as the therapeutic radioisotope Lu-177 was introduced as an alternative to Y-90. The lower energy β-emissions promised decreased collateral damage to healthy tissue, which was welcomed by the clinical departments. In November 2015 the first dose of commercially available Lu-177 DOTATATE was administered at AUH. At the end of 2015 three patients had received their first dose of Lu-177 at AUH. By January 2016 the last dose of Y-90 DOTATOC was administered, as all new patients were instead submitted for Lu-177 treatment. However the radioisotope, Y-90, was still going strong as the active component in Selective Internal RadioTherapy (SIRT) of hepatic tumors. This entails direct delivery of Y-90 impregnated resin beads; through a catheter inserted in the vein from the groin to the liver. In 2016 the number of SIRT procedures was increased form just four in the previous year to 11 treatments, and the doctors were looking to expand the scope of patients that this treatment was used for.

Since the introduction of Lu-177 DOTATE at the end of 2015, another 52 doses were administered during 2016. The change of radioisotope had allowed expansion of the patient group, to subjects whom could not previously receive internal radiotherapy. Immediately recognizing the success of Lu-177 treatments, validation of a Lu-177 DOTATOC production at AUH was initiated at the beginning of 2016 to keep up with the growing demand – by the end of the summer this permission to carry out this production was given by the Danish Medicines Agency. In September 2016 the first patient was treated with Lu-177 DOTATOC produced at AUH. By the end of the year 14 patients had been treated with Lu-177 DOTATOC at AUH, and Lu-177 DOTATATE was on the way out.

Apart from neuroendocrine tumors, treatment of thyroid cancers with I-131 is routinely carried out at the department. In 2015 a total of 110 I-131 doses were administered for treatment of thyroid cancers, while another 288 doses were administered for treatment of benign thyroid disease. In 2016 a slight decline was observed to 96 doses for treatment of cancers and 256 doses for treatment of benign thyroid diseases. Whether this ca. 12% decrease in I-131 doses is the beginning of a declining trend, or within the yearly variation remains to be seen in the coming years.

Even though therapy has captured the spotlight in the radiopharmacy in these years, tracers for diagnosis account for majority of the radioactive doses produced. Tracers are not only produced for use at NBG, Bldg 3, but are also distributed to departments of AUH at Palle-Juul Jensens Boulevard and Tage-Hansens Gade. The diagnostic radioisotopes that we prepare include Tc-99m, Cr-51, In-111, as well as I-123, I-131, and Se-75.

A total of 6472 doses were prepared in 2015, the largest single tracer, Cr-51, accounting for 1639 (25%) of these, followed by Tc-99m pertechnetate accounting for 1397 doses (22%). In 2016 the same amount of doses was prepared, a total of 6461 doses prepared at NBG, Bldg 3. Amongst these Tc-99m pertechnetate accounted for 1709 doses (26%), while Cr-51 accounted for 1570 doses (24%). The most remarkable change was observed in the number of In-111 radiolabelings of leukocytes. This laborious preparation was frequent in 2015 accounting for 47 prepared doses, while in 2016 only six such doses were prepared.

The coming years will be marked by preparations for- and moving the department to new facilities at the New Aarhus University Hospital in Skejby. One of the challenges being the constant development in the field of radiochemistry and changing demands for special preparations such as radiolabeling of DOTATOC or leukocytes, requiring unique facilities. Furthermore, the increase in therapeutic treatments is putting a strain on the isolation wards for patients, during treatment, which very well may end up bottlenecking internal radiotherapy at the new facilities.

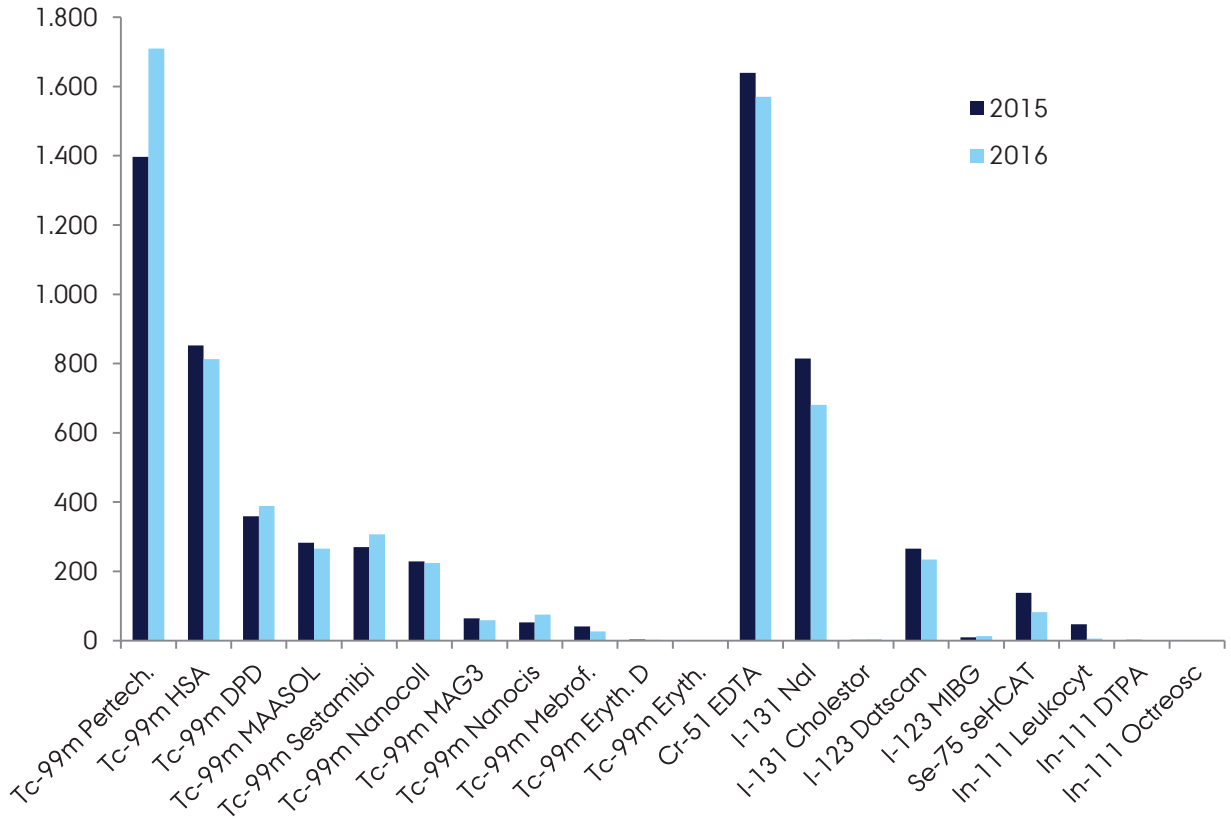


Figure 1Tracers prepared at NBG, Bldg 3 in 2015 and 2016 respectively

Neuroscience

Molecular imaging of brain disorders

Per Borghammer, Consultant, Associate Professor, MD, PhD, DMSc

Nuclear medicine is important for proper diagnosis in multiple brain disorders including dementia, Parkinson's disease, and brain tumors. In collaboration with the Department of Neurology and Neurosurgery, we are constantly focusing on improving and refining examinations to provide optimal information to the benefit of our patients. In addition, the PET Centre has a longstanding research tradition in the field of neuroscience with particular emphasis on neurodegenerative disorders including Alzheimer's disease and Parkinson's disease. Clinical and translational scientific projects are carried out in collaboration with national and international collaborators and span the full range from tracer discovery and validation to implementation in clinical practice.

Clinical nuclear medicine examinations in brain disorders

Per Borghammer, Consultant, Associate Professor, MD, PhD, DMSc and Joel Aanerud, MD, Specialist Registrar

There is an increasing demand for PET and SPECT scans in the field of neurological and neuro-oncological disorders. During the last 5 years, the number of clinical brain examinations at our department has increased by 125%.

In 2016, we performed 515 ^{18}F-FDG PET scans in patients under suspicion of dementia. This methodology provides a powerful tool for differentiating dementia disorders, including Alzheimer's disease, Lewy Body dementia, vascular dementia, and fronto-temporal dementia.

The ^{123}I-FP-CIT SPECT (DaT SPECT) has a diagnostic accuracy of 95% or more for detecting damage to the dopaminergic neurons of the substantia nigra. In 2016, a total of 236 DaT SPECT scans were performed in patients with suspected Parkinson's disease or other movement disorders. In selected movement disorder patients, the ^{123}I-MIBG scan is useful for measuring the integrity of the sympathetic nervous system. Parkinson patients exhibit an almost complete destruction of the sympathetic innervation to the heart, whereas patients with atypical movement disorders such as multiple system atrophy have normal cardiac innervation.

We recently implemented the amino acid tracer ^{18}F-FET for management of brain tumors. ^{18}F-FET accumulates in metabolically active tumor cells and is a valuable supplement to standard MRI scans for a more exact delineation of the true tumor extent. These PET scans are useful for differentiating brain tumors from benign brain lesions and for supporting stereotactic tumor biopsies.

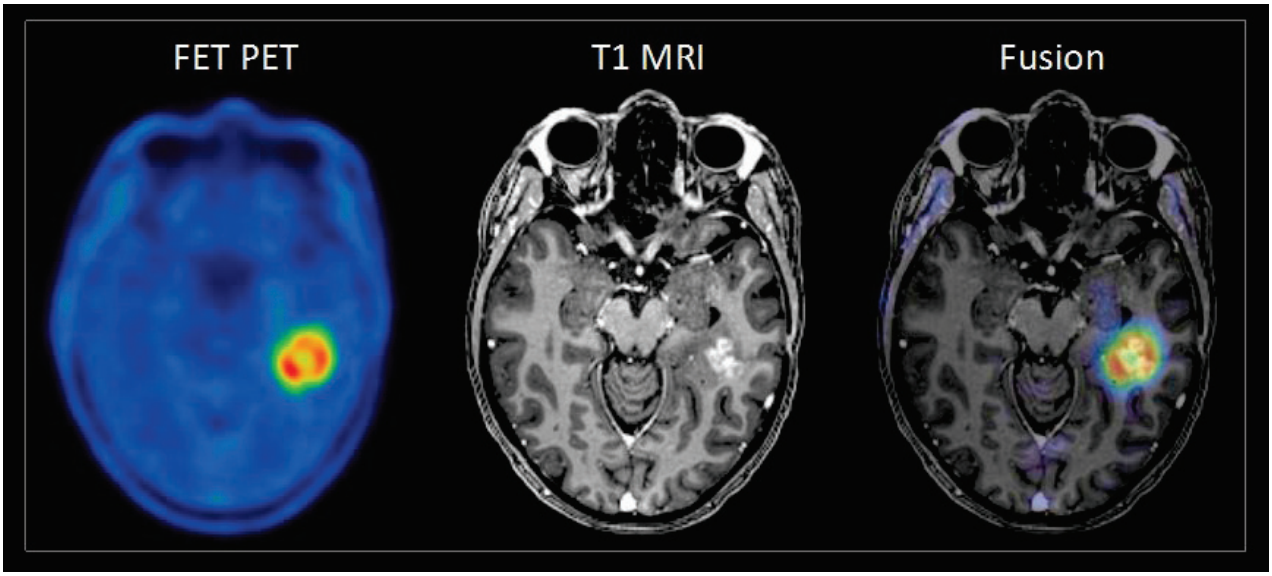
Patients with slowly developing but severe stenosis or even occlusion of the internal carotid artery often display intermittent neurological symptoms including paresis and aphasia. The cerebrovascular flow-reserve of these patients can be accurately determined using ^{15}O-H_2O PET scans, which measures cerebral blood flow. By comparing the

Number of scans in 2016:

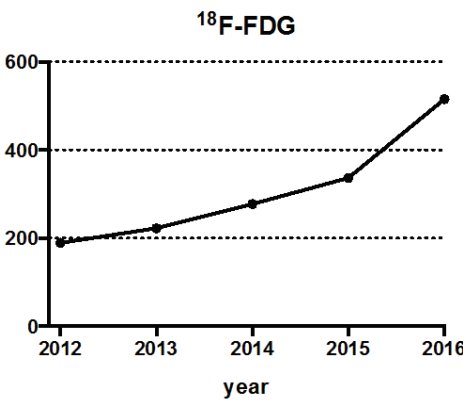
^{18}F-FDG	**- 515**
^{123}I-FP-CIT SPECT	**- 236**
^{18}F-FET	**- 82**
^{15}O-H_2O PET	**- 44**

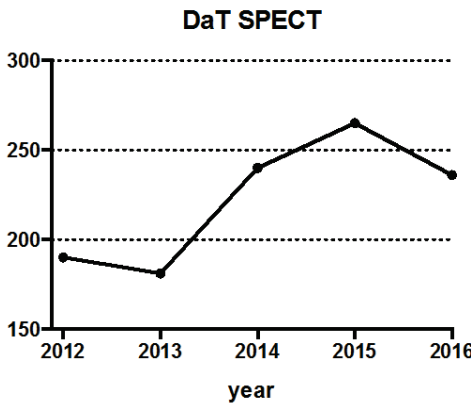
blood flow in baseline and after a vaso-dilatory challenge using acetazolamide, significant reductions in flow-reserve can be detected. This is an important clinical parameter for identifying patients eligible for extra-cranial/intra-cranial by-pass surgery.

^{15}O-H_2O perfusion PET scans are also used for precise localization of normal brain functions in the motor cortex and language areas. Such mapping of normal brain functions assists the neurosurgeon in the pre-operative planning of select brain tumor patients.



^{18}F-FET PET shows increased amino acid uptake in a malignant brain tumour. MRI demonstrates contrast enhancement suggestive of blood brain barrier disruption. On the fused images the FET-uptake extends beyond the contrast enhancement suggestive of tumour





Research in Parkinson's disease

Per Borghammer, Consultant, Associate Professor, MD, PhD, DMSc

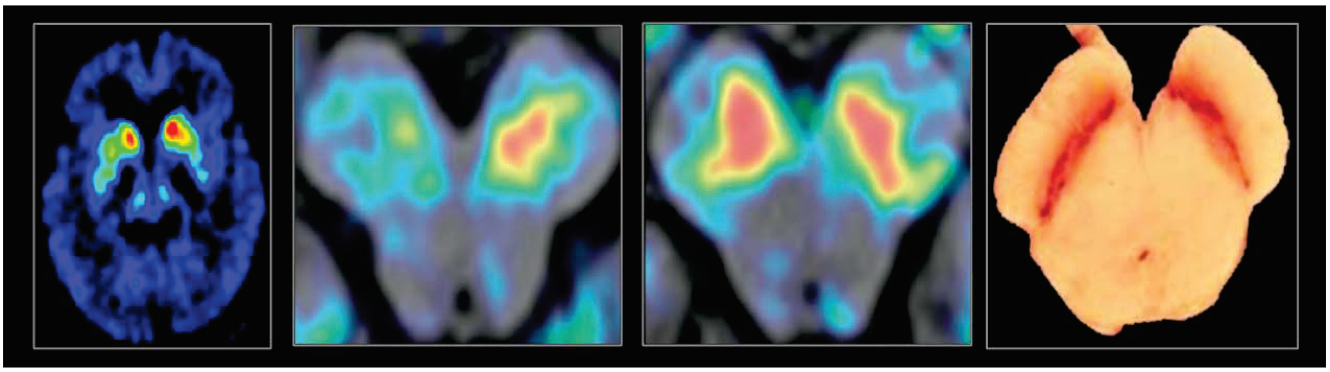


Figure 1. Left: Pigmented dopamine cells in the brain stem are evident at post-mortem. Middle: The PET tracer 18F-AV1451 clearly visualises the amount of pigment in a healthy control and a patient with PD. Right: 18F-FDOPA PET shows marked bilateral loss

Patients with Parkinson's disease (PD) have lost approximately 50% of their dopamine nerve terminals in the basal ganglia at the time of diagnosis, which can be accurately imaged using ^{18}F-FDOPA PET scans. It has been proposed that PD is a "dying-back" disorder and that the dopaminergic cell bodies are more resistant to damage. This concept is important in the context of future neuroprotective treatments, since surviving cell bodies may be able to regenerate their terminals. However, until recently we have been unable to directly image *in vivo* the dopamine cell loss in the substantia nigra. In 2015, we implemented the PET tracer ^{18}F-AV-1451, which binds to the pigment neuromelanin. This pigment is responsible for the dark coloration of dopamine neurons. When dopamine neurons die during the course of PD, the amount of pigment decreases. Using ^{18}F-AV-1451 PET and DaT scans, we have now demonstrated that early-to-moderate stage PD patients have lost 50% of their dopamine terminals but only 30% of the pigment in the substantia nigra [Hansen 2016]. This is the first direct *in vivo* evidence that the dopamine terminals are more severely affected than the cell bodies.

Many other neurotransmitter systems are known to degenerate in PD, including the noradrenergic neurons of the locus coeruleus. Due to the lack of suitable noradrenergic tracers, we recently implemented the PET tracer ^{11}C-MeNER, which binds to specific transporters in noradrenergic terminals. We have demonstrated that PD patients display a marked decrease of ^{11}C-MeNER signal in several high-binding regions including the thalamus and in the locus coeruleus itself [Nahimi et al, J Nucl Med 2017; Sommerauer et al, 2017 under preparation]. In on-going studies, we are now studying how noradrenergic damage is related to important symptoms in PD, including sleep disorders and dementia.

It has been hypothesized that the initial misfolding of pathological proteins in PD occurs in the autonomic nerve terminals of the gut and other internal organs many years prior to onset of motor symptoms. Post mortem studies have corroborated that the parasympathetic nuclei in the lower brain stem show characteristic pathology in the earliest stages of PD. However, no imaging tools have been able to show parasympathetic damage *in vivo*. We have validated the PET tracer ^{11}C-donepezil as a marker of cholinergic nerve terminals in the gut, and shown that the majority of PD patients exhibit decreased PET signal in the small and large intestine [Gjerløff 2015+ Fedorova 17]. Longitudinal studies are on-going to track the progression rate of this parasympathetic loss and to study the relationship with important symptoms, including constipation and perturbed peristalsis in PD.

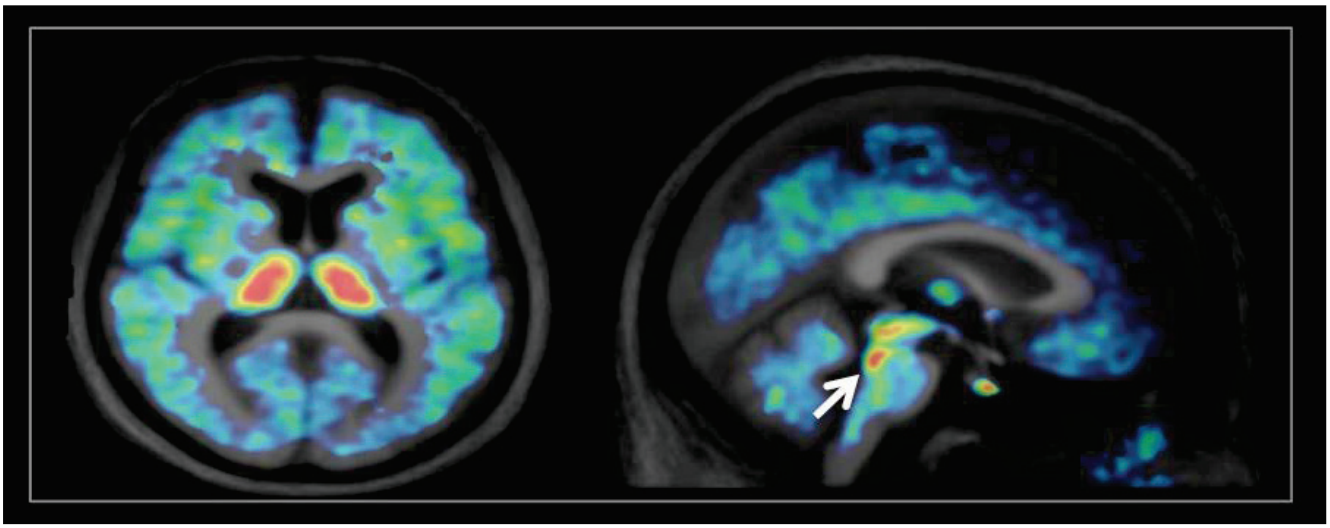


Figure 2. The noradrenergic system can now be imaged using 11C-MeNER PET. PD patients show a marked decrease of this tracer in the thalamus (left) and in the noradrenergic locus coeruleus it self (right; arrow).

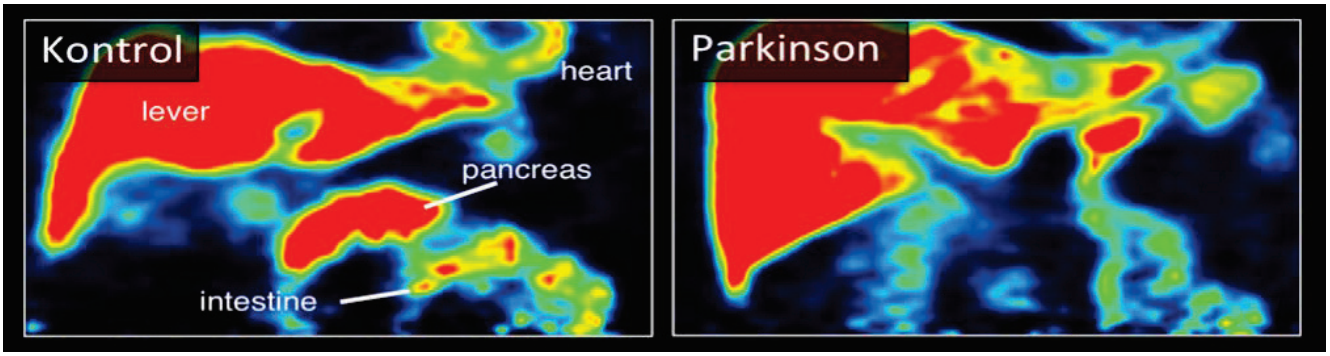


Figure 3. 11C-donepezil is a marker of cholinergic nerve terminals and may be the first method to image loss of parasympathetic terminals in the gut. Abdominal organs in a healthy control subject (left) and a PD patient (right) imaged with 11C-donepezil

Research in Alzheimer's disease

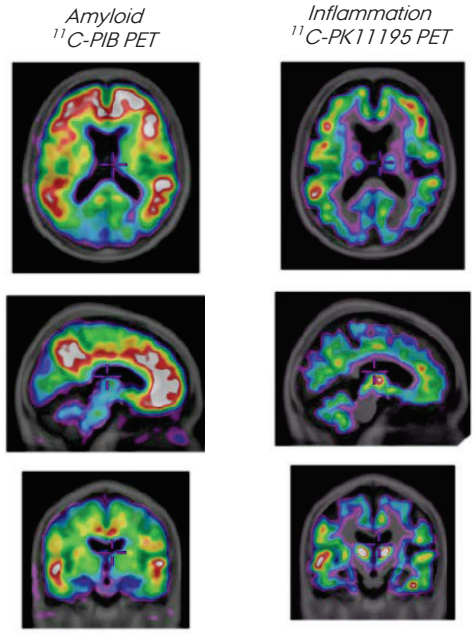
David Brooks, Professor, MD, DMSc

It is now accepted that, along with abnormal aggregation of the proteins β-amyloid and tau, inflammation in the form of microglial activation is part of the pathology of Alzheimer's disease. The exact relationship between these pathologies is still uncertain as they overlap in their spatial distribution but it is generally thought that β-amyloid plaques preceed and tau tangle formation and it is the latter that leads to nerve death and cognitive dysfunction.

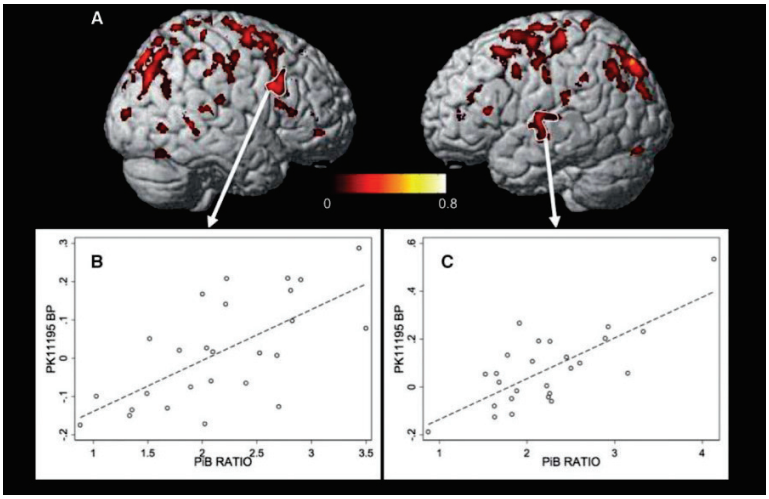
We have been studying levels of β-amyloid fibrils with ^{11}C-PiB PET, tau tangles with ^{18}F-AV1451 PET, and inflammation with ^{11}C-PK11195 PET in healthy controls, subjects with isolated memory impairment (mild cognitive impairment – MCI), and early Alzheimer disease (AD). We have found that two thirds of MCI cases show evidence of amyloid deposition and 80% of these have areas of brain inflammation. Levels of cortical inflammation β-

amyloid are correlated and inflammation, but not β-amyloid levels correlate with cognitive deficit. This work has now been reported (P Parbo et al. Brain 2017; 140 (7): 2002-2011). In healthy controls around one third in their seventh decade who carry the ApoE4 gene show amyloid deposition but this was not seen in those who were ApoE4 negative. Amyloid could be seen in the absence of inflammation. (F Husum Mårup – in preparation).

The relationship between β-amyloid plaques and tau tangles is complex as their distributions overlap but are different. Amyloid plaques can be seen without tau tangles in MCI but nearly all cases with tau also show amyloid. Tau tangles tend to target mesial temporal cortex and amyloid frontal and cingulate areas but both pathologies can be found in all brain areas. There was no clear correlation between levels of tau and inflammation in our series but tau levels correlated with cognitive decline (P Parbo – in preparation). The MCI cohort of 42 subjects and healthy normal controls are being followed longitudinally and will be scanned again.

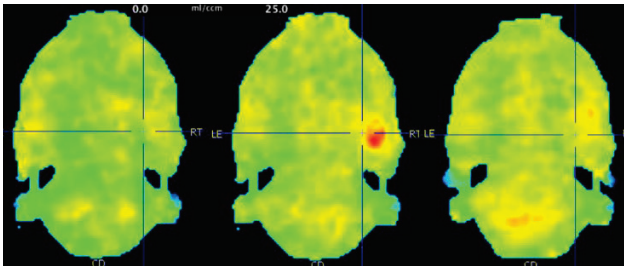


Correlation between amyloid load and inflammation in MCI

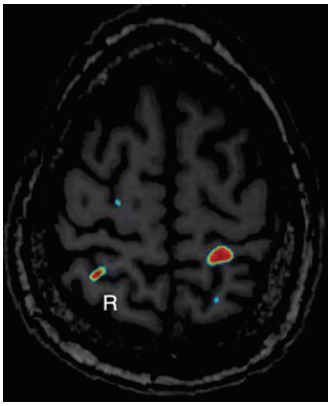


Imaging glutamate ion channel activation

GE179 PET is a use-dependent marker of NMDA glutamate ion channels. In rats, we have shown with PET that electrical stimulation of the hippocampus leads to focal uptake of GE179 that can be blocked with prior administration of ketamine. This confirms that GE179 is binding to the phencyclidine site in the glutamate ion channel (A Khalidan Viholm – PhD thesis). Subsequently we have scanned 10 cases of drug resistant focal epilepsy and 18 healthy controls with GE179 PET. Eight of the ten epilepsy cases showed foci, often multiple, of increased glutamate ion channel activity – some of which correlated with their EEG foci. No foci were seen in the healthy controls. We conclude that GE179 PET reveals networks of abnormal glutamate ion channel activity in cases of resistant epilepsy and may be useful for idenfiying subjects at risk of seizures after brain injury.



GE179 uptake after hippocampal stimulation in the rat
A Khalidan Viholm – PhD thasis



Two foci of GE179 uptake in an epilepsy case.
A Khalidan Viholm – PhD thesis

Research in REM sleep behavior disorder and prodromal Parkinson's disease

Nicola Pavese, MD, PhD, Associate Professor, and Morten Gersel Stokholm, MD, PhD Student

Idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is a sleep disorder characterized by abnormal motor activity during REM sleep, a sleep phase where, normally, an almost complete paralysis of the body occurs. Since REM sleep is closely associated with dreaming, iRBD patients characteristically 'act out" their dreams.

Over the last decade, there has been growing scientific interest in this condition because the clinical follow-up of these patients has shown that the majority of them develop Parkinson's disease or Dementia with Lewy body later in life. Therefore, it is very probable that these patients could already have some of the brain abnormalities typical of Parkinsonian disorders even before the onset of the classical symptoms of these conditions. A similar situation is likely to occur in subjects who carry mutations in one of the genes associated with Parkinson's disease, such as the LRRK2 gene and the glucocerebrosidase (GBA) gene.

We use neuroimaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance (MRI) in iRBD patients and asymptomatic carriers of genetic mutations linked to Parkinsonism to understand the earliest mechanisms underlying the development of Parkinson's disease and related disorders and possibly discover therapeutic targets to halt or delay disease progression. Using PET with 11C-PK11195, a ligand that binds to brain cells (activated microglia) involved in neuroinflammation, we have recently discovered that iRBD patients have increased levels of neuroinflammation in brain areas typically involved in Parkinson's disease, including the substantia nigra (Figure 1) and, to a lesser extent, the putamen and caudate nuclei, suggesting that neuroinflammation occurs in the early stages of the development of Parkinsonian syndromes [Stokholm et al., Lancet Neurology, 2017].

In iRBD patients, we have also detected the presence of activated microglia in the visual associative cortex of the occipital lobe, the area of the brain where visual images are processed and elaborated.

Finally, we have found evidence of neuroinflammation also in the substantia nigra of asymptomatic carriers of mutations in the glucocerebrosidase (GBA) gene and the LRRK2 gene (Figure 1), once again suggesting that neuroinflammation is an early event in these conditions and could represent a potential therapeutic target [unpublished data].

Currently, we are carrying out a clinical and imaging follow-up of the iRBD patients who took part in our previous studies to better understand the temporal relationship between neuroinflammation

and the degenerative process in the prodromal phase of parkinsonism and to identify early brain changes that can be used to predict time to onset of manifest disease and possibly the clinical subtype of parkinsonism (e.g. Parkinson's disease or Dementia with Lewy body).

These studies are founded by the Danish Council for Independent Research.

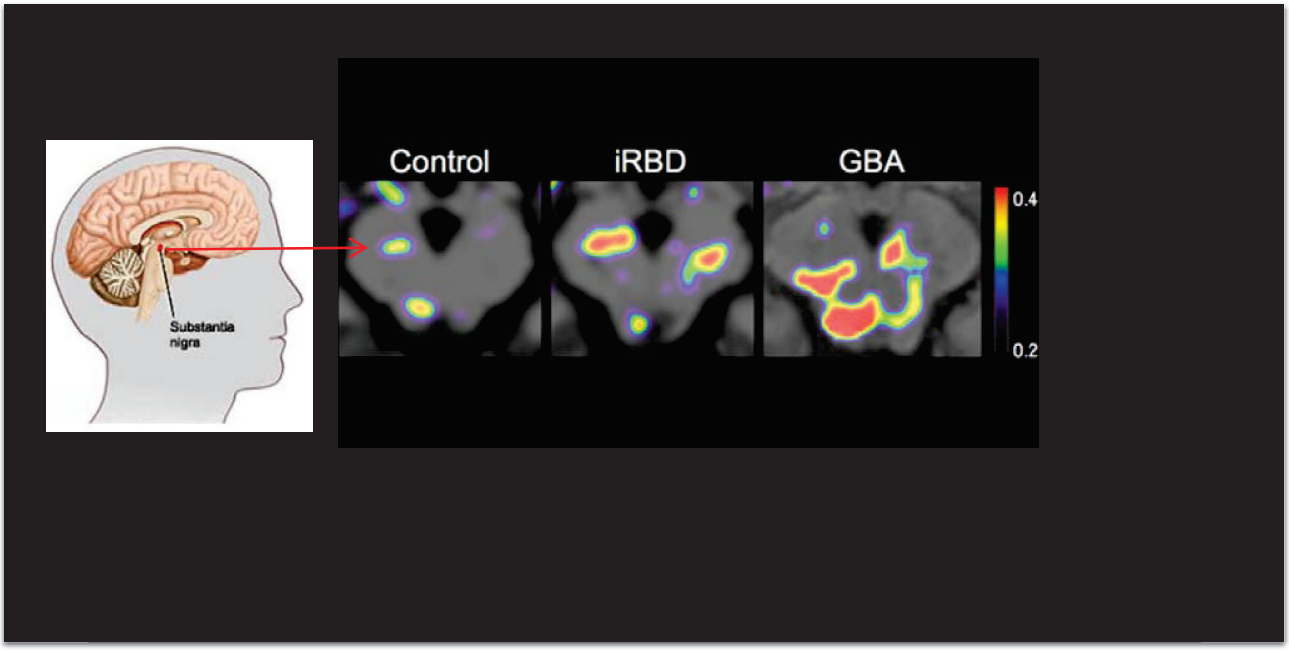


Figure 1. ^{11}C-PK11195 binding at the level of the substantia nigra in a control subject, in a patient with idiopathic rapid eye movement sleep behavior disorder (iRBD), and in an asymptomatic carrier of glucocerebrosidase gene mutation (GBA). Increased binding is noticeable in the iRBD patient and in the GBA mutation carrier.

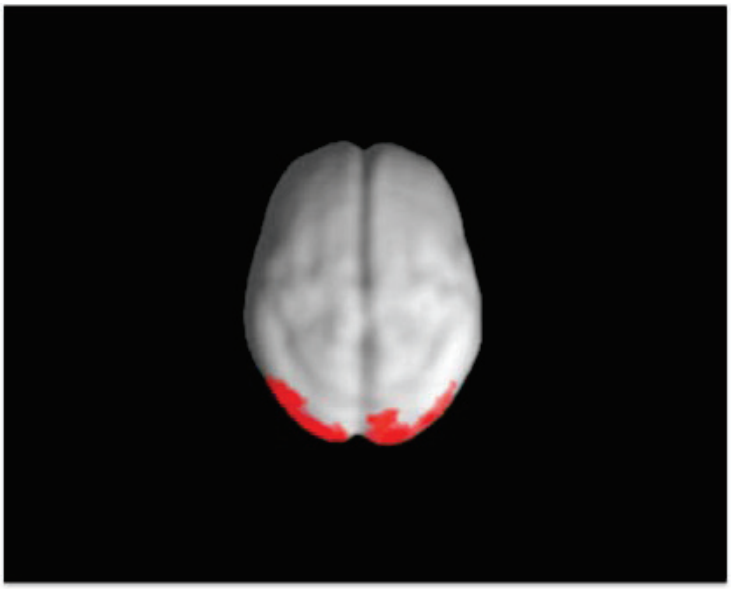


Figure 2. [Stokholm et al. 2017 submitted]. This finding could explain the difficulties that iRBD patients seem to have in tests assessing visuospatial skills.

Nuclear cardiology

Kirsten Bouchelouche, Chief Physician, Associate Professor, DMSc and Lars Tolbod Poulsen, Physicist, PhD

Department of Nuclear Medicine & PET-Centre is a core facility at Aarhus University Hospital in the diagnostic clinical evaluation of patients with cardiac diseases. During the past many years we have performed more than 1000 myocardial perfusion imaging (MPI) studies annually in patients with suspected or known ischemic heart disease, and approximately 900 MUGA studies annually for monitoring cardiac function (ejection fraction) during chemotherapy. Focusing on a multidisciplinary approach to patient care and research, we have a long-standing and very close collaboration with the Departments of Cardiology and Oncology at Aarhus University Hospital.

High quality scientific up-front research in nuclear cardiology is necessary, and the aim of our cardiac research is to develop, advance and evaluate new and established nuclear cardiac imaging methods in order to optimize and improve the diagnosis, management and clinical out-come of patients with various cardiac diseases including, ischemic heart disease, heart failure, diabetes and cardiomyopathies. The availability of two cyclotrons on site and a highly specialized radiochemistry laboratory gives us the possibility to work with both established, up-front, and novel PET-imaging agents and methods. ^{82}Rb-PET is used for evaluation of myocardial perfusion, both in clinical routine and in research studies. ^{18}F-FDG cardiac PET in combination with ^{82}Rb-PET is used clinically and in research projects for evaluation of myocardial viability. The routine use of hyperinsulinemic-euglycemic clamp for viability scans has been introduced and ^{82}Rb and ^{18}F-FDG scans are performed in one session. Other PET tracers used in cardiac research studies include ^{15}O-water PET, ^{11}C-acetate, ^{11}C-palmitate, ^{11}C-PIB and ^{123}I-MIBG. Furthermore, the Department is involved in the development of the aQuant software for automation in cardiac imaging and extraction of hemodynamic and volumetric data. The availability of automated analysis for ^{15}O-water and ^{11}C-acetate PET is currently being utilized in several clinical trials and studies. This part of the program is led by Professor Jens Sørensen and post.doc. Hendrik Johannes Harms. Our extensive cardiac research program is in close collaboration with Department of Cardiology at Aarhus University Hospital, and with international research groups in Uppsala, Amsterdam and Boston. More information about our projects and published results in nuclear cardiology can be found on our website: www.en.auh.dk.

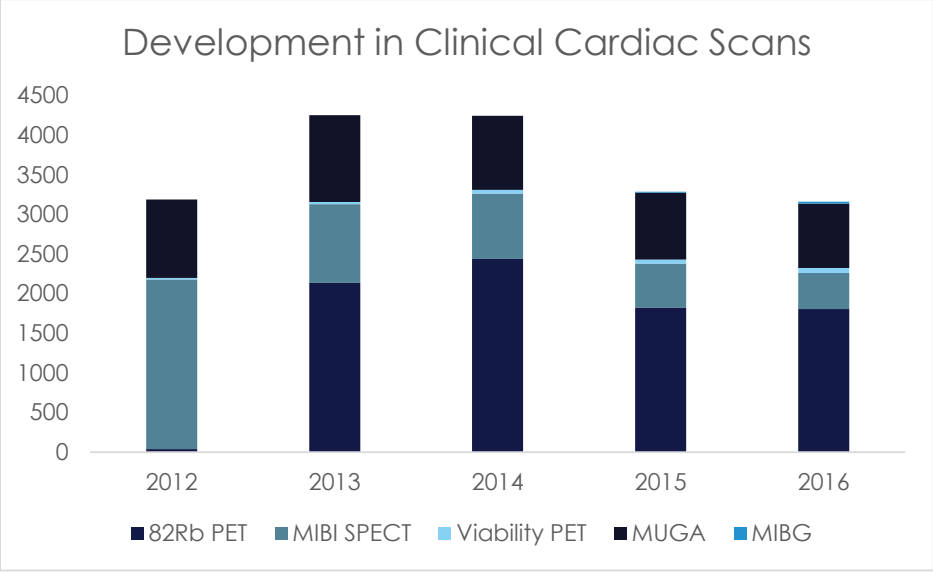


Figure 1: Development in cardiac scans on clinical indication over the last 5 years. ^{82}Rb PET is steadily replacing myocardial scintigraphy as the method of choice for myocardial perfusion imaging. Same day ^{82}Rb and hyperinsulinemic-euglycemic clamp ^{18F}-FDG.

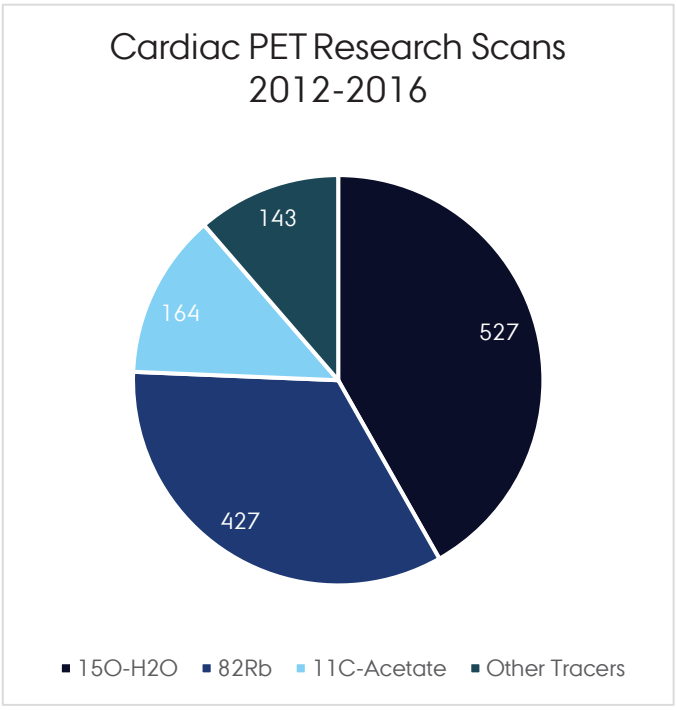


Figure 2. Total number of cardiac research scans over the last 5 years.

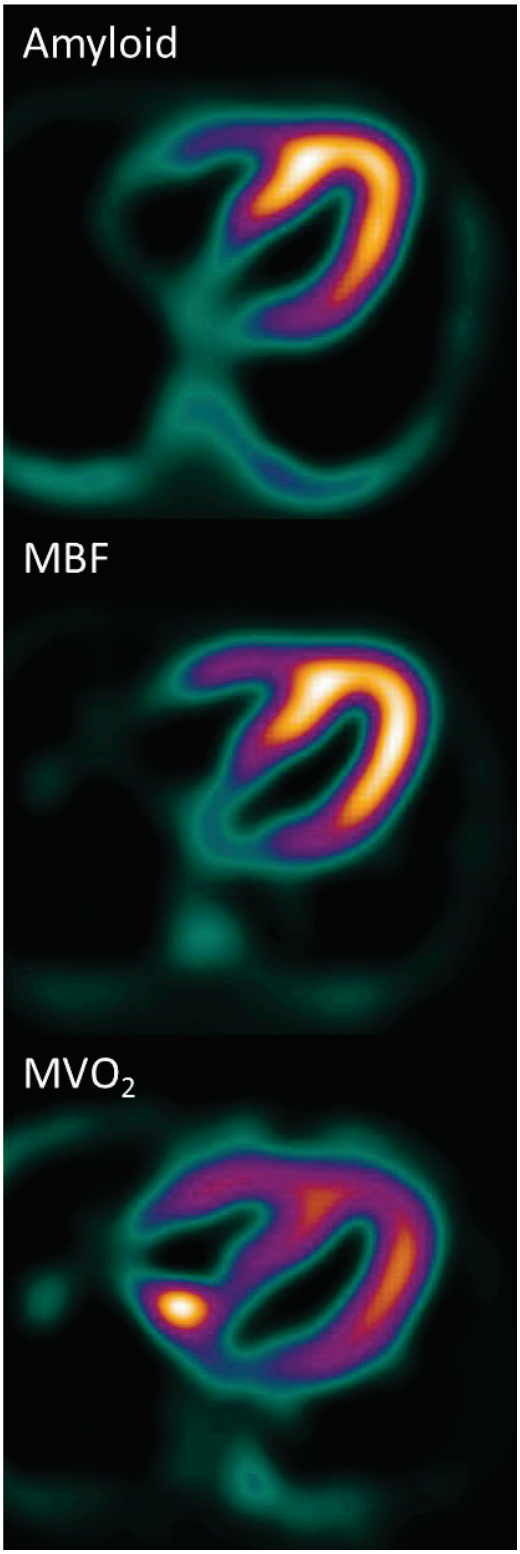


Figure 3. Characterization of cardiac amylodosis patient. Build-up of amyloid in the heart visualized by ^{11}C-PiB (top). Myocardial Blood Flow (MBF) and oxygen consumption (MVO2) (middle and bottom) measured by ^{11}C-acetate.

Nuclear oncology

Kirsten Bouchelouche, Chief Physician, Associate Professor, DMSc

PSMA PET/CT in prostate cancer

Prostate cancer (PCa), the most common cancer in men, is the second leading cause of cancer deaths among men. The clinical management of PCa is challenging due to the variable pathological and clinical behavior of the disease. Therefore, the treatment of PCa shall be optimized and specific to each patient in order to improve their clinical outcomes. Accurate staging of PCa is of high importance for treatment decisions and patient management. Increasing attention is being given to the development and improvement of precision medicine in oncology, where pharmaceutical therapies are tailored to the particular characteristics of the individual cancer patient. Precision medicine, also called personalized medicine, requires an accurate and precise characterization and location of the cancer.

In recent few years, there has been increasing focus on prostate-specific membrane antigen (PSMA) as a target for both imaging and therapy in PCa. PSMA is highly expressed by all PCa, and its expression increases with tumor aggressiveness, metastatic disease and disease recurrence. However, despite its name, PSMA is also expressed in some healthy tissues, in the neovasculature of other malignant tumors, and in few benign conditions. Introduction of ^{68}Ga-PSMA PET/CT for imaging of PCa is among the most remarkable developments in nuclear medicine in the recent years, and the use of this new PET agent for PET/CT imaging of PCa worldwide has happened in a very short time span of only a few years. PSMA PET/CT has a higher detection rate in PCa than choline PET/CT, which has been the most common used PET agent in PCa for many years.

The Department of Nuclear Medicine & PET Centre, Aarhus University Hospital was the first in Denmark to introduce PSMA PET/CT in clinical routine in PCa patients. PSMA PET/CT is used in high-risk newly diagnosed PCa patients and in patients with biochemical recurrence after primary therapy (prostatectomy, radiation therapy). In patients with disease outside the prostate gland or with local recurrence in the prostate bed on PSMA PET/CT, the clinical management is discussed on the weekly prostate MDT conference with participants from Departments of Urology, Oncology, Pathology, Radiology and Nuclear Medicine & PET Centre. In the first year, 300 PSMA PET/CT scans have been performed, and we expect to scan an increasing number of PCa patients with PSMA PET/CT in the near future. Furthermore, PSMA has the potential to be an excellent therapeutic target in PCa patients. The "Image and treat" strategy is possible with PSMA ligands labeled with radioisotopes for imaging and therapy, and PSMA molecular imaging is paving the way for personalized medicine in PCa. In order to further optimize the evaluation of PCa with PET/CT, new and promising PET agents like ^{11}C-Donepezil and ^{82}Rb are tested in clinical trials in close collaboration with Department of Urology, Aarhus University Hospital and the PET Centre in Uppsala, Sweden.

- In 2016, Department of Nuclear Medicine & PET Centre, Aarhus University Hospital was the first in Denmark to introduce PSMA PET/CT for the clinical management of PCa
- Molecular imaging with PSMA PET is paving the way for personalized medicine in PCa
- "Image and treat"theranostic strategy is possible with PSMA ligands labeled with radioisotopes for imaging and therapy

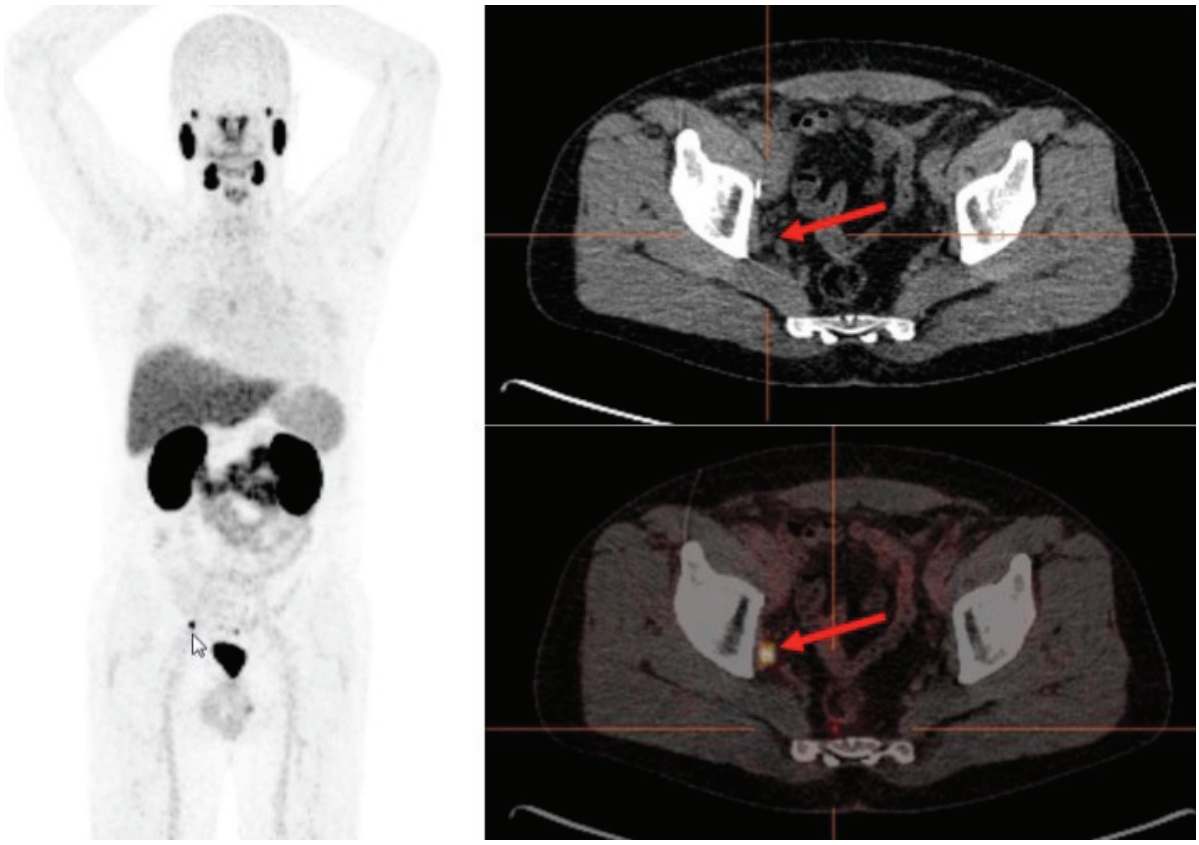


Figure 1. The images illustrate that 68Ga-PSMA PET in PCa can detect very small lymph node metastases not suspicious on CT.

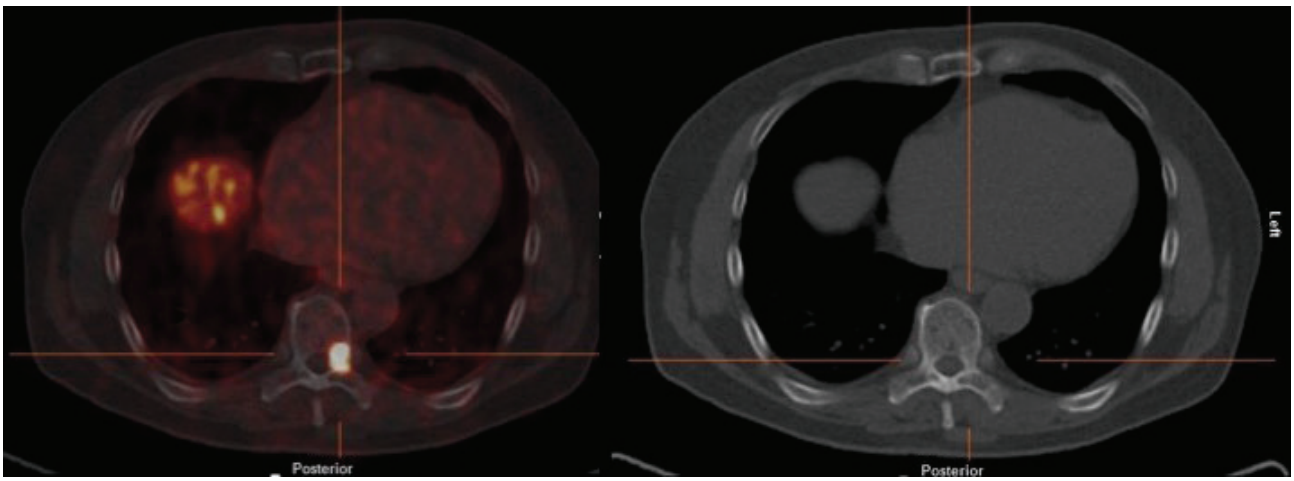


Figure 2. PSMA PET can detect bone metastases in PCa without changes on CT.

Metabolism

Lars Gormsen, Associate Professor, MD, PhD and Mikkel H. Vendelboe,, MD, PhD

Metabolism from a PET perspective

The Department of Nuclear Medicine & PET- Centre has a long-standing and excellent collaboration with the Departments of Cardiology and Endocrinology studying intermediary metabolism, function and perfusion of the heart. This has been done by ^{18}F-FDG PET and MIBI SPECT, well-established techniques that has been accessible in Aarhus since the late 1990's. More recently, we have expanded the scope of this basic metabolic research to other tissues and clinical settings whilst applying both the established models and tracers as well as more exploratory tracer techniques.

Broadly speaking, PET/CT is uniquely suited to study metabolic processes taking place in tissue not readily accessible by blood sampling (e.g. the brain, heart or liver) and may also provide an overview of whole-body metabolism of drugs (e.g. ^{11}C-metformin) and metabolites (e.g. ^{11}C-palmitate) that reflect particular disturbances in diseases characterized by dysfunctional metabolism (diabetes, heart failure and inflammatory diseases). At the Section for Metabolic Research at the PET-Centre, our main aims for the past 3 years have been focused on 1) acquiring and developing a PET tracer for the most widely prescribed anti-diabetic drug, ^{11}C-metformin, 2) validating and implementing the fatty acid PET tracer ^{11}C-palmitate as well as ^{11}C-acetate to monitor energy consumption, and 3) to use the full armamentarium of PET tracers to study the impact of changes in metabolic environment (hyperketonemia) or intervention with drugs (metformin).

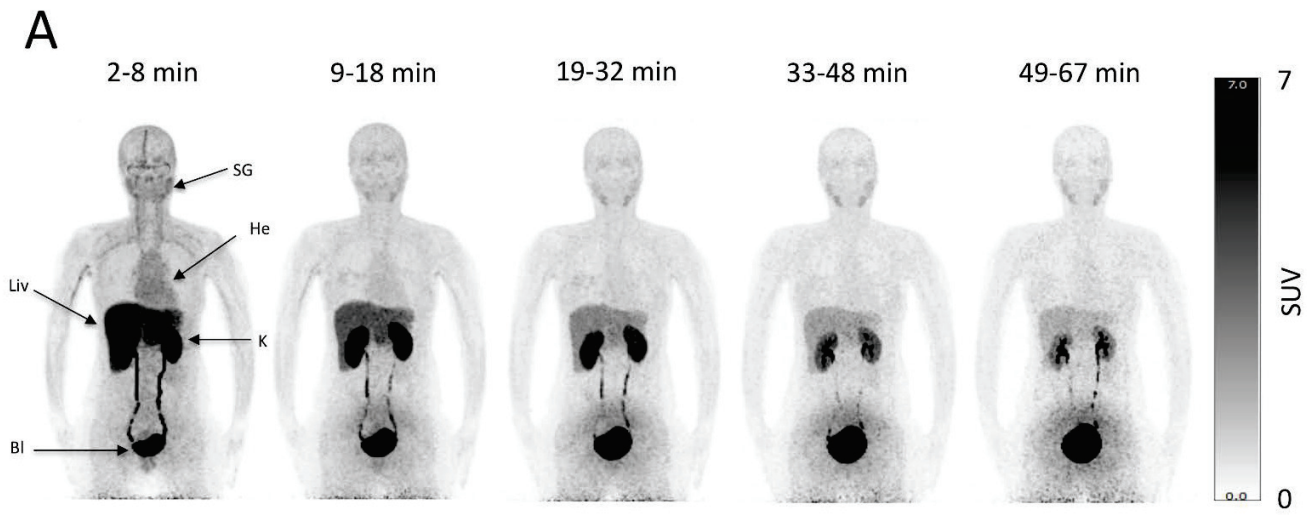


Figure 1. Pseudynamic images of 11C-metformin after i.v. administration.

Greased up ^{11}C-palmitate and fatty acid metabolism

^{11}C-palmitate and ^{11}C-acetate are notoriously difficult PET tracers since they do not differ from native palmitate and acetate in terms of processing by the cells. This indistinguishability from endogenous palmitate and acetate allows for more complex modelling and assessment of re-esterification and oxidation but also results in the formation of radioactive metabolites, which must be

accounted for during the kinetic analysis. At the PET-Centre, we have amassed a large volume of metabolite fraction measurements allowing for population based metabolite correction and image derived input analysis. These tools have been used to demonstrate that hyperketonemia does not modify the fatty acid uptake capacity of myocardial cells. Furthermore, we have conducted a large clinical trial designed to study the effect of 3 months metformin treatment on both cardiac and hepatic metabolism and are in the process of analyzing whether changes in lipid metabolism are independent of concomitant improvement in glycemic status. Preliminary data from that trial indicate that metformin only discretely impacts hepatic metabolism but also that the effect on cardiac metabolism may be more pronounced.

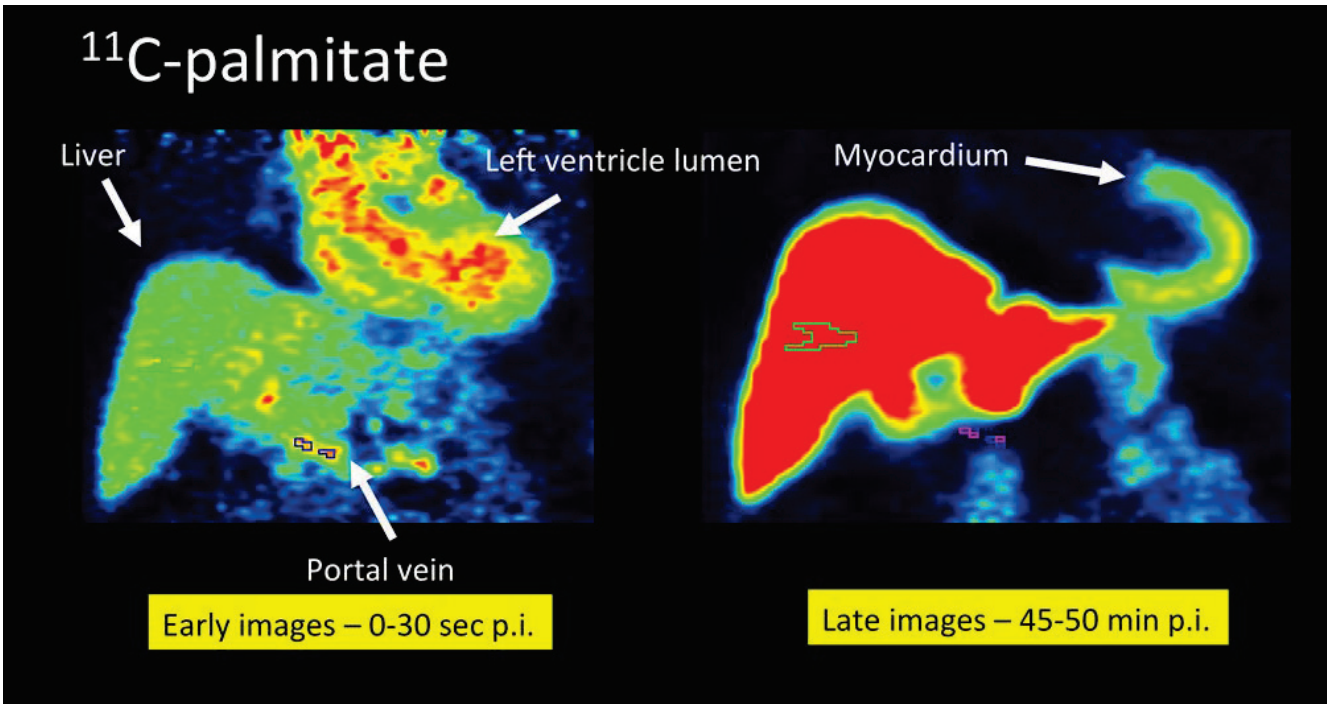


Figure 2. Coronal early and late images of 11C-palmitate. As seen, the portal vein and left ventricle are clearly visible allowing for dual input measurements of hepatic lipid metabolism.

It is cheap and effective. But how does it work? ^{11}C-metformin

Although metformin has been in use for nearly five decades, surprisingly little is known about its mechanism of action. Notably, there is an ongoing discussion as to whether metformin primarily exerts its effects in the liver or if the beneficial effects on glucose- and lipid metabolism also takes place in peripheral tissues like skeletal muscle, heart, and intestines. To address this, we have produced and validated ^{11}C-metformin as a novel PET tracer in collaboration with the Department of Biochemical Pathology. This has allowed us to trace the fate of both orally ingested and intravenously administered metformin. Through a series of studies in animals, healthy volunteers and subjects with mutations in the primary transmembrane carrier of metformin, OCT1, we have demonstrated that the primary target tissue of metformin is in fact the liver and that mutations in OCT1 results in significantly reduced hepatic metformin uptake. In addition, we have demonstrated a small, but not insignificant slower uptake of metformin in the intestines, which indicate that the glucose lowering effect of metformin may

be related to increased uptake of glucose by enterocytes. Branching into the field of oncology, the ^{11}C-metformin PET tracer is currently used to study whether the life-prolonging effect of metformin in patients with breast cancer may be caused by direct uptake of metformin in mammary tumors.

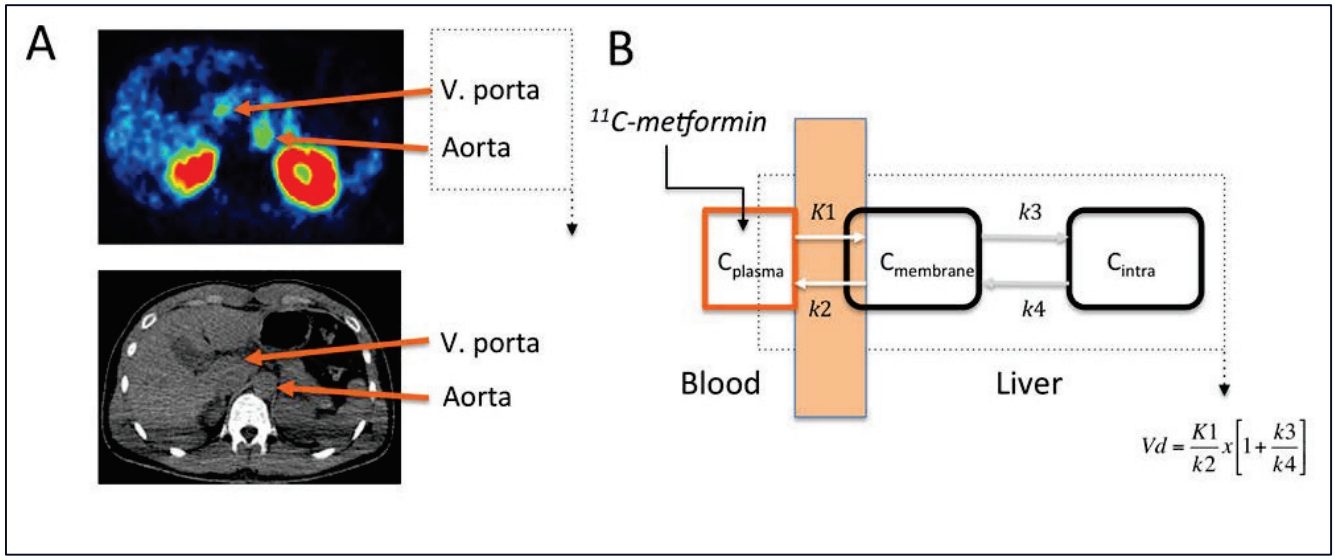


Figure 3. A: Transaxial images of the aorta and porta used to draw VOIs for the input function. B: The kinetic model applicable to metformin kinetics in the liver.

Feast or famine? The effects of hyperketonemia on whole body metabolism

Historically, humans have lived (and survived) in an environment far more hostile and with less easy access to foods. The resultant periods of fasting have been characterized by formation of ketone bodies by the liver, short-chain fatty acids readily oxidized by most tissues including the brain and heart. Recently, it has been postulated that the presence of elevated levels of circulating ketone bodies may ameliorate the adverse effects of a range of dysmetabolic conditions such as myocardial ischemia, heart failure and cognitive defects associated with dementia. To test the hypothesis that ketone bodies - when present in significant quantities - supplant glucose as a preferred oxidative fuel by the heart and brain, we conducted studies in healthy volunteers who were subjected to infusion of exogenous ketones. As expected, myocardial glucose consumption was halved by hyperketonemia, whereas the effect on cerebral uptake of ketone bodies was far less pronounced. These results indicate that ketone body uptake by the heart is facilitated by transporters present in the myocardial tissue at all times, whereas the cerebral uptake may be facilitated by a more adaptive system of carriers. We are therefore currently in the process of setting up a large clinical trial in which the effect of a month-long treatment with SGLT2 inhibitors – known to induce a 3-fold increase in circulating ketone bodies – on cardiac, cerebral and renal metabolism is studied. It is our hypothesis, that a discrete but sustained hyperketonemia results in a more pronounced shift from glucose and fatty acid oxidation towards oxidation of ketone bodies and that this shift may explain the improved survial among patients taking these newer anti-diabetic drugs.

Inflammation

Lars Gormsen, Associate Professor, MD, PhD

PET/CT and rheumatic diseases: Expanding

The diagnosis of inflammatory diseases like sarcoidosis, vasculitis, arthritis and polymyalgia rheumatica is challenging and are often based on more or less well defined biochemical, histological and clinical criteria. Historically, this has not been considered a major clinical problem since the range of treatment options has been limited to varying doses of corticosteroids. However, this is rapidly changing. Today, several biological treatment options targeting specific steps of the inflammatory cascade exist rendering long-term treatment far less prone to unwanted side effects. The flip side of this explosion in treatment options is the price of disease modifying rheumatoid drugs, which has increased more than 10-fold. Such an increase in the price of treatment has spurred a renewed interest in imaging modalities suited to diagnose and monitor the often-discrete metabolical changes associated with inflammation. As a reflection of this, referrals to the Department of Nuclear Medicine & PET-Centre on suspicion of inflammatory diseases has surged from a few per month to nearly 10 per week. Referrals can broadly be divided into the following:

Large-Vessel Vasculitis (LVV)

LVV is a potentially fatal inflammatory disease involving large arteries in the thorax, abdomen and head-neck region. Symptoms mimic occult cancer and may develop over months making a clinical diagnosis difficult. When LVV is suspected, treatment with high-dose corticosteroids must be initiated within days preceded by a sub-acute 18F-FDG PET/CT. In collaboration with the Department

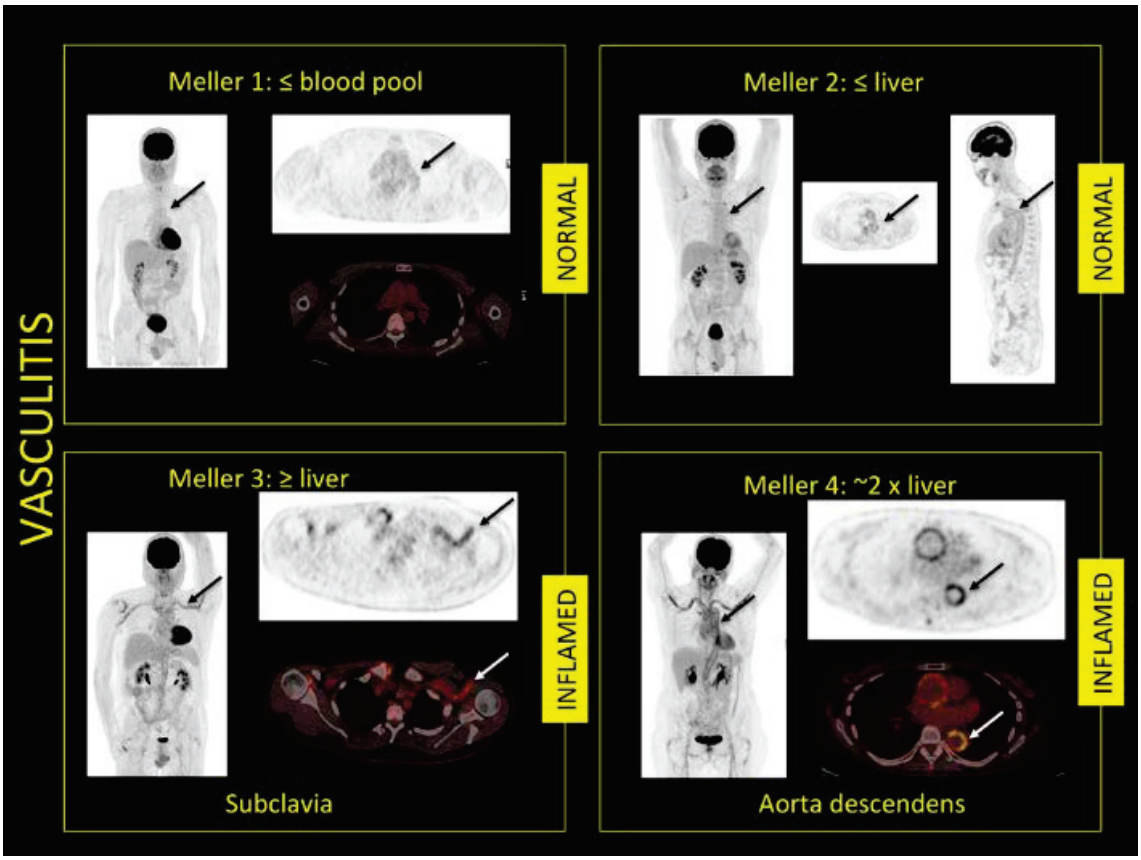


Figure 1

of Rheumatology, we therefore performed a study to investigate how high-dose corticosteroid therapy impacts on 18F-FDG uptake by inflamed vessels. That study revealed that a diagnostic window of 3 days exists in which 18F-FDG PET/CT still has an excellent diagnostic accuracy despite concomitant corticosteroid therapy. This finding was put forward as a topic of interest at the Conference of European League against Rheumatism (EULAR) and is now a general national recommendation for referral of patients with suspected LVV.

Polymyalgia rheumatic (PMR)

PMR is characterized by the same vague symptoms as LVV but also by proximal extremity fatigue and pain. Whereas the vessel walls are affected in LVV, the bursae and tendon adhesion points are severely inflamed in PMR, which is readily visualized by 18F-FDG PET/CT. In a subset of patients, both vessel wall inflammation and bursitis/enthesitis co-exists.

The choice of both initial treatment and treatment duration is dependent on whether the patient is diagnosed with PMR, LVV or a combination of both and the number of referrals is therefore increasing rapidly.

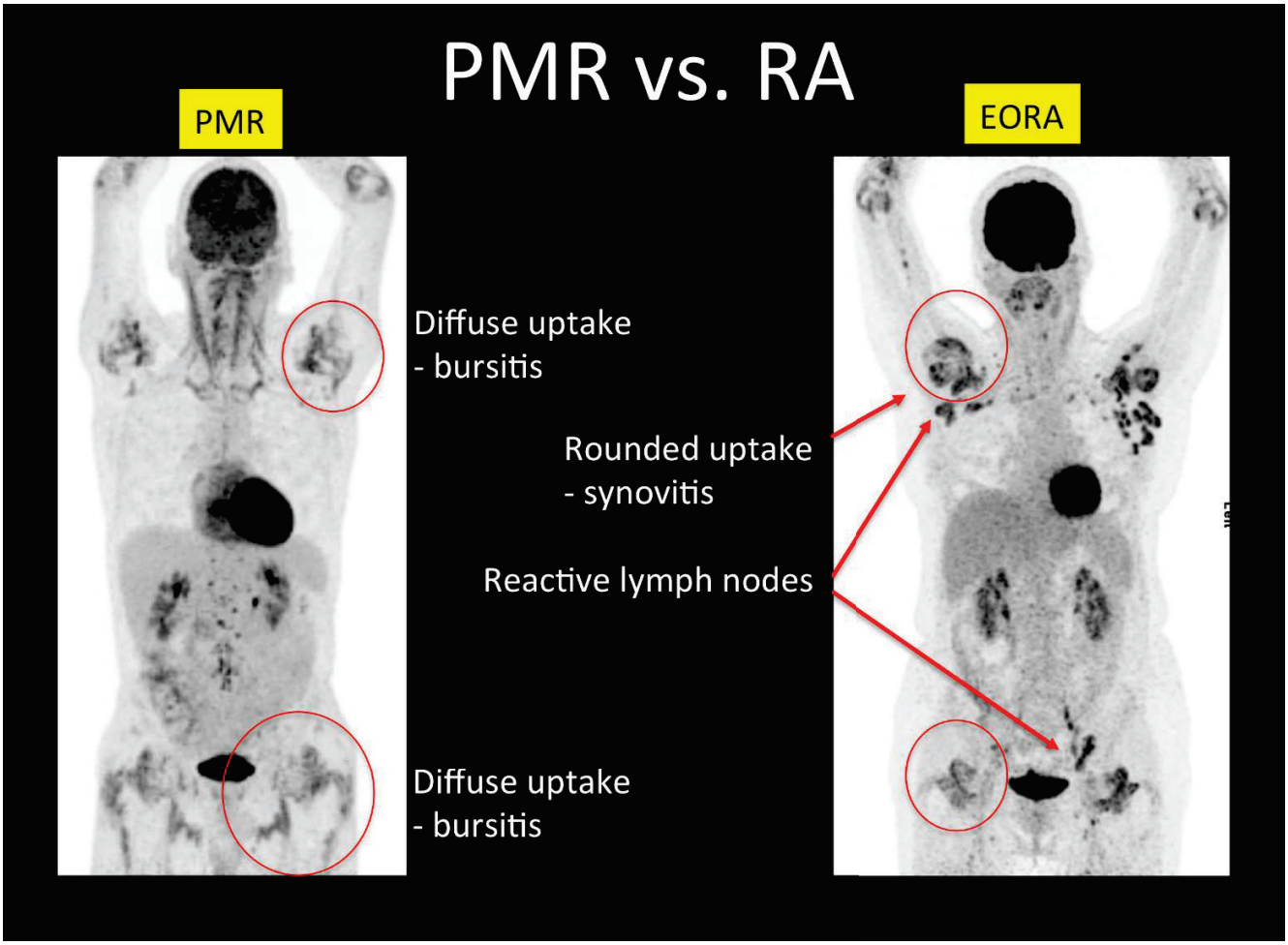


Figure 2

Sarcoidosis

Sarcoidosis is known as the great imitator of diseases and ^{18}F-FDG PET/CT is therefore not recommended in the initial evaluation of patients with suspected sarcoidosis. However, 18F-FDG PET/CT is an excellent tool to visualize active disease burden in patients with known sarcoidosis and is increasingly used to supplement subjective assessment of disease progression. In addition, sarcoidosis involvement of the myocardium is a potentially fatal complication, which can be visualized by ^{18}F-FDG PET if the patient is properly prepared with a starch-poor diet and 18 hours of fasting. In particularly challenging cases, a second 68Ga DOTATOC PET is performed to verify the existence of sarcoid granulomas in the myocardium.

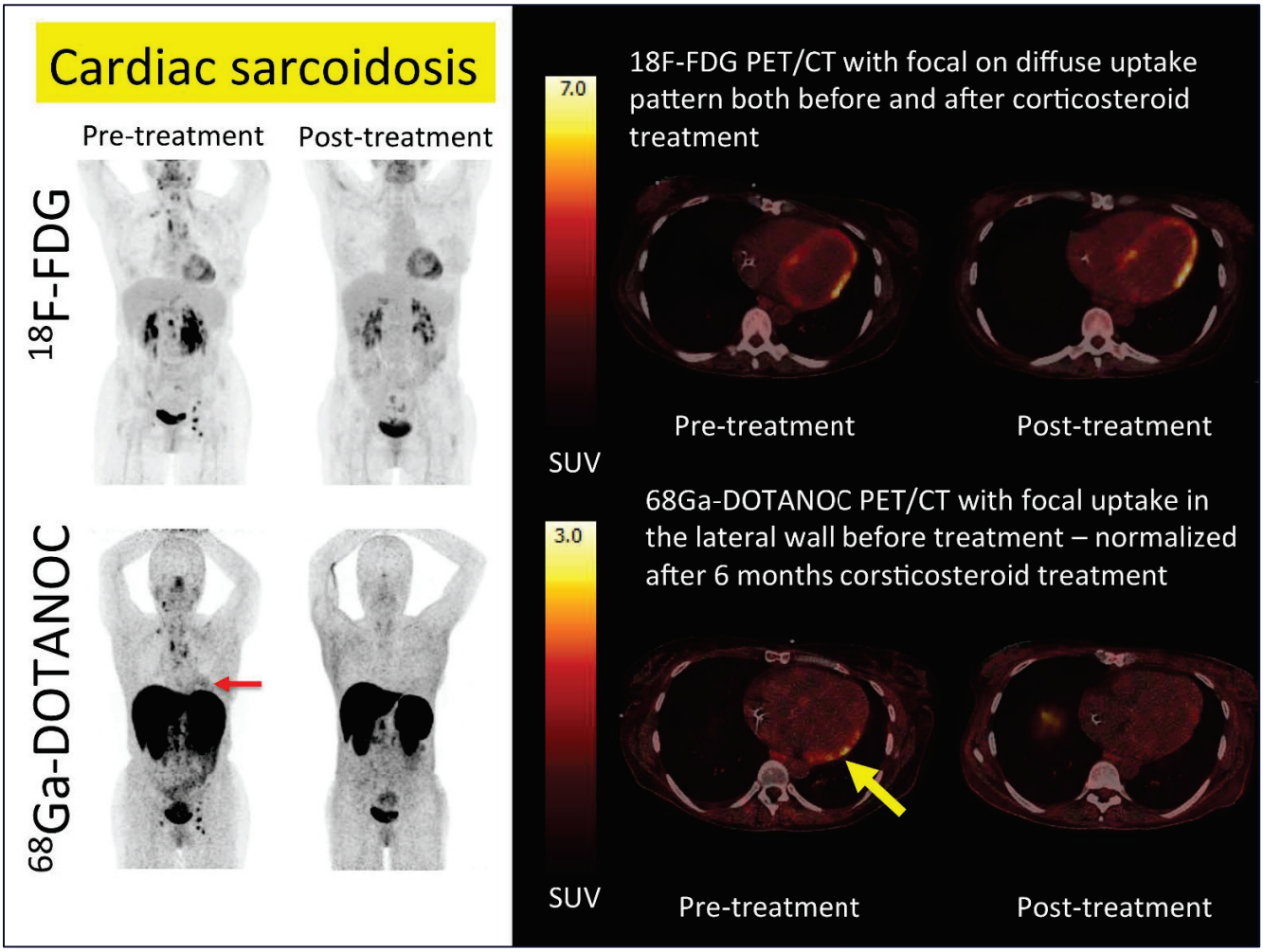


Figure 3

Other inflammatory diseases

Elderly onset rheumatoid arthritis (EORA) has overlapping symptoms with PMR but has a distinctively different ^{18}F-FDG uptake pattern. In that disease, synovitis of the wrists, shoulders and hips is particularly prominent on ^{18}F-FDG PET/CT. Synovitis is not an uncommon observation and is reported

whenever it may impact on the patients' future treatment. IgG4 related diseases are also characterized by metabolically active inflammatory cells and PET/CT may aid in differentiating e.g. vasculitis from IgG4 related retroperitoneal fibrosis.

Perspectives

Patient-tailored biological treatment of rheumatoid diseases is ever expanding and increasingly expensive. In light of this, we expect a growing number of referrals aimed at 1) establishing definite diagnosis of vasculitis and PMR, and 2) monitoring treatment response in patients undergoing biological treatment. Particularly the latter indication for PET/CT may prompt development of more specific inflammation tracers than 18F-FDG

Pediatric nuclear medicine

André Dias, MD, Specialist Registrar and Jørgen Frøkiær, Professor, Head of Department, DMSc

At the Department of Nuclear Medicine and PET Centre we have a longstanding close collaboration with the Department of Pediatrics in order to provide the most optimal diagnostic procedures to sick children. The annual productivity has over the past years been around 500 examinations, but PET/CT examinations are increasing.

The use of PET/CT as an evaluation tool of pediatric cancers has been steadily increasing in the last few years. In addition to the traditional use of 18F-Fludeoxyglucose (18F-FDG) PET/CT as a tracer for imaging of pediatric tumors including lymphomas and sarcomas, the Department of Nuclear Medicine and PET Centre has now accumulated a considerable experience in using 18F-fluoro-ethyl-tyrosine (18F-FET) PET/CT to evaluate brain/neurological tumors.

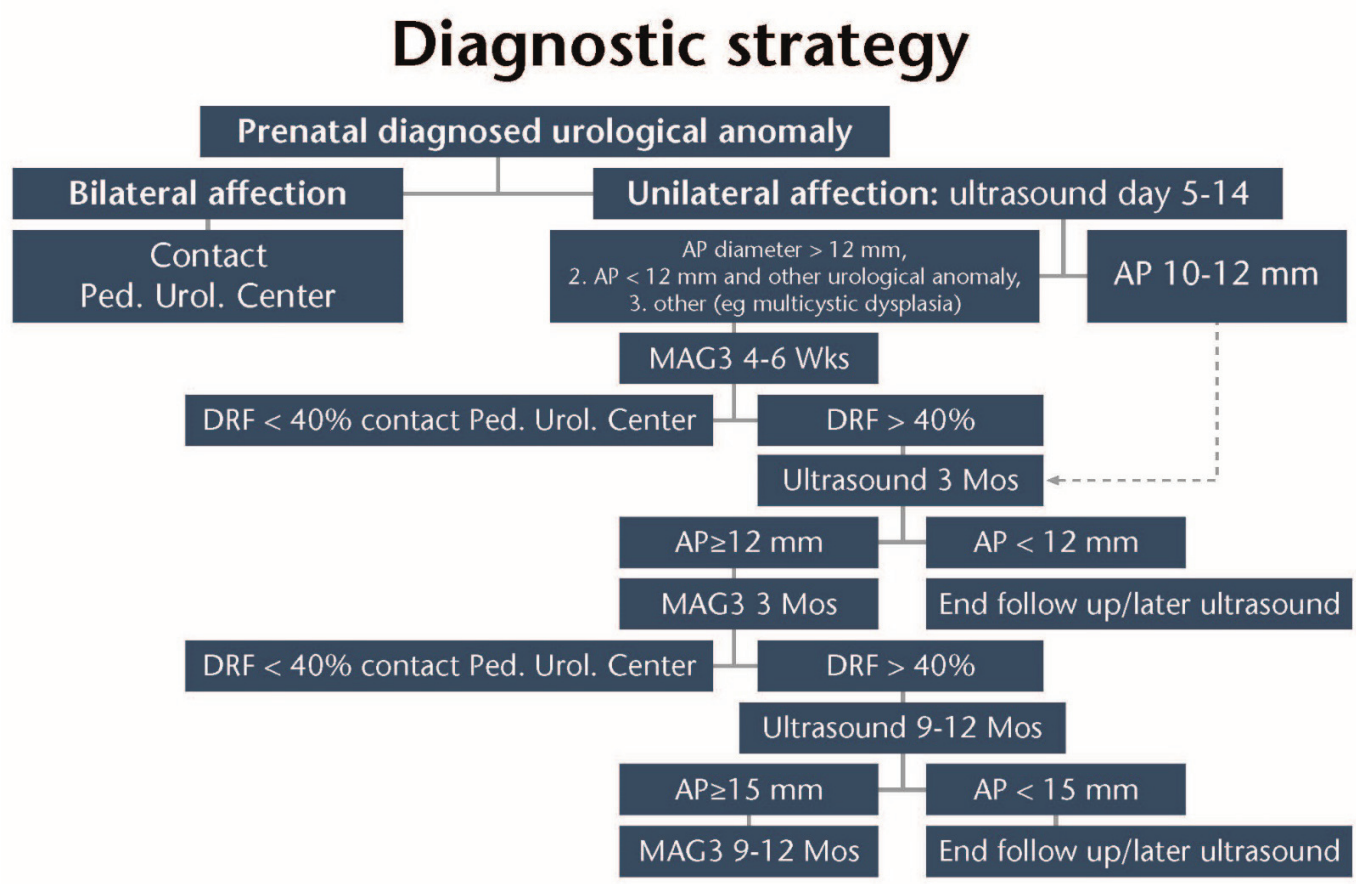
Furthermore, the Department of Nuclear Medicine and PET Center participates weekly in pediatric-oncology multidisciplinary conferences. At these meetings relevant pediatric oncological patients are discussed amongst medical peers, including a review of diagnostic imaging, in particular MRI and PET/CT and a common decision is taken regarding treatment possibilities. At the moment mostly neurological/brain cancers patients are discussed, but the clinicians at the Department of Pediatrics are free to include any patients they feel relevant to discuss in a group setting.

Another particularly important group of patients, who presently take up most of our examination slots at our Department are individuals with congenital malformations of the kidneys and urinary tract, which are responsible for 20-30% of all prenatally detected anomalies and are the most common cause of chronic kidney disease in childhood.

Prenatal hydronephrosis is one of the most common birth defects and postnatal evaluation of prenatally detected hydronephrosis remains a topic of debate and controversy. However, the understanding that any degree of prenatally detected hydronephrosis can be associated with significant uropathy can set the stage for deriving a consistent approach to the evaluation of these infants in order to prevent deterioration of renal function and urinary tract infections.

Renal imaging plays a central role in the investigation and follow-up of these infants and includes both ultrasonography and reno-scintigraphies. Although some prenatally hydronephrotic kidneys resolve spontaneously after birth, in many children hydronephrosis and dilatation of the urinary tract persists and are therefore subjected to long-term followup. This also appllies to individuals who are being operated due to progressive dilatation/obstruction of the urinary tract.

A multidisciplinary team approach is required to diagnose and treat these complex disorders. At Aarhus University Hospital we have had multidisciplinary conferences for almost 30 years on this group of patients. Together with pediatric nephrologists, pediatric urologists, pediatric uroradiologists we as nuclear medicine physicians participate in the careful planning and followup of these patiens. Based on our close international cooperation within this challenging group of patients, our strong research profile including both basic, preclinical and clinical research within this area our department provides the highest international standard in nuclear medicine diagnostic work-up in these conditions. We have a long-standing close interaction in the EANM Pediatric Committee. Together with colleagues in Denmark we have build a platform with a diagnostic algorhytm for individuals with congenital malformations of the urinary tract which secures rational and safe monitoring of these patiens who often enter a chronic condition with careful follow-up of kidney function with multiple visits and examinations.



Algorhytm for examining children with congentital malformations of the urinary tract.
Modifed after Cortes et al: Ugeskr Laeger. 2006 Jun 26;168(26-32):2544-50

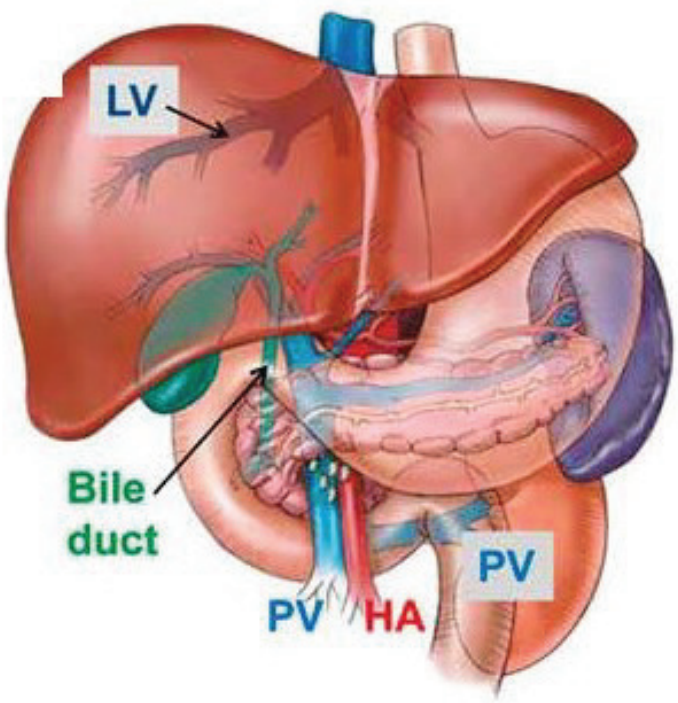
Liver PET

Susanne Keiding MD, Consultant, DMSci, Head of the Liver/PET Group at Aarhus University Hospital

Quantitative Imaging of Liver Functions by PET

The liver plays a key role in the regulation of body metabolic homeostasis, first-pass metabolism of substrates absorbed from the intestines, and hepatobiliary excretion. Impairment of these functions in a patient with liver disease may have serious, often life-threatening consequences. Direct *in vivo* examination is difficult or impossible because of the "hidden" position of the liver between the splanchnic and systemic circulation, its special hemodynamics, and the enterohepatic circulation of bile acids. Consequently, most clinical liver tests are quite non-specific and our understanding of basic liver physiology and pathophysiology bothered by conceptual problems. Some of these challenges can be successfully solved by functional PET, which may benefit therapy of the patients.

The work of the Liver-PET group at AUH focuses on physiologically based quantitative PET/CT of the liver and organs affected by liver disease (www.liver.dk). Study designs are translational: New tracers are developed and tested *in vivo* using tracer-specific novel kinetic models in rats, pigs and humans. I 2016, we worked on these aspects of functional PET of the liver.



The liver is located in upper right part of abdominal cavity. It receives blood from the portal vein (PV), which drains the intestines. Blood from the hepatic artery (HA) mixes with PV blood before entering the sinusoids, which empty into the liver veins.

New tracers are developed and tested in vivo

Taurine conjugated bile acids

Bile acids are conjugated in the liver predominantly with glycine in humans, but predominately with taurine in many other species and in some humans with cholestatic liver disease. Following our recently developed radiosynthesis of the glycine conjugated bile acid *N*-^{11}C-methyl-glycocholic acid, i.e. ^{11}C-cholylsarcosine (^{11}C-CSar), we developed a novel radiosynthesis of five *N*-^{11}C-methyl-taurine-conjugated bile acids and determined their biodistribution in pigs by PET/CT. The results show that the additional *N*-methyl-group makes the novel tracer analogues only slightly more lipophilic than their corresponding endogenous conjugates; their overall ranking according to lipophilicity still corresponds to that of the endogenous conjugates. We believe that these new *N*-^{11}C-methyl-taurine-conjugated bile acids will prove useful for preclinical tests in animals with a naturally high level of taurine-conjugated bile acids and for detailed studies of patients with intrahepatic cholestatic disorders.

^{11}C-CSar dosimetry in humans.

We have optimized the procedures for radiosynthesis and quality control of ^{11}C-CSar and are now determining its biodistribution and

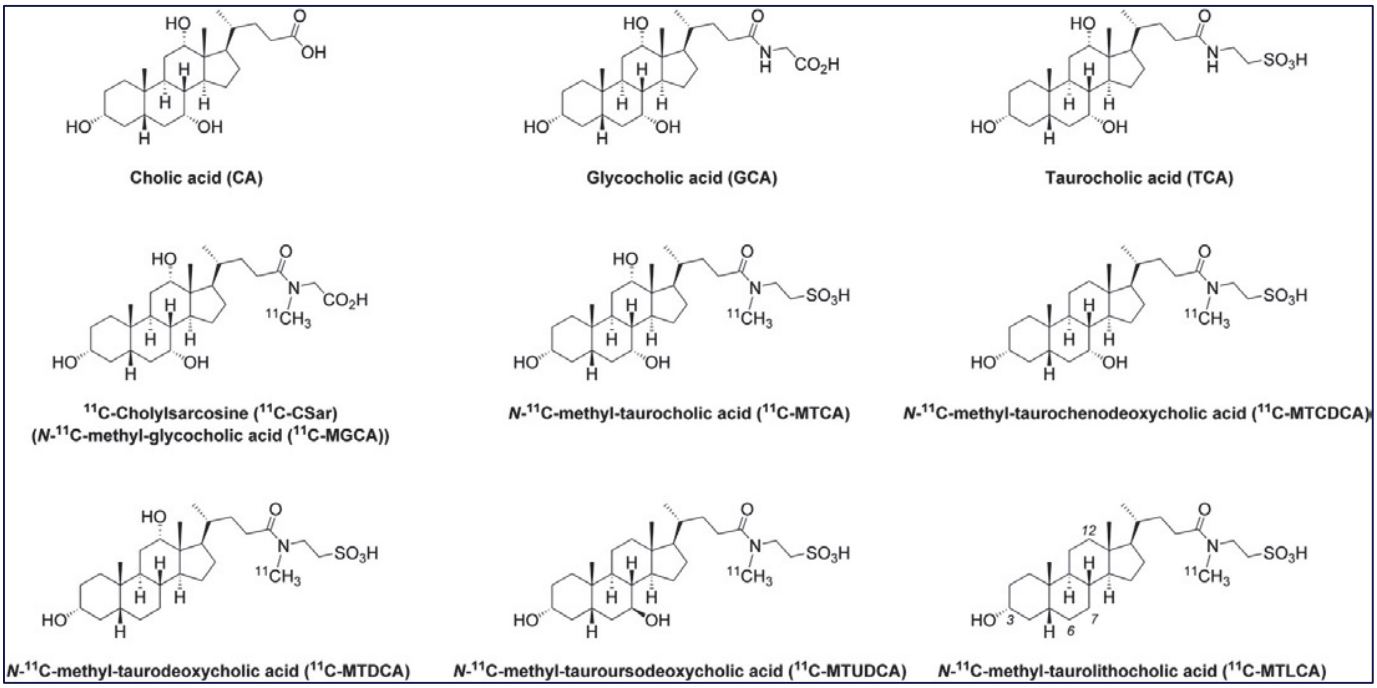
dosimetri in healthy humans and patients with cholestasis (Kim Frisch et al. On-going studies).

^{18}F-labelled bile acid

Enterohepatic circulation of conjugated bile acids is an important physiological process crucial for regulation of bile acid function as detergents for lipid absorption and signal carriers. Because of the short radioactive half-life of ^{11}C (20 minutes), ^{11}C-labelled bile acids are not suitable for quantification of the enterohepatic circulation (hours). We envision that ^{18}F-labelled bile acids (109 minutes) might be and we have developed a radiosynthesis for a ^{18}F-labelled derivative of glycocholic acid (Kim Frisch work at the Centre for Advanced Imaging at University of Queensland, Brisbane). PET of rats (AUH) demonstrated enterohepatic circulation 60-70 minutes after iv injection of the tracer. This novel tracer may prove useful in future PET studies on the enterohepatic circulation of conjugated bile acids and bile acid malabsorption as well as hepatic transport of conjugated bile acids in the liver (Kim Frisch et al. Submitted).

Copper metabolism in patients with Wilson's disease

This project was approved by the Ethics Committee and the Danish Medicine Agency for PET using ^{64}Cu Cl_2 in 2016 and the first dosimetry and kinetic study was performed in a healthy human subject primo 2017 and showed rapid hepatic uptake and excretion into bile (dosimetri, Kim Frisch et al. and tracer kinetics, Lars Gormsen et al. On-going studies).



Chemical structures of N-11C-methyl-glycine and N-11C-methyl-taurine-conjugated bile acid tracers. Anna Schacht et al. J Nucl Med 2016;57:628-633

Highlights 2016

1 January 2016

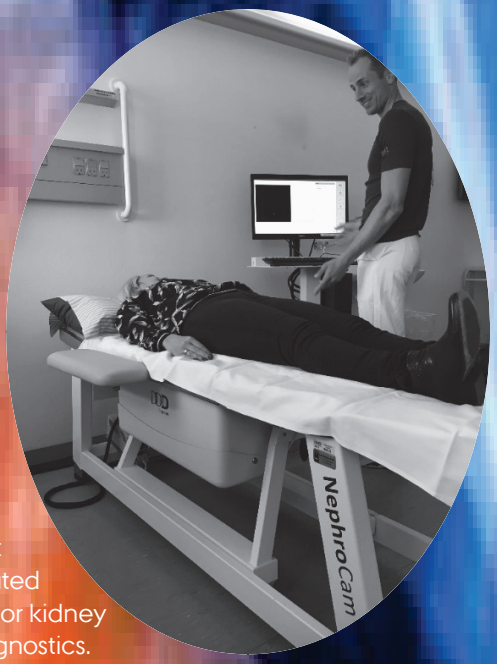
Per Borghammer starts his Lundbeck Fellowship, which was granted in 2015.

15 January 2016

Line Nilsson defends her PhD thesis entitled "The role of COX-2 for development of oxidative stress in obstructive kidney disease".

29 February 2016

Nikolaj Worm Ørntoft defends his PhD Thesis entitled: "Hepatic Transport of Conjugated Bile Acids Quantified by ^{11}C-Cholylsarcosine PET".



August 2016

Installation of our first Nephro-Cam dedicated for patients referred for kidney and urinary tract diagnostics.

20 May 2016

Honorary Symposium for Professor Jørgen Frøkiær.
"Surgical and medical treatment of kidney diseases in children"

10 August 2016

"Topping-out ceremony" for the N5 – the new large building complex housing the united Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital.

Topping-out ceremony N5

The new Aarhus University Hospital

16 September 2016

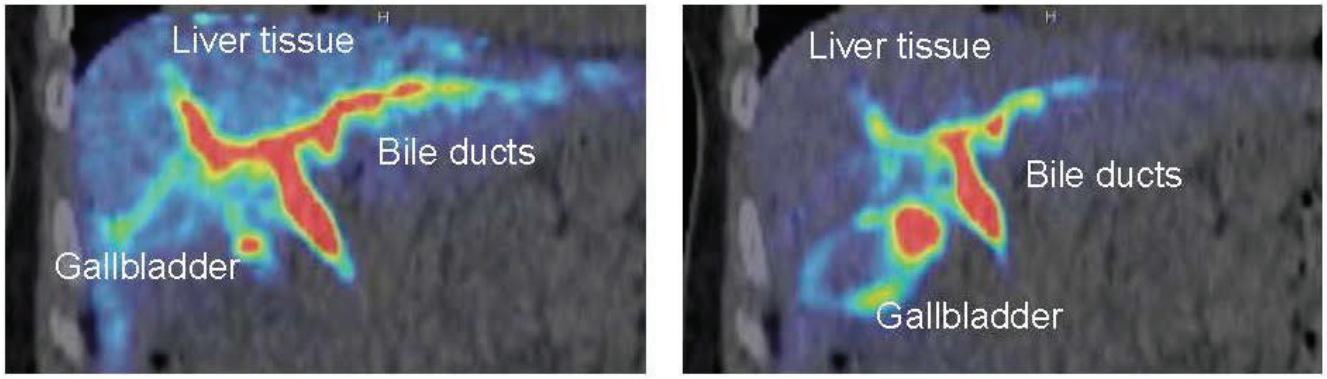
Bodil Schmidt-Nielsen Honorary Symposium supported by the Novo Nordisk Foundation.

23 September 2016

Morten Gersel Stokholm is the first winner of the Stanley Fahn Young Investigator Award for his cutting edge and novel research on neuroinflammation in prediagnostic Parkinson´s disease.

21 September 2016

David Brooks receives the Alzheimer Award 2016 from the Danish Alzheimer Research Foundation.



Liver PET/CT of a pig 5 min (left) and 20 min (right) after iv ^{11}C-CSar

Tracer-specific kinetic models are developed, tested and used in pig and rat studies

Hepatic ^{11}C-CSar kinetics in pigs
We investigated the hepatobiliary secretion kinetics of ^{11}C-CSar in pigs by dynamic PET of the liver combined with measurements of hepatic blood perfusion (ICG infusion) and ^{11}C-CSar concentrations in arterial, portal, hepatic venous blood, and bile samples. Rate constants were calculated for the individual transport steps for ^{11}C-CSar from blood to bile using a 2-tissue PET-compartment model with biliary excretion out of the liver.

Drugs may affect hepatic ^{11}C-CSar kinetics
This is examined for various drugs by micro-PET/MRI in rats (Kim Frisch et al. On-going studies).

Effect of taurocholate on ^{11}C-CSar kinetics in pigs
For taurocholate being native conjugated bile acids, we thought it would be interesting to study its effect on the transport of ^{11}C-CSar through the liver. Taurocholate inhibited the transport of ^{11}C-CSar from blood to hepatocytes and from hepatocytes to bile in a dose-dependent manner and affected splanchnic hemodynamics (Michael Sørensen et al. On-going studies).

Hepatic metabolism of ^{11}C-methionine and secretion of ^{11}C-protein in pigs
We examined these essential liver functions in pigs (subjected to either laparotomy or pneumoperitoneum 24 hours before PET but without any difference in results and therefore reported together). Dynamic PET measurements and arterial blood ^{11}C-concentrations were analyzed by an extended Gjedde-Patlak representation of data that accounted for irreversible metabolism of ^{11}C-methionine (hepatic systemic metabolic clearance K_{met}) and secretion of ^{11}C-protein and ^{11}C-metabolites into blood. K_{met} was significantly correlated to the appearance rate of ^{11}C-proteins in plasma. It would be interesting to translate this method to human studies for the development of a clinical quantitative test of hepatic protein secretion which is a fascinating aspect because other quantitative liver function tests measure uptake from blood and metabolism or hepatobiliary excretion (Jacob Horsager et al. Submitted).

Regional metabolic liver function in rats with fatty liver
This is examined by ^{18}F-FDGal micro-PET/MRI in relation to autoradiography and liver tissue histology (Peter Lykke Eriksen et al. On-going studies).

Effect of transjugular intrahepatic portosystemic stent shunting (TIPS) on regional hepatic metabolic function measured by ^{18}F-FDGal PET
We assess how partial deprivation of portal venous blood by TIPS may affect regional hepatic metabolic function in patients with decompensated cirrhosis examined before and 3 months after TIPS (Kirstine Bak-Fredslund et al. On-going studies).

Human pathophysiology

^{11}C-CSar kinetics in patients with liver disease
We transferred the PET method developed in pigs of the hepatobiliary excretion of the conjugated bile acid ^{11}C-CSar to studies in healthy subjects and patients with liver disease using combined dynamic PET of the liver and ^{11}C-CSar concentration measurements in blood samples from a radial artery and hepatic vein. Rate constants for the individual transport steps of the hepatic transport from blood to bile of ^{11}C-CSar were determined and gave new insight into pathophysiological topics in patients with liver disease: The rate constant for the transport of ^{11}C-CSar from hepatocytes to bile was decreased and the residence time of ^{11}C-CSar in hepatocytes increased in patients with cholestasis (as expected, but here quantified); moreover, the rate constant for the transport across the hepatocyte plasma membrane from blood to hepatocytes was unexpectedly reduced in patients with alcoholic liver disease, possibly because of tightening of the fenestrated endothelial cell due to collagen deposits.

Effect of food intake on ^{11}C-CSar kinetics in healthy human subjects
Subsequent to food intake, the gall bladder empties, bile flow increases, and the hepatic blood flow increases about 50% in healthy subjects. According to the modelling, the above-mentioned kinetic parameters are flow-dependent except the hepatic intrinsic clearance, a measure of the overall excretory capacity. We test these predictions in studies of hepatic ^{11}C-CSar kinetics before and after intake of a standard gut stimulating meal (Nikolaj Worm Ørntoft et al. On-going studies).

Effect of Obeticholic Acid (OCA) on ^{11}C-CSar kinetics in patients with primary biliary cholangitis (PBC)
For patients with PBC who do not respond adequately to the routine treatment with the bile acid Ursodeoxycholic acid (UDCA), treatment with a new synthetic bile acid OCA improves biochemistry and possibly survival and it has recently been approved by the American FDA and European Medicine Agencies for this indication. In the present project, we examine if OCA affects hepatic ^{11}C-CSar kinetics in patients with PBC and inadequate response to UDCA in a double-blind placebo-controlled, crossover study design (Susanne Keiding et al. On-going studies).

Metabolic liver functions in patients with non-alcoholic fatty liver disease
In this study we investigate the relationship between fat content in the liver (MRI) and metabolic liver function (dynamic ^{18}F-FDGal PET/CT), regional heterogeneity and whole-liver values in patients with varying degrees of fatty livers (liver biopsy and ultrasound), incl. non-alcoholic steato-hepatitis (Peter Lykke Eriksen et al. On-going studies).

Liver regeneration in humans after surgery
Here we assess liver regeneration by comparing contrast-enhanced CT-estimated liver volume and whole-liver-liver metabolic function studied by "Functional hepatic nitrogen clearance" and ^{18}F-FDGal PET/CT in patients with and without liver cirrhosis (Kasper Jarlhelt Andersen et al. On-going studies).

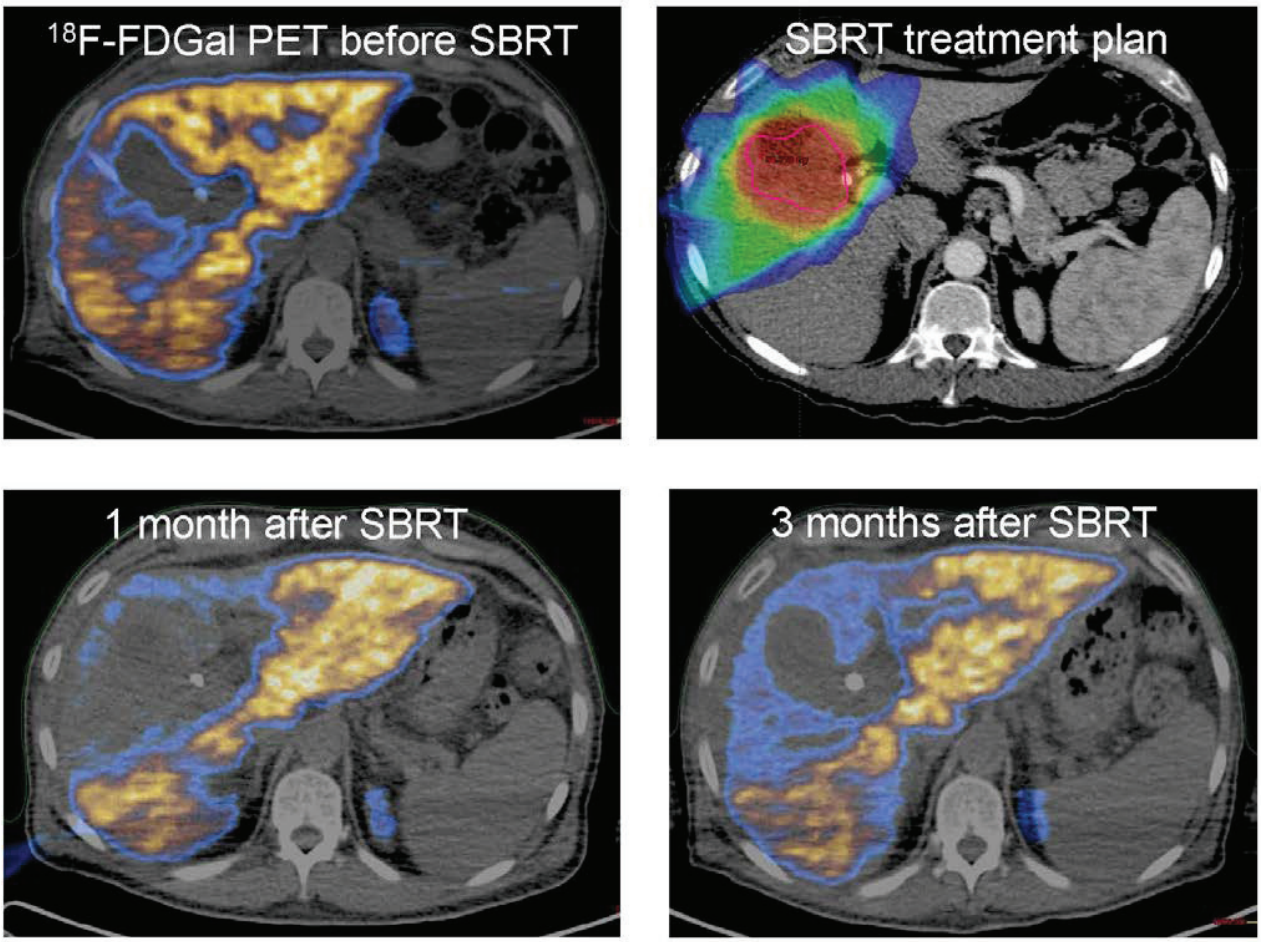
Novel image analysis of PET with ^{18}F-FDG of colo-rectal liver metastases for better prognostication of clinical outcome.
In collaboration with Johns Hopkins University, Baltimore and Memorial Sloan Kettering Cancer Center, New York, we test a novel quantitative image analysis of ^{18}F-FDG PET images, which put individual unequal emphases on PET tumor ^{18}F-FDG uptake vs. volume information, to assess prognostic value in patients with intrahepatic-only colorectal metastases (60 patients from AUH). The proposed framework resulted in enhanced prediction of clinical outcome for the patients (Arman Rahmim et al. Oral presentation at SNMMI 2016; On-going studies).

Methods are made non-invasive and simplified for clinical use in humans

PET ^{18}F-FDGal for quantification of metabolic liver function in humans

Dynamic PET/CT with the radioactively labelled galactose analogue ^{18}F-FDGal is used experimentally to quantify the hepatic metabolic function and visualize regional metabolic heterogeneity in terms of the enzyme-determined metabolic hepatic clearance of ^{18}F-FDGal K_{met} (mL blood/mL liver tissue/min). In attempts to simplify the method, we previously showed that an image-derived input function can replace arterial blood sampling for ^{18}F-FDGal concentrations in the kinetic calculation of K_{met}. In the present study we showed that the standardized uptake value (SUV of ^{18}F-FDGal, i.e. radioactivity concentration in liver tissue, normalized for injected dose and body weight) from static scans 10-20 min after ^{18}F-FDGal injection was linearly related to K_{met} from dynamic scans in humans with and without liver disease. Reproducibility of SUV (and K_{met}) was good with insignificant day-to-day variation, a prerequisite for use in daily clinical practice. We therefore believe SUV can substitute K_{met} in clinical practice (Kirstine Bak-Fredslund et al. Submitted).

Liver-PET in the clinical management of patients with liver tumours

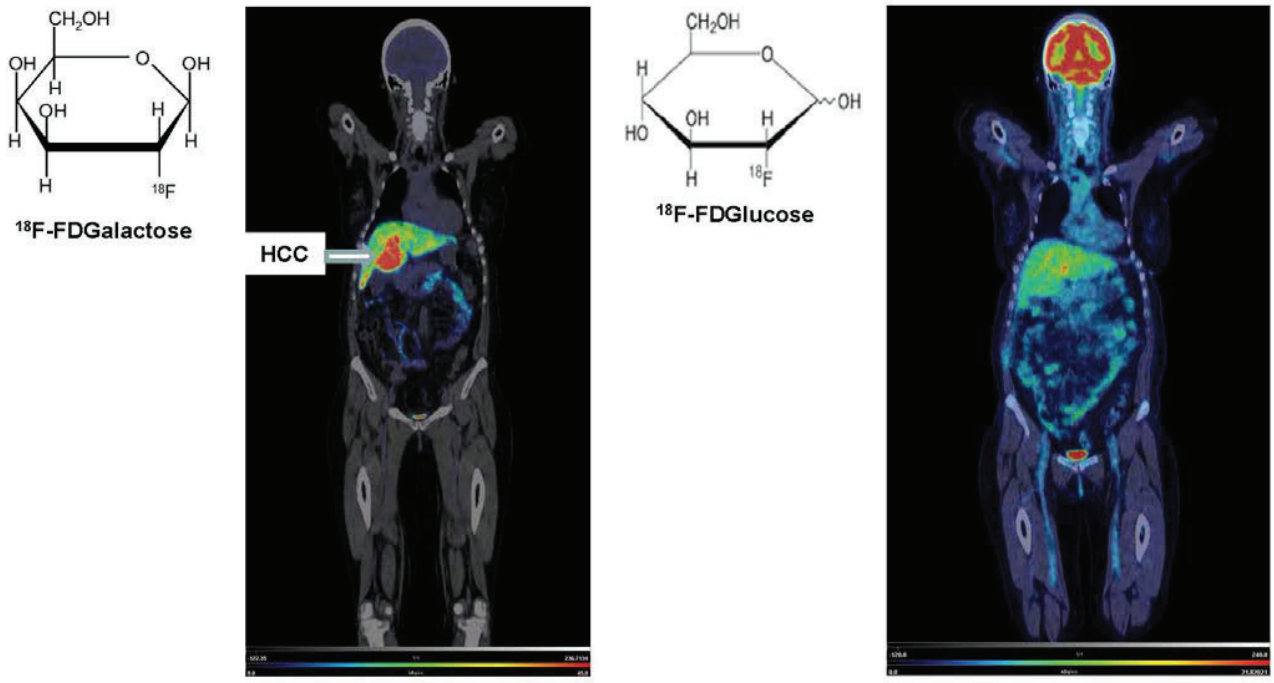


8F-FDGal PET / SBRT of colo-rectal liver metastasis

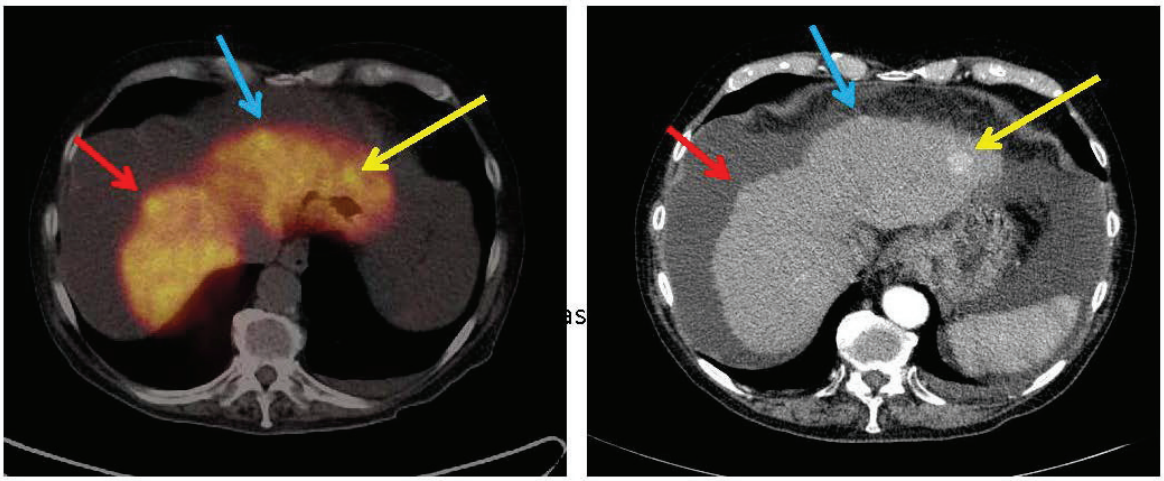
Clinical impact of ^{18}F-FDGal PET/CT of patients with HCC

The survival of patients with HCC after intended curative treatment is burdened by early reappearance of the primary tumours and metastases, one of the main reasons being poor sensitivity of today's diagnostic imaging tools, i.e. contrast-enhanced 4-phase CT, contrast-enhanced ultrasound and MRI of changes in tumour tissue morphology and blood perfusion. There is therefore much interest in molecular imaging of HCC using PET but none of the tested tracers today have, however, reasonable sensitivity for clinical use. In the search for a suitable PET tracer for HCC, we observed, incidentally, that many patients with HCC have a remarkable increased galactose metabolism when measured as the "galactose elimination capacity" (GEC) test used clinically for the assessment of liver function. We therefore conducted a proof-of-concept study with ^{18}F-FDGal PET of 39 selected patients suspected for or with known HCC with encouraging results concerning detection of small HCC foci in the liver and detection of extrahepatic metastases.

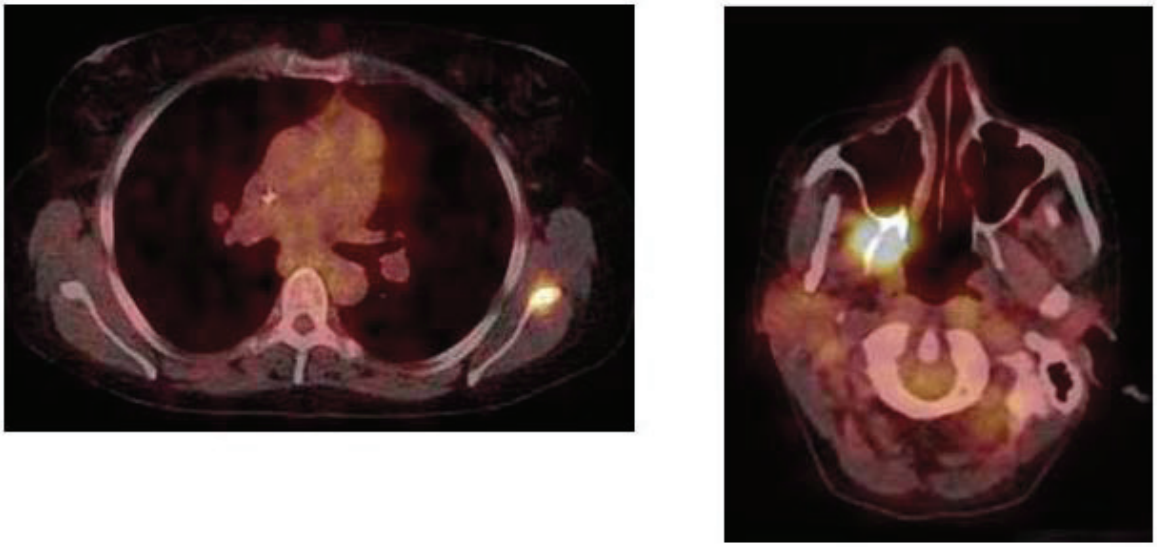
In the present study, we wished to validate the preliminary results in a prospective consecutive controlled clinical study comprising 50 patients suspected for or with known HCC: Does ^{18}F-FDGal PET (SUV) supplementary to the standard CT benefit therapeutic decision-making? Does additional PET with the glucose analogue ^{18}F-FDG, assumed to detect poorly differentiated tumours, benefit therapeutic decision making? (Kirstine Bak-Fredslund et al. On-going studies).



Patient with HCC, PET/CT with 18F-FDGal (left) and 18F-FDG (right)



M 76, cirrhosis, ascites, HCC. CT shows a 2 cm contrast enhanced lesion in the liver left lobe (yellow arrow). 18F-FDGal PET/CT detects further two small subcapsular lesions (left lobe blue arrow, right lobe red) suspicious for HCC.



^{18}F-FDGal PET/CT detects two extrahepatic HCC metastases

^{18}F-FDGal PET/CT before and after treatment of HCC

In this study we perform dynamic ^{18}F-FDGal PET/CT (K_{met} and SUV) before (above study) and 3 months after treatment of HCC with liver resection, radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), selective intraarterial radioembolisation (SIRT), nexavar (Sorafenib), or combinations hereof. We test the hypothesis that ^{18}F-FDGal PET/CT three months after treatment detects more recurrences and distant metastases than CT and thereby significantly affects additional diagnostic strategy and/or treatment plan (Kirstine Bak-Fredslund et al. On-going studies).

Radionuclide therapy

Peter Iversen, Specialist Registrar, Peter Frølich Staanum, Medical physicist, PhD, Anne K. Arveschoug, Senior Consultant

Therapy of malignant diseases with radionuclides is a rapidly evolving field enabling highly specific and targeted treatment regimens. Using radionuclides emitting both gamma and beta rays provides the unique opportunity for both diagnostic imaging and therapy (Theranostics) with the same tracer. This strategy allows to target specific cells in the body via specific binding to a receptor, thus providing a unique possibility for selective treatment and to monitor treatment response. The concept is called peptide receptor radionuclide therapy (PRRT) and the clinical demand for this continue to increase.

Neuroendocrine tumours

The Department of Nuclear Medicine & PET-Centre was the first department in Denmark to introduce Y-90 bound to DOTATOC (Y-90-DOTATOC) as therapy of patients with progressive neuroendocrine tumours (NET) in 2008.

In 2015, we introduced the radionuclide Lu-177 for treatment of NET, since it is known to be less nephrotoxic than Y-90. Treatment with Lu-177 soon became the standard treatment; first bound to DOTATATE (Lu-177-DOTATATE). With our modern radiochemistry, facilities and a highly experienced staff in the field we changed to in-house production of Lu-177 bound to DOTATOC (Lu-177-DOTATOC) in 2016. Our large expertise in radiopharmacy enables our department to offer tandem- or duo-therapy using both Y-90- and Lu-177-DOTATOC in the treatment of NET.

Since the introduction of Peptide-Receptor-Radionuclide Therapy (PRRT) in 2008, we have been focused on optimizing the diagnostic and treatment procedures including nephroprotection [A. K. Arveschoug et al. Curr Radiopharm. 2015;8(1):49-55]. In 2016, we introduced the arginine/lysine nephroprotection protocol recommended by the European Association of Nuclear Medicine as being the best-validated protocol for kidney protection using a mixture of two amino acids.

The use of Lu-177-DOTA-peptides, quantitative SPECT/CT scans of Lu-177 for calculation of the radiation dose to the kidneys have been introduced along with bone marrow dosimetry based on blood samples. This has made the treatments become increasingly multidisciplinary including involvement of medical physicists and technologists.

As a supplement to PRRT, in the last two years Selective Internal Radiation Therapy (SIRT) using Y-90 microspheres has been offered to NET patients with progression of liver-dominant disease. This treatment protects the kidneys and enables treatment of a subgroup of patients with a very low kidney function disqualifying for PRRT.

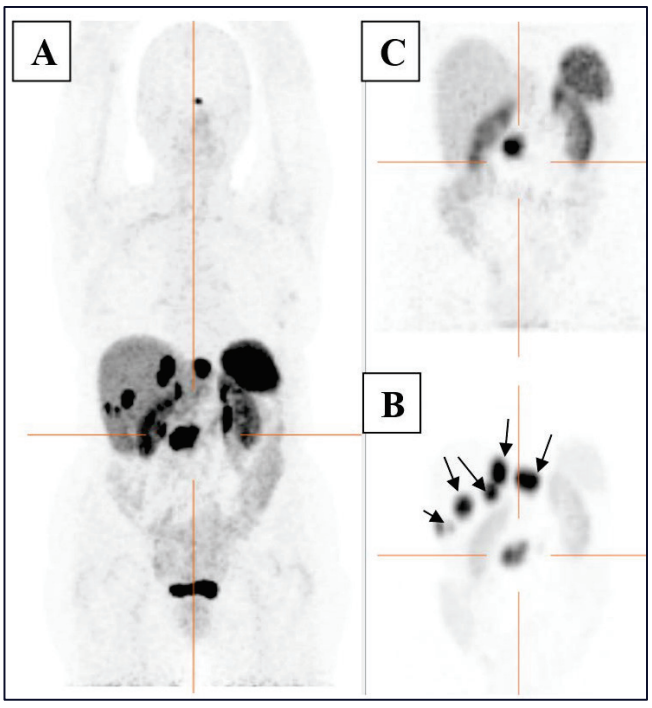


Figure 1. Pre- therapeutic Ga-68-DOTATOC PET in a patient with pancreatic NET and liver metastasis (A).

Since 2012 Ga-68 DOTA-peptide PET/CT has been used for diagnostic evaluation and staging. In 2016, 200 Ga-68 DOTATOC PET/CT scans were performed in gastroentero-pancreatic neuroendocrine tumour patients and more than 60

F-18 FDG PET/CT scans were performed in NET patients in order to evaluate the extent of de-differentiated disease and give a prognosis of the neuroendocrine tumour disease.

In close collaboration with the Departments of Hepatology and Gastroenterology, Oncology and Radiology, we have now treated more than 125 patients since 2008, and in 2016, the number of patients increased to 28 patients, an increase of more than twenty percent compared to the year before. Therapy and follow up are carefully planned for these complex patients at biweekly multidisciplinary conferences. The high level of expertise combined with the close cooperation between different specialties involved in the handling of NET patients resulted in 2016 in re–certification for a five-year period as Centre of Excellence by the European Neuroendocrine Tumor Society (eNETS).

Hepatic malignancies

During the last three years (2014-2016), there has been a gradual increase in patients being treated with intra-arterial radiotherapy using Y-90 labelled microspheres – so-called Selective Internal Radiation Therapy (SIRT). Mainly patients with primary liver cancer (hepatocellular carcinomas (HCC)) are treated by SIRT, but, as mentioned above, also patients with neuroendocrine tumours have been treated. In HCC treatment, the inclusion criteria for SIRT have been gradually broadened and the progression in this area has been highly dependent on support from the Central Denmark Region. The treatment is performed in close collaboration with the Departments of Hepatology and Gastroenterology and Radiology and involve new imaging techniques such as Bremsstrahlung SPECT/CT and Y-90 PET/CT scanning for post-therapeutic response and the Tc-99m MAA-scintigraphy for pre-therapeutic evaluation of treatment eligibility [Staanum et al., Ugeskr Læger 2017;179:V09160629]. In 2016, eleven patients were treated with SIRT. The injected activity of Y-90 is individually determined for each patient, carefully evaluating dosimetry models, the patients liver condition and the extent of liver disease.

MAA-scintigraphy before SIRT and PET/CT after SIRT in HCC patient

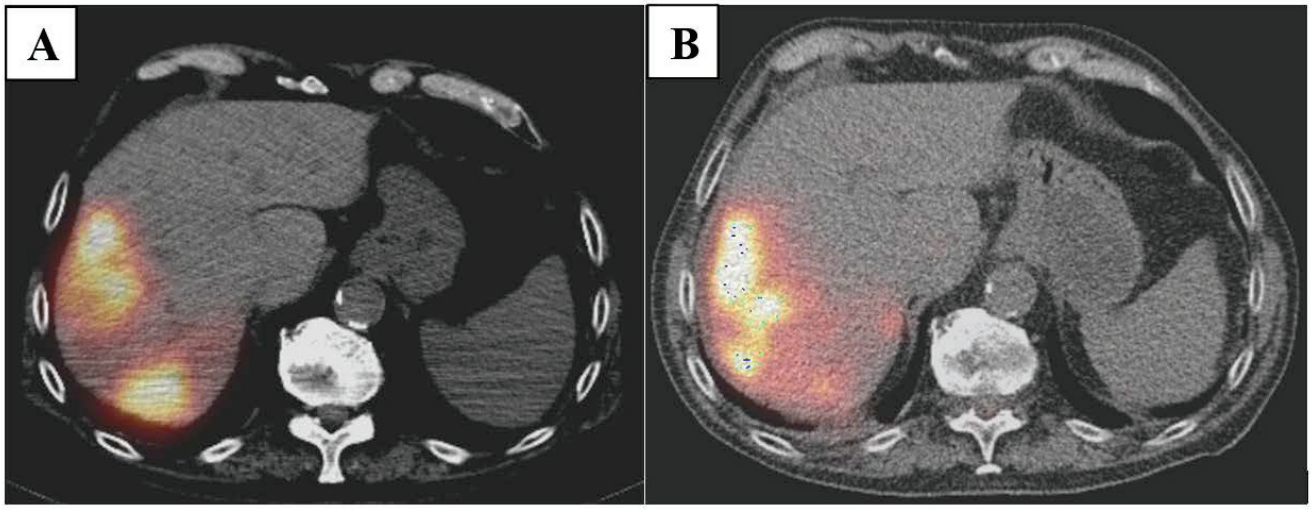


Figure 2. Pre-therapeutic Tc-99m MAA scintigraphy showing MAA uptake in HCC elements in the right hemi-liver (A). PET/CT after therapy with Y-90-microspheres, showing tumour uptake in the same areas of the liver (B)

Thyroid disease

Differentiated thyrois cancer

Primary treatment for differentiated thyroid cancer (DTC) is surgery. After total removal of the thyroid gland and relevant lymph nodes, the patient is referred for ablation treatment with Iodine-131 in order to remove healthy tissue and micro metastasis. This makes it possible to do a long-term follow up using blood samples (thyroglobulin), which is produced by both healthy and malignant thyroid cells, and by pathological uptake, future iodine scans. Many patients are referred for multiple treatments with 6 months intervals, as studies have shown a better prognosis for disease free survival and death in successful ablation within the first year after surgery.

After each treatment, theranostic scans are performed using state-of-the-art evaluation methods (SPECT/CT). Patients with no iodine uptake with consistent elevated values of thyroglobulin are normally referred for a PET/CT in order to find pathologic metabolic active tissue. In such cases, the patient might need additional surgery or radiation therapy.

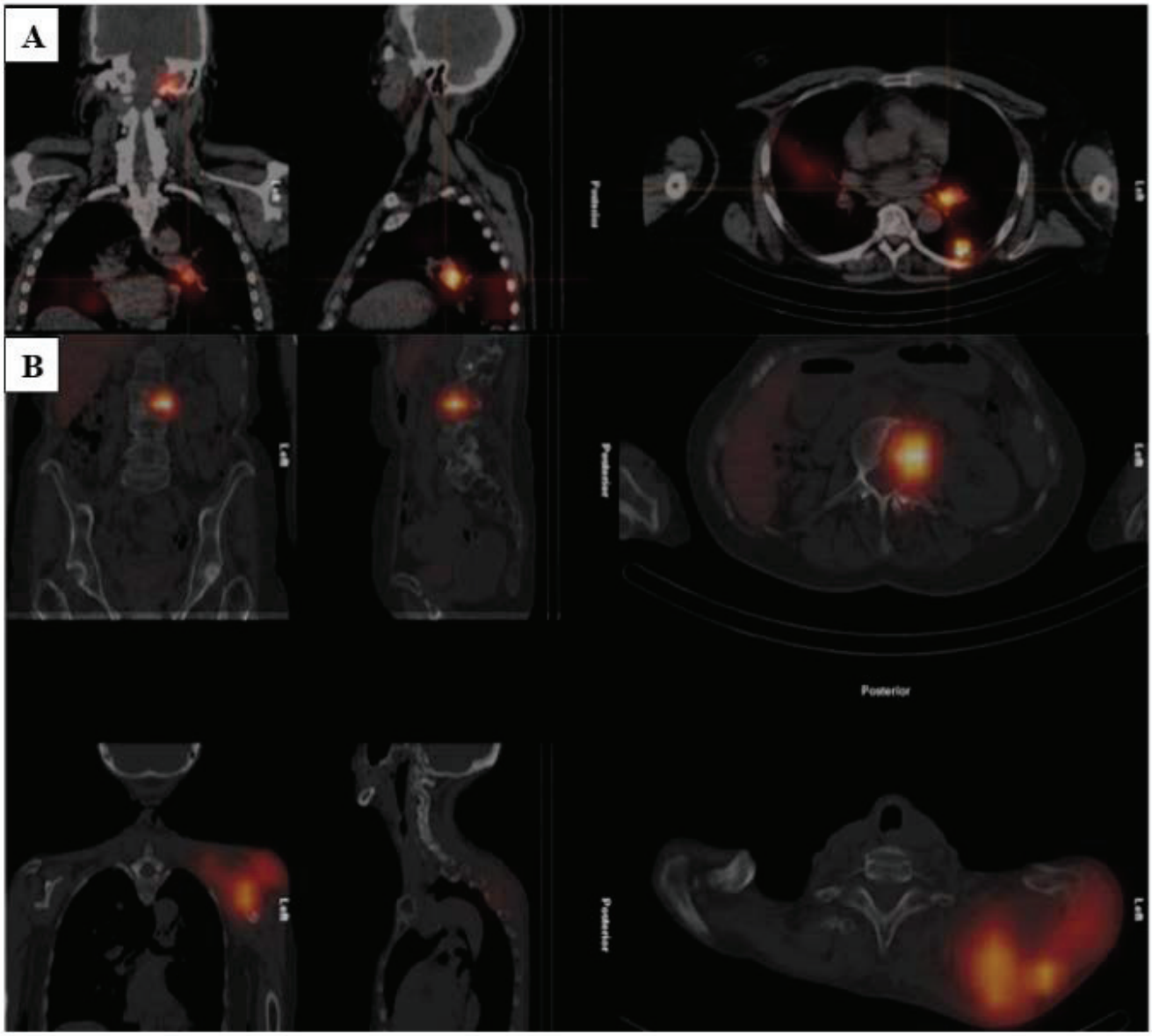


Figure 3. Theranostic SPECT/CT 3 days after a after a standard treatment of 3,7 GBq Ioidine-131. Scans are superimposed on a low dose CT used for attenuation and anatomic location of the SPECT scan.

The number of newly treated patients (ablation) has decreased since introduction of new Danish guidelines (fully implemented September 2015), as the group of patients with a low risk is no longer being offered radioiodine ablation (for graphical data, figure 4B).

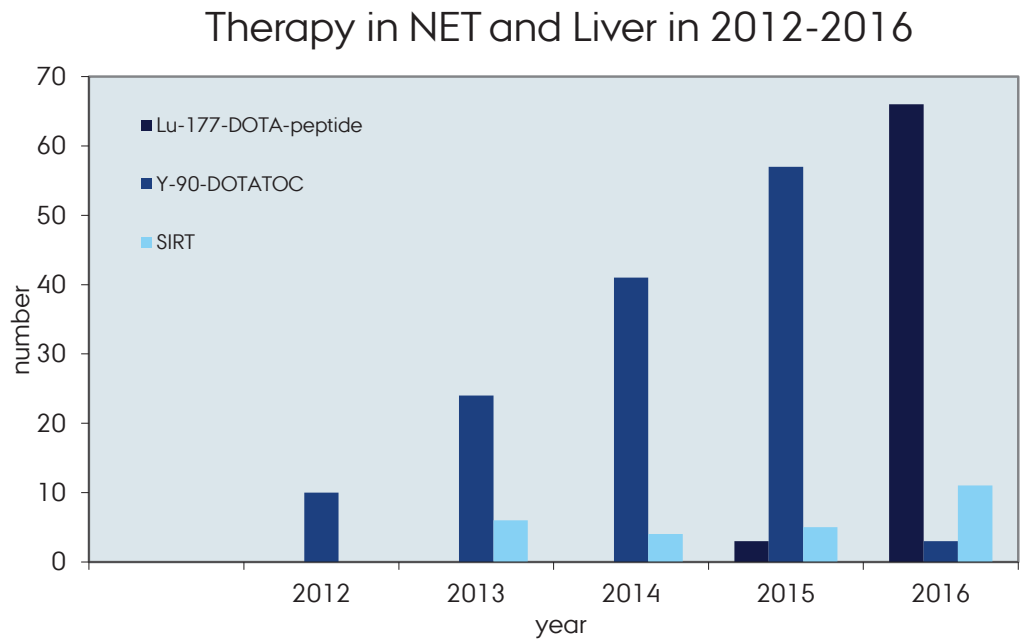


Figure 4A

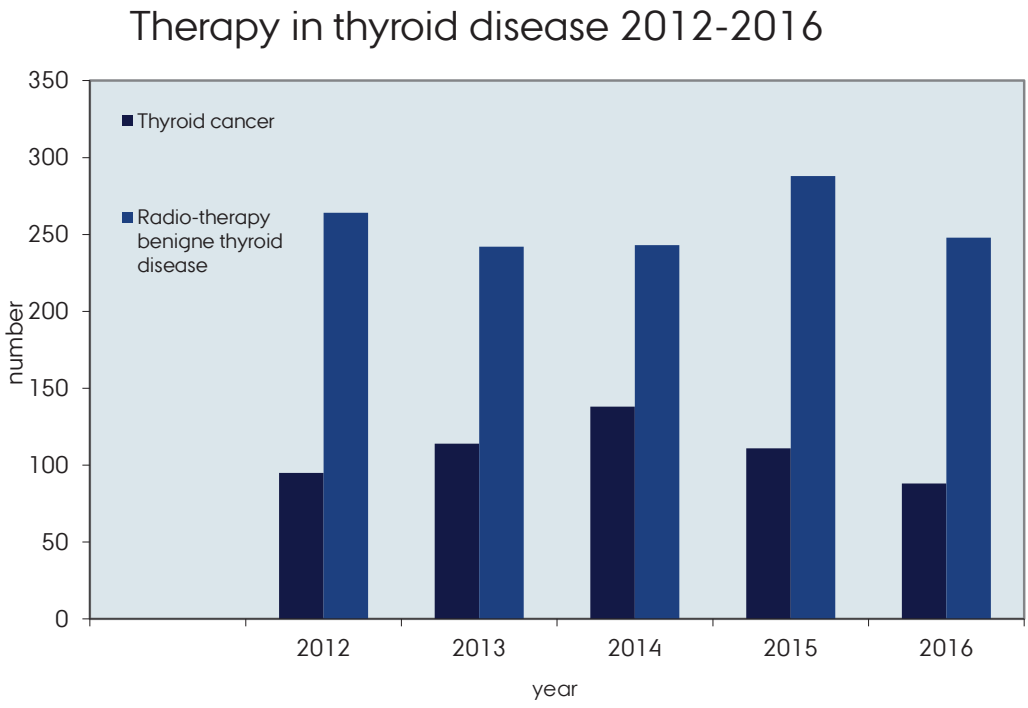


Figure 4B

Training and teaching

Training and teaching are highly prioritized by our department. The department offers teaching on the pre- and postgraduate levels to the many different groups including medical doctors from many specialties, medical students, PhD students, medical laboratory technologists, molecular medicine students, medical secretaries, radiologists, physicists and chemists. In addition, many university students from science and psychology do their bachelor or master thesis at our department..

Medical doctors/specialists

Anne Arveschoug,, MD, Senior Consultant

There is a rich tradition for training medical doctors/specialists from the basic departmental level to the theoretical level. The department runs courses, which are specifically aimed at educating and training Danish specialists in clinical physiology and nuclear medicine.

For more than 40 years, the department has been the responsible organizer of the isotope course, which qualifies for becoming certified by the Danish Health Authorities to handle radioactive isotopes. The course is also offered as a part of the PhD programme at The Graduate School, Aarhus University (see below). The department´s physicists and chemists contribute greatly to this course just as the department's medical doctors/specialists have done within the course of renal physiology and pathophysiology.

Training is also provided to younger doctors who come from nuclear medicine departments within the training catchment Education Region North.

In recent years, the department has also trained medical doctors from other focused educational stays.

The department has three junior doctors following a foundation programme and another three junior doctors in early and late specialist training. Senior consultant Anne K Arveschoug is responsible for education. The junior doctor who was responsible for training in 2016 was Michael Alle Madsen.

The inspection report from the National Board of Health in 2016 described the department as a place where training is paramount and is a well-integrated part of the daily clinical programme.

The department has scheduled supervisor meetings for all specialists and main supervisors and in 2015 – 2016, prioritized an updated supervisor-training programme (faculty development) for all specialists in the department.

In 2014, there was a general revision of the specialty objectives of the Danish Society of Clinical Physiology and Nuclear Medicine and this led to an increased focus on the different roles of the doctor. In addition to the well-known role of being a medical expert, the roles of each physician as a communicator, collaborator, academician, leader, professional and health advocate have received much more attention during the formal training programmes. This has been highlighted in the 360-degree feedback of all junior physicians and the department now has three specialists who are qualified to assess the feedback.

As for the doctor's role of administrator and leader, there has also been a focus on distributing the administrative tasks amongst the younger doctors and the introduction of teaching with case studies has strengthened the training process for the whole department.

Improved communication and coordination has helped improve the collaborative double reporting of hybrid scans (PET/CT and SPECT/CT).

A regular workplace-based assessment of the younger doctors' clinical training is on the agenda in line with the increasing demand for competence assessment. There is constant focus on training and feedback.

With the introduction of the electronic logbook and Central Denmark Region's digital interview system for supervisors, the specialist training programme has been brought into the 21st century.

Medical and Molecular Medicine Student

Jørgen Frøkiær, Professor, Head of Department, MD, DMSc

The undergraduate clinical teaching is undertaken by the department's Clinical Associate Professors Lars C Gormsen, Kirsten Bouchelouche and Per Borghammer. The medical education at the Faculty of Health, Aarhus University is organized in thematic blocks when students enter the master programme. The programme consists of six blocks each taking up one semester including areas such as cardiovascular medicine, neuro and inflammation among others. Together with colleagues from adjacent disciplines we provide a variety of lectures in general nuclear medicine and molecular imaging in all these blocks in the format of both ordinary lectures and cross-disciplinary symposia. This interaction is very important and it results in recruitment of students who show a special interest in our department and in nuclear medicine, and decides to spend additional time at our department for their volunteer student rotation.

Similarly, we also provide teaching for the molecular medicine students. Molecular Medicine is a joint programme provided by the faculty of Science and Technology and the Faculty of Health, and students will meet teachers from both fields including teachers from The Department of Nuclear Medicine and PET-Centre. On the Molecular Medicine Bachelor's degree programme the students study anatomy, physiology, and genetics of the human body in combination with attending science courses in e.g. molecular biology and biochemistry. Teaching on the Molecular Medicine programme includes practical exercises in the laboratory, theoretical lectures as well as problem solving in smaller groups. Thus, the students' understanding of the principles and perspectives of molecular imaging is optimal. In particular, our department is relevant in diseases like diabetes, cardio-vascular diseases, cancer, diseases of the brain and nervous system and arthritis affect a large proportion of the population. The Master's degree programme includes teaching in the molecular mechanisms that have an impact on the development of these diseases; as well as teaching in their diagnosis, treatment and possible prevention

Medical Phycisists and Chemists

Anders Floor Frellsen, Chemist, PhD

Training is also available for medical physicists where the department's own physicists can provide training.

In 2016, Peter Frøhlich Staanum was the supervisor for Paw Simesen, Randers, in his formal education as a medical doctor under the National Board of Health and Søren Baarsgaard Hansen was the supervisor for PhD student Lars Jødal's project "Kinetic modelling of PET tracer uptake in a porcine *S. aureus* osteomyelitis model".

All newly employed chemists are signed up for the basic isotope course, which is taught at the hospital, to provide a basic understanding of radioactive isotopes and ionizing radiation. Furthermore mandatory continuing education of all chemists includes the Postgraduate European Radiopharmacy Course, which is a 3 x 2 weeks course spread over two years. The course is offered by the Swiss Technical University, Zürich, and recognized by the European Association of Nuclear Medicine (EANM). In addition to this formal education a wealth of relevant techniques are taught locally by apprenticeship due to the unique nature of a radioisotope laboratory.

PhD-Education at Aarhus University Graduate School

Jørgen Frøkiær, Professor, Head of Department, MD, DMSc

The Department of Nuclear Medicine and PET-Centre is responsible for organizing the course in Biomedical Isotope Technique at the Graduate School in Health, Aarhus University. This course is unique in the sense that after passing the examination, the course holder can apply for approval from The Danish Health Authority to become board certified in handling radioactive isotopes for biological use. As such all physicians from the departments in the western part of Denmark who are training to become board certified specialists in nuclear medicine are requested to pass this course. In addition to physicians in training, the course is also offered to physicians in other disciplines: dentists, nurses, PhD students, and other researchers at Aarhus University. The course consists of a mixture of lectures and experiments and provides a thorough presentation of the necessary physics and mathematics for measuring radiation, biological effects of radiation, application of radioactive isotopes and associated risks. A number of the physicists and chemists from the department deliver the majority of the lectures and as such provide all the basics for always making this course very successful and highly requested.

Medical Laboratory Technologists

Christian Juul, Biomedical Laboratory Technologist and Responsible for Training

The department plays an important role in the training of medical laboratory technologists. The students come from VIA University College, Aarhus at different stages in their training. In 2016, there were 30 students who undertook a placement in the department. The placements lasted between 3 and 15 weeks. Of these 30 students, 15 completed their training here followed by a clinical exam and 3 students carried out and completed their training by writing their dissertation here.

In 2016, training underwent a comprehensive overhaul. One of the effects of this will be a longer clinical training period for the students. Training is now more concentrated on the patient, the development of generic skills and a closer relationship between theory and practice. These changes were started in the autumn of 2016 and are expected to be implemented by 2018.

Over the last four years, the number of ECT points for medical laboratory technologists and radiography students has doubled. This has been due to a larger intake of students from VIA University College, Aarhus, and fewer training departments in the Central Denmark Region as well as a new and exciting collaboration with the radiography course at University College Lillebaelt, Odense (UCL) and University College of Northern Denmark, Aalborg (UCN). In 2016, there were 18 radiography students on a clinical placement at the department.

Christian Juhl is the medical laboratory technologist who is responsible for training and Annette Dysterdich is responsible for the teaching. The clinical supervisor, Rikke Bertelsen is responsible for the administrative and teaching assignments in connection with the department's contribution to the training of future medical laboratory technologists and radiographers. Furthermore, the department has three external examiners in the Danish National Censor Corps.

Participation in the advancement of the profession as a whole as well as other health science professions is actively encouraged through collaboration with other educational institutions.

Courses are also held for qualified technologists as well as the yearly isotope course.

Medical secretaries

Elisabeth Jemina Rønne, Medical Secretary

Training is well established and well integrated throughout the department with focus on learning and feedback as well as the ongoing implementation of different systems, logbooks and supervisor interviews. The politically determined and mandatory goals of the training programme are also taken into account.

Elisabeth Jemima Rønne has been responsible for the training of medical secretaries since the department first participated in the training programme in 2010 and has been qualified in the supervisor training of medical secretary students since 2013.

The medical secretaries contribute greatly to the training of students and there is exceptional teamwork with the other groups of staff. As well as teaching, the students also participate in the clinic.

In 2016, there were three medical secretary students on an 8-month placement in the department.

Studies/Patient Investigations 2015-2016

Radiotherapy planning	2015	2016
Radiotherapy planning delineation, PET/CT	584	589

PET research scanning	2015	2016
Human research scanning, PET/CT	553	655

CT examinations	2015	2016
In total	*2666*	*2797*
CT WholeBody PET/CT	2658	2782
CT WholeBody on SPECT/CT	8	15

Blood and lymph system	2015	2016
In total	*305*	*291*
Bone marrow scintigraphy	43	4
Spleen scintigraphy, Tc-99-erythrocyte, heated	3	2
Sentinel node scintigraphy, tumour drainage, c. mammae	8	3
Sentinel node scintigraphy, tumour drainage, c. vulva	22	18
Sentinel node scintigraphy, tumour drainage, c. penis	52	47
Sentinel node scintigraphy, tumour drainage, MM	177	217

CNS og peripheral nervous system	2015	2016
In total	*733*	*910*
Regional cerebral receptor, C-11-XX	9	4
Regional cerebral receptor, C-11-PIB	0	25
Regional cerebrale blood flow, pharm. prov., O-15-H2O	25	36
Regional cerebrale blood flow, physiol. prov., O-15-H2O	6	14
Regional cerebrale metabolism, F-18-FDG	340	515
Cisternography, In-111-DTPA	5	0
Regional cerebral receptor, F-18-FET	80	79
Regional Dopamine Transporter Receptor Imaging, I-123-FP-CIT (DAT-Scan)	268	237

Bone and Joint	2015	2016
In total	*745*	*731*
Bone Scintigraphy, multi phased	9	13
Bone Scintigraphy, regional, static	1	0
Bone Scintigraphy, whole body, static	233	77
Bone Scintigraphy, SPECT	502	641

Other diagnostic procedures	2015	2016
In total	*13350*	*14095*
White blood cell scintigraphy, In-111-leuco	47	6
PET infection scanning, F-18-FDG	342	428
Image fusion	8019	8307
Neuro endocrine receptor scanning, F-18-DOPA	14	19
Tumourscintigraphy, In-111-Octreotide	1	0
Tumourscintigraphy, I-123-jodid	3	1
Tumourscintigraphy, I-131-jodid	243	163
Whole body scintigraphy following Lu-177-therapy	3	70
PET tumour scanning, F-18-FDG	4232	4364
PET tumour scanning, F-18-Cholin	294	94
PET tumour scanning, GA-68-DOTANOC	17	23
PET tumour scanning, GA-68-DOTATOC	98	205
PET tumour scanning, GA-68-PSMA	0	298
PET tumour scanning following Y-90-SIRT therapy	4	11
Tumourscintigraphy, I-123-MIBG	14	14
Tumourscintigraphy following Lu-177 therapy	3	70
Intraarteriel tumour-/shunt scintigraphy, Tc-99m	11	11
Tumourscintigraphy following Y-90-SIRT therapy	5	11

STUDIES/PATIENT INVESTIGATIONS 2015-2016

Gastrin intestinal tract, liver, biliary tract and pancreas	2015	2016
In total	*280*	*232*
Meckels diverticulum scintigraphy, Tc-99m-pertechnetat	1	2
Gastric emptying scintigraphy, solid food, Tc-99m	77	90
Liver metabolisme, F-18-FDGal	9	10
Gall bladder scintigraphy, Tc-99m-Mebrofenin	36	26
Biliary tract scintigraphy, Tc-99m-Mebrofenin	18	22
Bile acid turnover, Se-75-SeHCAT	138	82
Bleeding scintigraphy, abdomen, Tc-88-erythrocyte	1	0

Heart and cardiovascular system	2015	2016
In total	*4652*	*4429*
Hyperinsulinemic euglycemic clamp	60	63
ECG, physiol.stress, Tc-99m-MIBI	66	59
ECG, pharm. stress,Tc-99m-MIBI	1230	1152
Isotope cardiography, LVEF, Tc-99m-HSA	844	813
Myocardiel perfusion, Rb-82, pharm. stress	909	897
Myocardiel perfusion, Rb- 82, rest	917	900
Myocardiel metabolisme, F-18-FDG	60	63
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, adenosine	284	229
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, physiol. stress	70	60
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, dipyr	3	0
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, dobu	29	25
Myocardiel perfusion scintigraphy, Tc-99m-MIBI,rest	168	144
Myocardiel sympaticus activity, I-123-MIBG	12	24

Respiratory organs	2015	2016
In total	*924*	*1052*
Lung perfusion scintigraphy, regional, Tc-99m-MAA	195	174
Lung perfusion scintigraphy, Tc-99m-MAA	78	6
Lung ventilation scintigraphy, regional, Tc-99m-MAA	23	32
Lung ventilation scintigraphy, Tc-99m-MAA	77	6
Lung function test, spirometry	126	219
Lung perfusion scintigraphy, SPECT, Tc-99m-MAA	212	308
Lung ventilation scintigraphy, SPECT, Tc-99m-technegas	213	307

Peripheral vessels	2015	2016
In total	*534*	*556*
Systolic blood pressure, fingers	1	1
Skin perfusion pressure measurement	7	7
Systolic blood pressure, ancle and toes	526	548

Endocrine organs	2015	2016
In total	*1967*	*2172*
Thyroid scintigraphy, Tc-99-Pertechnatet	1398	1598
Iodine uptake test, I-131-Iodide	296	263
Parathyreoid scintigraphy, Tc-99m-MIBI	271	307
Adrenocortical scintigraphy, I-131-norcholesterol	2	4

Kidneys and urinary tract	2015	2016
In total	*3187*	*3113*
Renography, Tc-99m-MAG3, diuresis	555	653
Renography, Tc-99m-MAG3	139	117
Renography, Tc-99m-DTPA, ACE-inhibitor	85	73
Renography, Tc-99m-DTPA	8	18
Renal scintigraphy, Tc-99m-DMSA	181	86
Glomerular filtration, Cr-51-EDTA, multi samples	369	357
Glomerular filtration, Cr-51-EDTA, single sample	1794	1761
Micturition cystourethrography scintigraphy, Tc99m-MAG3	56	48

Radioisotope therapy	2015	2016
In total	*455*	*440*
Isotope therapy with Lu-177-DOTA-TATE	3	70
Isotope therapy with Y-90-DOTATOC	60	4
Isotope therapy with I-131-MIBG	1	0
Isotope treatment with I-131, benign	273	257
Isotope treatment with I-131, malignant	113	98
Selective internal radiotherapy with Y-90-SIRTEX	5	11

Summer School

Michael Winterdahl, Associate Professor, PhD

The Interdisciplinary Summer School on Neuroimaging (ISSN)

The Interdisciplinary Summer School on Neuroimaging (ISSN), at the Faculty of Health, wasfounded at the PET-Centre in 2015. Led by Associate Professor Michael Winterdahl, this course aims to introduce students to theoretical and practical aspects of preclinical and clinical brain imaging.

ISSN 2015

Embracing the interdisciplinary nature of the field, our program is targeted at graduate university students from psychological, medical and biological sciences as well as the natural sciences (such as chemistry, medicinal chemistry, physics, math, statistics and computer science). This course has attracted students from around the world from as far away as Australia, India and Canada. It has rapidly become one of the most popular summer schools at Aarhus University with the highest number of applicants.

The two-week course held in early July is taught mainly by a number of local experts in imaging at the associate professor and professor levels as well as teachers from abroad including Belgium and Finland. In order to promote the academic development of PhD students at the PET-Centre, a number of teaching slots were allocated to PhD students where they were given a platform to present their projects. This is part of a higher aim to support excellent training of the PhD students and to promote Danish research in general.

The ISSN aims to provide a solid foundation in state-of-the-art functional neuroimaging methods. Using lecture format and active learning approaches, students delve into topics of modern imaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI), as these tools hold a great potential to expand current knowledge in many life science areas. Students also learn a number of additional imaging methods such as histology/stereology, electroencephalography, magnetoencephalography and autoradiography. Medical ethics, animal modeling, study design and kinetic processing of PET data are also key topics included in the course.

Group work was emphasized and each group consisted of students from different disciplines. Groups were given topics related to the course content and evaluated on their ability to present an original research paper, and to design a novel study in which neuroimaging tools are applied in order to answer a research question. Student presentations were held on the last day of the course.

The program highlights the most current research in order to illustrate how neuroimaging can be used to test hypotheses and to provide evidence-based answers to issues related to diverse aspects of brain

function in both health and disease. Students will be encouraged to interact closely with teachers, both in lectures and in practical laboratory exercises, so that they become better prepared to carry out research projects in neuroimaging and to evaluate published findings.

A modified version of the ISSN course has now been added to the course catalogue in Psychology in the Faculty of Business under the name Cognitive Neuroscience.

ISSN 2016

CFIN

Arne Møller, Associate Professor, MD

Collaborations between the Department of Nuclear Medicine and PET-Centre (NUK/PET) and the Center of Functionally Integrative Neuroscience (CFIN) within neuroscience

The strong collaborations between NUK/PET and CFIN within neuroscience date back more than twenty years. The founding director of the PET-Centre, professor Albert Gjedde and Leif Østergaard, who did some of his graduate work at the PET-Centre and later became head of the Neuroradiology research unit, joined forces to form a center, in which scientists could combine the strengths of PET and MRI as tools to study the brain. With a vision to test novel ideas on how the human brain adapts to experience, they won a Center-of-Excellence grant from the Danish National Research Foundation to establish CFIN in 2001. The grant was extended in 2005 to a full 10-year funding period, laying an important cornerstone for the strong neuroimaging-based neuroscience research at Aarhus University Hospital and Aarhus University. Professor Leif Østergaard is now director for CFIN, which is subdivided into several research groups (http://cfin.au.dk/cfinmindlab-labs-research-groups/). Group Leaders meet several times a year to develop and coordinate research between the groups, and NUK/PET is represented by David Brooks, Arne Møller, and Per Borghammer.

NUK/PET – CFIN collaborations in 2016

A recent example of the synergies and ideas that arise from NUK/PET-CFIN collaborations is a study that investigates new avenues to treating patients with Alzheimer's disease (AD). In this randomized, placebo-controlled, double-blinded clinical study, half of the enrolled patients received a GLP-1 Analog, while the other half received placebo for a period of 6 months. They were carefully evaluated to assess their cognitive symptoms and scanned by PET and MR both before and after the study period. The PET scans quantified the uptake of [C^{11}]-PIB, that binds to the toxic amyloid proteins, which are characteristic of Alzheimer's disease, in brain tissue, and of [F^{18}]-FDG, a glucose analog which reflects the metabolism of brain tissue. The patients were also imaged by MRI, including a volumetric T1 weighted imaging sequence to quantify cortical atrophy and to allow PET scans and MRI to be co-registered. The MRI examination also included perfusion MRI – a technique that tracks the passage of a standard, intravascular MRI contrast agent through the brain vasculature after intravenous bolus injection. With a newly developed method, these data allow the characterization of both cerebral blood flow and the way in which blood is distributed across the microvasculature.

The PET study showed that treatment with GLP-1 Analog prevented the decline in brain glucose metabolism, which is well known for the disease and, as expected, was found in the placebo group:

Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, Vang K, Rodell A, Brændgaard H, Gottrup H, Schacht H, Møller N, Brock B, Rungby J. In Alzheimer's Disease, 6-Month Treatment with GLP-1 Analog Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial (2016) *Front. Aging Neurosci; doi: 10.3389/fnagi.2016.00108*

The MR part of the study showed a correlation between the cognitive symptom severity and both the degree of neurodegeneration, as measured by cortical atrophy, and the extent of capillary dysfunction. The latter denotes a maldistribution of blood across the microvasculature, which the researchers believe gradually leads to tissue hypoxia and neuronal dysfunction.

Nielsen RB, Egefjord L, Angleys H, Mouridsen K, Gejl M, Møller A, Brock B, Brændgaard H, Gottrup H, Rungby J, Eskildsen SF, Østergaard L. Capillary dysfunction is associated with symptom severity and neurodegeneration in Alzheimer's disease. (2017) *Alzheimer's and Dementia, 1-11 doi: /10.1016/j.jalz.2017.02.007*

These studies provide important new insights into the pathophysiology of Alzheimer's disease, as well as clues to how we might prevent and manage this devastating condition in the future.
PET/NUK and CFIN researchers currently collaborate closely on a range of other dementia-related projects, led by professor David Brooks. Three PhD students are currently affiliated to both NUK/PET and CFIN:

Visse Moestrup works with a promising molecular agent that - in animal models of AD – can remove

the increased levels of toxic amyloid beta protein observed in the brain tissue of these models. As part of her project, this promising molecule will be radiolabeled to allow the detection of its uptake in brain tissue by PET. Dirk Bender, Head of Radiochemistry acts as co-supervisor for Visse.

Carsten Gleesborg studies the sense of smell in patients with depression as compared to control subjects. Using a new method, developed in collaboration with Professor Morten Kringelbach, who holds joint appointments in Oxford and Aarhus, he has discovered changes in the structural connectivity of the brain in depressed patients relative to healthy controls.

Casper Schmidt works with the effects of two neurotransmitters, dopamine and serotonin, on impulsivity and compulsivity. He is particularly interested in these relations in patients with pathological gambling. The knowledge gained in this project may prove important in understanding and managing this serious condition.

Funding

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