Moving in

Annual report 2018

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

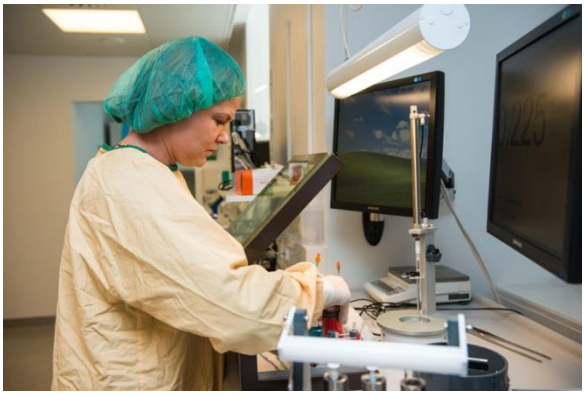
Aarhus University Hospital

Department of Nuclear Medicine & PET-Centre

AARHUS UNIVERSITY

Department of Nuclear Medicine & PET-Centre

2018



Building 3, Nørrebrogade

Building 10, Nørrebrogade

Skejby

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Preface

2018 has been a very special year in the history of the Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital. In 2018 we were finally able to start the physical merger of the Department's 3 sections, at the new buildings at Palle Juul-Jensens Boulevard, 8200 Aarhus N, and thereby watch the careful planning of the relocation of the Department be carried out. It has been a tremendous effort by the entire department, but every single member of our organization has been up to the task and the results are better than we could have dreamed of, when we started the planning several years ago.

We want to express our deepest gratitude to the dedication and hard work from everyone in our organization during all of 2018. The relocation will carry on well into 2019, and many important milestones have already been met. There have been several other joyful events in the Department in 2018 and therefore, it is our great pleasure to present the annual report from the Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital.

2018 marked the 25th anniversary of PET in Aarhus. A very happy and special day which was celebrated with a scientific symposium. On this day we looked back at 25 years of continuous development and excellence in research, and the translation of many years research into clinical routine, as well as a peek into the future of PET in Aarhus.

A big thank you to the many friends and colleagues who attended and contributed in making it a very special day for the Department. We also want to send our warmest thank you to the management of Aarhus University, Aarhus University Hospital and Central Denmark Region for the continuous support over the last 25 years to the Department. Running a highly active PET-Centre is a demanding task, which requires sufficient funding for infrastructure and personnel, which is impossible without the high level support we are given.

One of the many brilliant researchers at our department, Per Borghammer, was able to mark a preliminary highlight of an already outstanding career in 2018, when he was appointed Clinical Professor in Nuclear Medicine and Neuroscience. Per's research program is seeking to develop new scanning techniques which may help to finally understand the complicated nature of the early stages of Parkinson's Disease. Our warmest congratulations to Professor Per Borghammer.

During the summer of 2018, Professor, Head of Department Jørgen Frøkiær was given the opportunity to become Head of Department at the Department of Clinical Medicine at Aarhus University. After more than 25 years at the Department of Nuclear Medicine and PET-Center, Jørgen started a new career at Aarhus University, where he is now responsible for the pre-graduate education in medical science as well as

PREFACE

the basic health science research and clinical research within all medical specialties at the hospitals in Central Denmark Region. Therefore, we continue to enjoy collaborating with Jørgen and benefit from his great research skills. With Jørgen's departure, the position as Head Consultant was available and luckily Consultant Ate Haraldsen was up to the task and was appointed new Head Consultant.

This annual report is devoted to presenting some of the highlights of a very busy year. A year which in many ways, has been packed with preparations for the future of the Department. A future which is going to be built on an impressive infrastructure at our new facility, a strong inter-professional collaboration between the many disciplines working together both inside the Department and with good colleagues from Aarhus University and Aarhus University Hospital, and to a great extent on the dedication and excellence of all members of the staff.

We continue to strive towards the highest level of performance in every aspect of our Department's activities, emphasising the equal importance of our clinical work, our research and our educational activities as well as ensuring the most efficient use of equipment and personnel.

We are most grateful for the generous external financial support to our department, which is necessary to secure the development of new investigations based on research. This year we were graced with a most generous donation from A.P. Møller og Hustru Chastine Mc-Kinney Møllers Fond til almene Formaal to the purchase of a PET/MR scanner. This exciting modality is now entering a more mature stage and we look forward to implementing PET/MR into our existing research program and clinical activities, as well as exploring the many new possibilities that PET/MR brings to research and clinical work in the fields of nuclear medicine and clinical physiology.

Once again, we warmly thank our staff and colleagues from collaborating departments for their great effort. The collaboration with Aarhus University is fundamental for the excellent research achievements and we are grateful for the support from Aarhus University. Finally we thank the management of the hospital for their extensive support throughout a very busy year.

Ate Haraldsen

Michael Werenberg Mikkelsen

Jørgen Frøkiær

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Marianne Daugaard Junge, *Medical Laboratory Technologist* • **Marie Louise Olesen**, *Radiochemist, Production Manager* • **Marlene B. Øllgaard**, *Medical Laboratory Technologist* • **Martin Byskov Kinnerup**, *PhD Student* • **Mathias Mortensen**, *Medical Laboratory Technologist* • **Mette Abildgaard Pedersen** • **Mette Flarup Pedersen**, *Medical Laboratory Technologist* • **Mette Irene Theilgaard Simonsen**, *Medical Laboratory Technologist* • **Mette Lundborg**, *Medical Secretary* • **Michael Alle Madsen**, *MD, Registrar* • **Michael Werenberg Mikkelsen**, *Head Biomedical Laboratory Technologist* • **Michael Volmer**, *Electronics Engineer* • **Michael Winterdahl**, *Associate Professor, PhD* • **Michela Dahl Simonsen**, *Cleaning/Support Worker* • **Michele Gammeltoft**, *PA to Michael Werenberg Mikkelsen/Research Secretary* • **Mie Ringgaard Dollerup**, *Medical Laboratory Technologist* • **Mikkel Holm Vendelboe**, *MD, PhD* • **Morten Gersel Stokholm**, *MD, PhD Student* • **Nana Christensen**, *Medical Laboratory Technologist* • **Nanna Bløes**, *Medical Laboratory Technologist* • **Natalie Nielsen**, *Medical Laboratory Technologist* • **Natalie Van Den Berge**, *Postdoc* • **Neda Ahmadian**, *MD, Registrar* • **Nicola Pavese**, *Associate Professor, MD, PhD* •**Niels Nielsen**,*Electronics Engineer* • **Nohadra Younan**, *Medical Laboratory Technologist* • **Ole Lajord Munk**, *Medical physicist, PhD* • **Orhan Cankaya**, *Bachelor* • **Otto Bennike Kær**, *Medical Laboratory Technologist* •**Ove Noer**, *Research Assistant* • **Per Borghammer**, *Clinical Professor, MD, PhD, DMSc* • **Pernille Harbo Christensen**, *Medical Laboratory Technologist* • **Pernille Helga Juel-Jespersen**, *Medical Laboratory Technologist* • **Peter Frøhlich Staanum**, *Medical Physicist, PhD* • **Peter Iversen**, *MD, Specialist Registrar, PhD* • **Peter Parbo**, *MD, PhD student* • **Philip Jakobsen**, *Medical Laboratory Technologist* • **Pia Bliesmann Kithler**, *Cleaning/Support Worker* • **Pia Kjær Kristensen**, *Medical Secretary* • **Pia Loft Raunkjær**, *Cleaning/Support Worker* • **Rie Feldstein Nielsen**, *Cleaning/Support Worker* • **Rikke Bertelsen**, *Medical Laboratory Technologist* • **Rikke Kraack**, *Medical Laboratory Technologist* • **Rola Ismail**, *MD, PhD student* • **Shakti Nicolai Johansen**, *Medical Laboratory Technologist* • **Simon Maretti Tornbjerg**, *MD, Registrar* • **Steen Jakobsen**, *Radiochemist, PhD* • **Steffan Bruun Jensen**, *Electronics Engineer* • **Stine Mark Nielsen Gunni**, *Medical Secretary* • **Stine Kramer**, *MD, Consultant* • **Stine Ledet Methmann**, *Veterinary Nurse* • **Susanne Hansen**, *Medical Laboratory Technologist* • **Susanne Keiding**, *MD, Associate Professor* • **Søren Baarsgaard Hansen**, *Medical Physicist, PhD* • **Tanja Würtz Rasmussen**, *Department Medical Laboratory Technologist*

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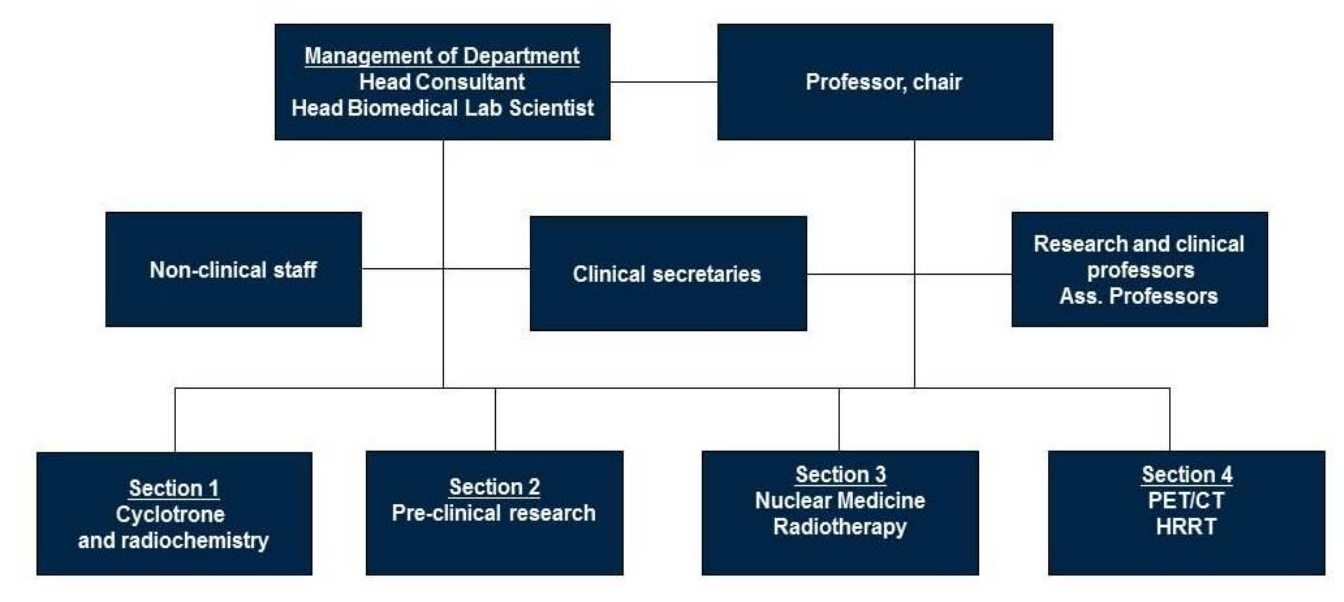
Tatyana D Fedorova, *MD, PhD student* • **Thanussan Tharumathas** •**Thea Pinholt Lillethorup**, *PhD Student* • **Thomas Knak**, *Electronics Engineer* • **Tina Bahn Larsen Niebuhr**, *Medical Laboratory Technologist* • **Tina Brang Christensen**, *Medical Secretary* • **Tine Nygaard Gregersen**, *MD, Registrar, PhD* • **Tinna Borchmann Budtz**, *Medical Secretary* • **Trond Velde Bogsrud**, *MD, Consultant, PhD* • **Vikie Engelbrekt Larsen**, *Medical Laboratory Technologist* • **Aage Kristian Olsen Alstrup**, *Veterinarian*



The organisation is divided into 4 sections, where all clinical, educational and research activities are carried out. The 4 sections are supported by a team of non-clinical staff and all research is coordinated in a research secretariat.

25 years anniversary of PET at Aarhus University Hospital

Søren Baarsgaard Hansen, Medical Physicist, PhD

On Friday the 26th of October, present and former staff of the department, key collaborators from several Danish institutions and special invited guests were gathered to celebrate the 25th anniversary of the launch of PET at Aarhus University Hospital.

The main part of the celebration was a very entertaining symposium, looking back on a rather impressive development of PET instrumentation and practice during the past 25 years, and also revealing some views of an exciting future to come.

The official inauguration of the PET centre took place on the 20th of October 1993, coinciding with the 100 years anniversary of the main city hospital in Aarhus, at that time known under the name of Aarhus Kommunehospital.

The new centre was organised as an independent hospital department, but with a strong mandate to perform biomedical research in collaboration with institutes and departments at Aarhus University and Aarhus University Hospital. The initial core staff consisted of 7.5 full-time positions under the leadership of Albert Gjedde. Thanks to generous support from various external sources the total staff at the PET centre soon reached over 25 people consisting of an interdisciplinary team of chemists, physicists, doctors, computer scientists, technologists, and PhD students. The research activities encompassed basically all aspects of human physiology using PET as the central methodological approach, in particular within clinical specialties like neurology, cardiology, oncology, and hepatology.

Absolutely crucial for the foundation of the PET centre was a generous grant from Karen Elise Jensens Fond, covering the purchase of the two main pieces of equipment necessary for PET, a PETtrace cyclotron from General Electric and an ECAT EXACT HR PET scanner from Siemens. In addition, hot-cells and a substantial list of auxiliary equipment were acquired based on support from the hospital and several external sources.

Already during the first decade with ever increasing activities, the PET centre was beginning to experience the limits of the allocated physical space as well as the finite capacity of the single PET scanner. Therefore, discussions soon commenced regarding the possibilities for expanding the centre, however, being part of a crowded city hospital, there was no easy solution, Despite the tight physical conditions, two new PET scanners were installed almost concurrently in 2005, a combined PET/CT scanner and a dedicated high-performance brain scanner (HRRT), both delivered by Siemens.

The next major milestone in the continued development of the PET centre was the establishment of the Danish Neuroscience Centre (DNC) as a collaboration between the Central Region Denmark and Aarhus University. This new building intended to facilitate the integration between the clinical environment and basic research laboratories within neuroscience was formally inaugurated on the 18th of September 2009. As part of this new facility the PET centre was upgraded with two additional PET/CT scanners, a second cyclotron, hot-cells and other equipment.

The establishment of the PET centre as an independent department with focus on research was a favourable strategy in 1993, however, with the exceptional clinical breakthrough of clinical PET during the 2000s, the organizational setup with PET and traditional nuclear medicine in two independent departments turned out to be impractical. As a consequence the two departments were merged on 1st of April 2011, although still located at three separate premises at Aarhus University hospital. During the spring of 2019 the physical integration will be completed after moving into modern buildings at the unified Aarhus University Hospital in Skejby.

Delivery of cyclotron 1993.
Photo: Søren Baarsgaard Hansen

Delivery of the first PET/CT scanner 2009
Photo: Søren Baarsgaard Hansen

HIGHLIGHTS 2018

January

Seminar for medical specialists.
Annual seminar for all medical specialists in the department. The theme in 2018 was future organisation of medical doctors in the department in the light of a new era coming up in the merged department.

February

Peter Parbo: PhD defence
Supervisor: David J. Brooks
A PET study of the relationship between microglial activation amyloid-β plaques and tau tangles in early Alzheimer's disease.

Professor, Department Chair, Consultant, DMSc, Jørgen Frøkiær was recognised by the Danish Physicians' Insurance Society for his extensive efforts within clinical and experimental organ function examinations with focus on the kidneys.

March

Jørgen Frøkiær, Jens Sørensen and Lars Tolbod received a grant from the International Network Programme of the Danish Agency for Science and Higher Education for exploring a collaboration with Osaka University on Tumor Blood Flow Imaging with 15O-water. This has been important for establishing an extensive relationship with the Department of Nuclear Medicine and Tracer Kinetics , Osaka University Graduate School of Medicine.

HIGHLIGHTS 2018

April

Morten G. Stokholm: PhD defence
Supervisor: Nicola Pavese
Early markers of synucleinopathy disorders in patients with idiopathic rapid eye movement sleep behaviour disorder.

New, as well as old equipment ,was delivered and installed in the new laboratory facilities at Skejby.

In april the new Comecer Theodorico II dispenser and ITD double stack hotcells were delivered.
Comecer stack hotcells from the facility at Nørrebrogade were moved.

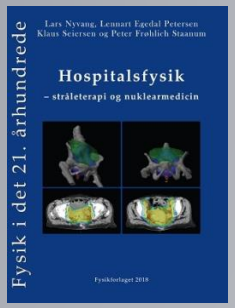
Photo: Niels Nielsen

May

Photo: Tonny Foghmar

GE PETtrace 800 cyclotron was delivered in May.
This was the first of three cyclotrons, that have been installed in the department.

Medical Physicist Peter Frøhlich Staanum co-authored the book "Hospitalsfysik - stråleterapi og nuklearmedicin" published by Fysikforlaget 2018 in May.



HIGHLIGHTS 2018

Kathrine Stokholm: PhD part A, defence
Supervisor: Annie Landau
Microglial activation and dopaminergic neurotransmission in an alpha-synuclein rat model of Parkinson's Disease.

Thea Pinholt Lillethorup: PhD defence
Supervisors: David J. Brooks and Annie Landau
Evaluating Göttingen minipig models of Parkinson's disease with PET imaging.

Medical secretary
Stine Gunni graduated
as Supervisor of clinical medical secretaries.

June

Jørgen Frøkiær received a grant of DKK 20 million from the Møller Foundation towards the co-financing of a combined PET-MRI scanner.
Jørgen Frøkiær has applied for the grant in collaboration with a wide circle of professors and consultants at AU and AUH.

Siemens Intevo SPECT/CT bold was delivered and installed in June.

The first patient was scanned on this scanner in August, just a few days before the official opening of the new department.

HIGHLIGHTS 2018

August

Kirstine Bak Petersen: PhD defence
Supervisor: Susanne Keiding
2-[18F]-fluoro-2-deoxy-D-galactose PET/CT in patients with hepatocellular carcinoma – methodological aspects and clinical impact.

September

Official opening of The Department of Nuclear Medicine and PET-Centre in AUH, Skejby. Directors Poul Blaabjerg and Henrik Bech Nielsen marked the opening with a gift for the department.

Medical Physicist Ole Munk welcomes the new GE Discovery MI5 PET/CT scanner.
The scanner was installed in November, and the first patient was scanned on November 15th.

Scanners from the existing department in Skejby, were moved: GE NM/CT 670 SPECT/CT, Mediso Th-45 and DDD Nephrocam.

HIGHLIGHTS 2018

October

Allan Hansen: PhD defence
Supervisor: Per Borghammer
Flortaucipir PET imaging of Parkinson's disease.

On the 26th of October the department celebrated the 25th anniversary of the PET modality in Aarhus.

Invited guests, colleagues and friends participated in a symposium.

The first of three Siemens Vision 600 PET/CT scanners was delivered and installed in oktober.

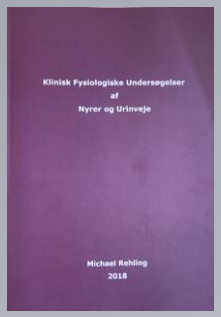
The first patient was scanned on November 27th.

November

Karoline Knudsen: PhD defence
Supervisor: Per Borghammer
Measures of Gastrointestinal Function in Parkinson's Disease

Karoline Knudsen is the first Medical Laboratory Technologist with a PhD, in the department.

Book release by Michael Rehling.
"Kliniske fysiologiske Undersøgelser af Nyrer og Urinveje"



In July Per Borghammer was appointed Clinical Professor of Nuclear Medicine and Neuroscience.

This was celebrated on November 14th, with a lecture by Per Borghammer, " Starter Parkinsons sygdom I tarmen? followed by a reception at the department.

December

Medical Physicist Søren Baarsgaard Hansen makes sure, that the new GE Signa PET-MR scanner is transported to the correct location.

The scanner arrived at the department just before Christmas on December 21th.

The departments GE MI-Digital Ready PET/CT scanner was moved from the existing department at Skejby to the new facilities.

Equipment

Equipment type	Model	Year of purchase
Gamma camera	Mediso TH-45	2005
	Mediso TH-45	2015
	DDD Nephrocam	2016
SPECT cameras	Philips CardioMD	2007
SPECT/CT scanners	GE Discovery NM/CT 670	2011
	Siemens Symbia T-16	2011
	Siemens Symbia T-16	2012
	Siemens Symbia Intevo Bold	2018
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
	Siemens Biograph Vision	2018
	GE Discovery MI	2018
	GE Discovery MI Digital Ready	2017
PET/MR scanner	GE Signa (Delievered, not installed)	2018
Cyclotrons	GE PETtrace	1993/2010
	IBA Cyclone 18/18	2009
	GE PETtrace 880+	2018
Pre-clinical equipment		
Phosphor imager	FujiFilm BAS-5000	2002
SPECT camera	Philips BrightView	2009
MicroPET/MRI	Mediso Nanoscan	2014

Molecular imaging of brain disorders

Per Borghammer, Clinical 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 Departments 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 partners and span the full range from tracer discovery and validation to implementation in clinical practice.

Clinical nuclear medicine examinations in brain disorders

Per Borghammer,Clinical Professor, MD, PhD, DMSc

Joel Aanerud, Specialist Registrar, MD, PhD

There is an increasing demand for PET and SPECT scans in the field of neurological and neuro-oncological disorders. During the past 8 years, the number of clinical brain examinations at our department has increased by almost 500%.

In 2018, we performed 650 18F-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 123I-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 select patients, 11C-PiB PET is used to verify the

presence pathological beta-amyloid, the defining feature of Alzheimer's disease.

In 2018, a total of 350 DaT SPECT scans were performed in patients with suspected Parkinson's disease or other movement disorders. In select movement disorder patients, the 123I-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.

Amino acid PET imaging is important in the management of patients with brain tumors. 18F-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 15O-H2O PET scans, which measure cerebral blood flow. By comparing the 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. 15O-H2O perfusion PET scans are also useful 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.

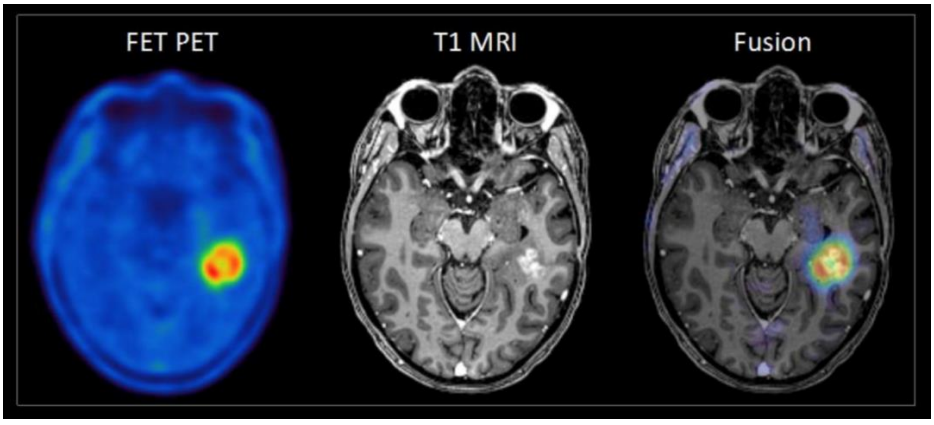


Figure 1: 18F-FET PET shows increased amino acid uptake in a malignant brain tumour. MRI demonstrates contrast enhancement suggestive of blood brain barrier disruption. On the fused images the FET-uptake extends beyond the contrast enhancement suggestive of tumour.

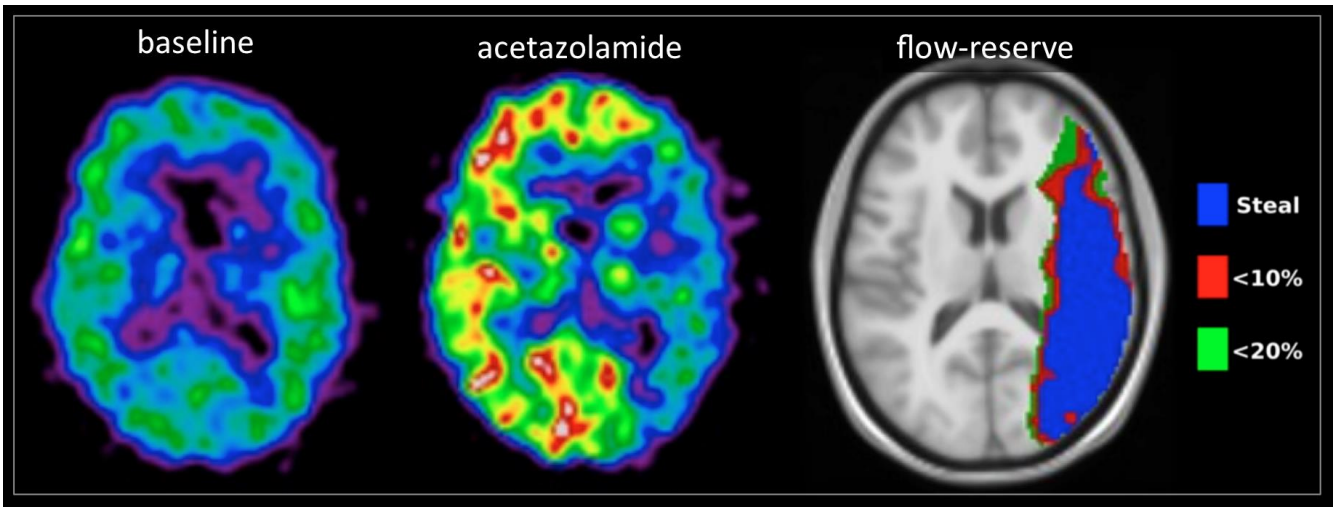


Figure 2: Cerebral perfusion in a patient with occluded left carotid artery is measured with ^{15}O-H_2O PET in baseline and after vaso-dilatory challenge using acetazolamide. Subtraction-analyses identify regions with significantly decreased flow-reserve (<10%) or paradoxical drop in perfusion (steal phenomenon)

Parametric whole body FDG PET/CT – next generation functional imaging


Lars Christian Gormsen, Clinical Associate Professor


Ole Lajord Munk, Medical physicist, PhD

Disease detection, staging and treatment response by 18F-FDG PET/CT (FDG PET/CT) has grown increasingly important, over the past 15 years. In short, FDG PET/CT provides a relative or static image of glucose accumulation in highly energy consuming tissues, notably in active malignant tumors but also in a range of inflammatory cells. As such, FDG PET/CT provides a marker of whether any abnormal structure detected by traditional imaging (CT, MRI and ultrasound) is active. However, current FDG PET/CT imaging systems still have several limitations of which slow image acquisition, poor resolution, tracer retention in the circulation and limited ability to quantify glucose uptake in absolute terms are the most important. The introduction of new PET/CT systems may overcome some of these obstacles.

In our department we have recently introduced state-of-the-science PET/CT systems (Siemens Vision) with improved resolution and the capacity to dynamically and accurately measure absolute glucose uptake in any tissue. This imaging method is termed **parametric imaging**.

Limitations of static FDG PET/CT

The essentially qualitative reading of standard static FDG PET images has several drawbacks. First, detection of radioactivity in a suspicious structure or organ does not contain information as to whether the radiotracer has been taken up by cells or is still in the blood pool. This is particularly a problem in highly perfused organs such as the liver or in the head and neck region but also when assessing inflammation in the large arteries. Secondly, the accumulated radioactivity is dependent on the exact time-point at which the PET scan is performed. In a clinical setting with frail and often seriously ill patients, who may not be able to co-operate optimally, it is not uncommon that the total uptake time of FDG can vary by as much as 30 minutes. Whereas this is usually not a problem at initial diagnosis, it may seriously hamper interpretation of treatment response. Any increase in uptake time at the treatment response scan will increase the likelihood that radioactivity in a structure increases and thus that the response is deemed insufficient. Thirdly, SUV values and therefore the signal-to-noise in the PET images are calculated with the

assumption that the entire injected tracer dose reaches the circulation. However, extravasation of radiotracer is possible in which case the SUV measurements will be erroneous. And finally, SUV values are highly dependent on the exact reconstruction algorithms and PET/CT systems used to produce the images and the inter-institutional variation is therefore significant. It has therefore proved impossible to reach international agreement on what level of FDG uptake should be considered malignant, particularly in smaller structures such as lymph nodes or pulmonary nodules.

Dynamic imaging

The challenges inherent to static FDG PET/CT outlined above can be overcome by dynamic imaging. In dynamic imaging, time-related changes in tissue radioactivity are detected throughout the entire duration of the scan as opposed to standard static imaging in which tissue radioactivity measurement is confined to a single time-point. Dynamic PET imaging has been used extensively in research – not least in our PET centre - and with a range of radiotracers. Translation to a clinical setting has primarily been limited by the complexity of concurrent blood sampling and the limited field of view. In short, dynamic PET imaging involves continous measurement of available radiotracer in the circulation (the **input function**) coupled with measurement of radioactivity in the tissue of interest. Transfer of radiotracer to the tissue and its subsequent intracellular fate can then be calculated based on more or less elaborate kinetic models. Since the tracer reflects the metabolism of the endogenous substance (the tracee), absolute uptake can be quantitated when the concentration of tracee in the blood stream is known. The absolute uptake values can then be displayed as a parametric image where each voxel of the image contains information of the uptake. In theory, absolute uptake values are less prone to inter-institutional variation and agreement on threshold values to determine pathology is therefore feasible.

Dynamic imaging with FDG

FDG is trapped in the cell after an initial phosphorylation and FDG kinetics can be quite accurately described by a model involving two intracellular compartments (two-tissue compartmental model). All transfer rates between the compartments can then be solved by differential equations fitted to the measured data. However, simpler methods to calculate FDG uptake also exists, not least the Gjedde-Patlak method. FDG uptake is overwhelmingly irreversible and the build-up of tracer in the tissue over time allows for simpler estimation using linearisation methods. The Gjedde-Patlak plot only requires exact measurements of the integrated input from the blood stream and 3-4 measurements of tissue radioactivity at a later time point when equilibrium between the circulation and tissue has been reached. In practice, radiotracer activity in the blood stream can be measured over the cardiac region for the initial 6 minutes after injection and subsequent imaging over the remaining part of the body can be done in several passes ensuring correct measurements of the buildup of tissue radioactivity (see figure 1).

The slope (k-value) of the Gjedde-Patlak curve then equals tissue uptake whereas the intercept is the volume of distribution, an estimation of radiotracer in the blood stream.

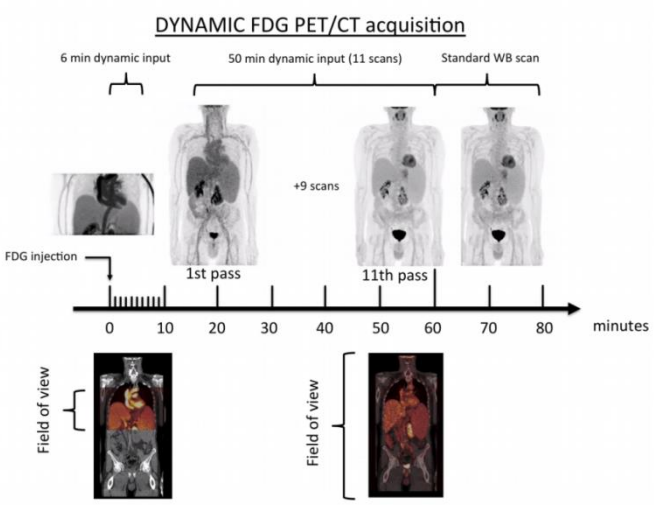


Figure 1

Preliminary data

The first of three Siemens Vision PET/CT systems was installed in our department in December 2018 and the first clinical patients underwent parametric FDG PET/CT scans at the same time. These patients were injected with the same FDG dose as is used for standard FDG PET/CT acquisitions and standard PET/CT images were obtained after 60-75 minutes. Thus patients were subjected to standard-of-care PET/CT and PET/CT images were comparable to any existing previous examinations. However, instead of injecting the radiotracer with the patient lying in a bed in a waiting room, the radiotracer was injected while the patients were lying in the scanner allowing us to obtain time-activity curves in the blood stream as well as in all organs within the designated area-of-interest (skull to mid-thigh). The resultant parametric images, FDG volume of distribution as well as static FDG PET images are shown in figure 2. Interestingly, we observed a greater number of processes than by standard static FDG PET/CT illustrating the enhanced sensitivity of the technique.

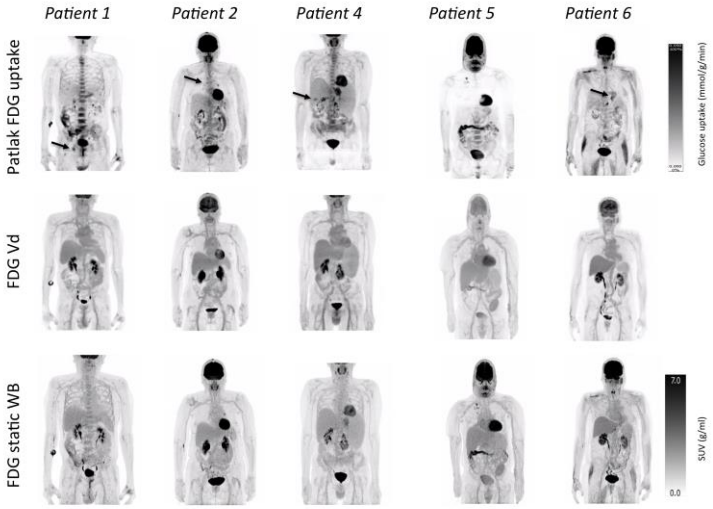


Figure 2

Perspectives

If parametric FDG PET/CT yields diagnostic information over and above what can be obtained by standard static FDG PET/CT, it is our aim to implement the technique in routine clinical practice for select patient groups and to continually expand the scope of indications as we gather information on patient related outcomes and their association with the parametric FDG PET/CT information. It is also our aim to test whether parametric PET/CT can be applied to other PET radiotracers such as tumor markers (DOTATOC and PSMA). It is our hope that the results of these studies will help us establish rational decision algorithms for selecting the most relevant PET/CT acquisition protocol for most patient groups.

Lymphoma

Joel Aanerud, Specialist Registrar, MD, PhD

The Department of Nuclear Medicine and PET-center, Aarhus University Hospital adheres to "Billediagnostiske guidelines for malignt lymfom 2015" (www.lymphoma.dk) regarding staging and treatment monitoring of malignant lymphoma. Hence, all patients with malignant lymphoma are scanned with FDG-PET, and diagnostic or low-dose CT prior to treatment (pretherapeutic staging), after a few (one to three) courses of chemotherapy (interim assessment) and after treatment (end-of-treatment assessment).

Our goal is to provide FDG-PET/CT reports of high quality, tailored to the needs of referring physicians, and in order to achieve this goal we strive to:

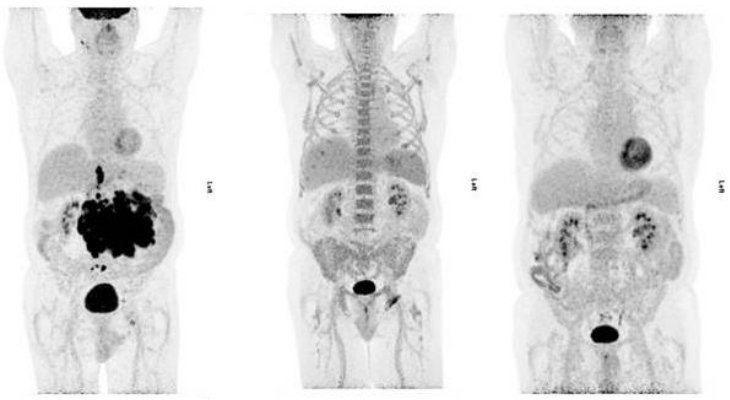
1. scan newly diagnosed patients and patients with prior lymphoma under suspicion of relapse, as fast as possible.
2. provide reports that answer questions posed by referring physicians, as precisely as possible.
3. use clear and consistent language in reports, in order to optimize understanding on the receiving end.
4. use Lugano and Deauville classifications for the purpose of comparability between scans and reports, and to make conclusions unambiguous.
5. work closely with physicians from the radiological department, so that imaging findings relevant for choice of treatment and evaluation of treatment response, are presented in a common summary for both FDG-PET and CT.

In 2018, we performed 735 FDG-PET scans on patients with malignant lymphoma at NUKPET AUH. Distribution between different types of lymphoma, is shown in **table 1.**

Table 1

Subtype of lymphoma	Number	[%]
Diffuse large B-cell lymphoma	221	30
Hodgkin lymphoma	122	17
Malignant lymphoma – not otherwise specified	103	14
Follicular lymphoma	84	11
Peripheral T-cell lymphoma	82	11
Mantel-cell lymphoma	52	7
Non-Hodgkin lymphoma - not otherwise specified	49	7
Multiple myeloma and plasmacytoma	22	3
Total	735	100

When observing the mentioned imaging guidelines, one would expect pretherapeutic staging, interim assessment and end-of-treatment assessment to account for roughly one third of scans each. However, pretherapeutic staging and interim assessment account for 27 and 28% of scans, respectively. End-of-treatment assessment accounts for only 18%, reflecting the fact that a proportion of lymphomas do not respond favorably to treatment, and treatment is consequently changed after interim assessment. In these cases, interim assessment has the role of a new pretherapeutic assessment, and after switching treatment, a new interim assessment is made. The remaining 27% of indications for FDG-PET/CT are made up of possible Richter's transformation, possible recurrence of prior lymphoma, or assessment after radiation therapy or bone marrow transplant.



Pretherapeutic staging | Interrim assessment | End-of-treatment assessment

Nuclear Cardiology

Kirsten Bouchelouche, Associate Professor, Senior Consultant, DMSc

The Department of Nuclear Medicine & PET-Centre is a core facility at Aarhus University Hospital in the diagnostic evaluation of patients with cardiac diseases. In the past 15 years we have performed more than 1000 myocardial perfusion imaging (MPI) studies annualy, in patients with suspected or known ischemic heart disease, and more than 800 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 Department of Cardiology and Department of Oncology at Aarhus University Hospital. Two cyclotrons and a highly specialized radiochemistry laboratory give us the possibility to work with both established and novel PET-tracers and methods. Several radiolabeled tracers are available for PET scanners. The most validated tracers for determination of cardiac PET perfusion are: ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb. Both ^{15}O-water and ^{13}N-ammonia require an on-site cyclotron, whereas ^{82}Rb only requires a generator with replacement every 4-6 weeks, thereby offering an alternative to departments without a cyclotron. ^{82}Rb-PET was implemented in 2012 in our Department, and we have performed more than 6000 ^{82}Rb-PET scans in cardiac patients for evaluation of myocardial perfusion, both in clinical practice and in research studies. Furthermore, more than 300 ^{15}O-water PET scans for myocardial perfusion have been performed since 2011 in research protocols. ^{15}O-water PET is the reference standard for measuring myocardial blood flow (MBF) in absolute values (ml/min/g), and in 2019 we plan to replace ^{82}Rb-PET with ^{15}O-water PET for clinical myocardial perfusion imaging (MPI).

The short half-life of both ^{82}Rb (75 min) and ^{15}O-water (2 min) makes it possible to perform rest/stress paired PET MBF studies within a short study period of less than 30 minutes, while improving patient comfort and throughput. Furthermore, patient and staff radiation exposure is significantly reduced compared to conventional technetium-99m (^{99m}Tc) SPECT MPI due to the much shorter scan time and no waiting time to clear background radiation. The high number of cardiac PET MPI per day is only possible because of very close and excellent team work between the technicians, medical students and physicians. A team consisting of 4 dedicated and trained medical students help the staff with the ^{82}Rb-PET scans approximately 2 days per week.

The quantitative perfusion analysis with both ^{82}Rb and ^{15}O-water extends the scope and adds valuable information to the traditional semi-quantitative MPI assessment with conventional ^{99m}Tc SPECT MPI; e.g. in 1) identification of the extent of a multivessel coronary artery disease (CAD) burden, 2) patients with balanced 3-vessel CAD, 3) patients with subclinical CAD, and 4) patients with regional flow variance despite of a high global myocardial flow reserve (MFR). We only use SPECT MPI in patients not suited for adenosine stress or if there is suspicion of an intramural coronary artery.

^{18}F-FDG cardiac PET in combination with ^{82}Rb-PET is used in clinical and research settings for evaluation of myocardial viability. ^{18}F-FDG PET is the most sensitive non-invasive test for distinguishing between necrotic and hibernating myocardium in patients with severe CAD and impaired left ventricular function. As one of very few sites worldwide (and perhaps the only site), hyperinsulinemic-euglycemic-clamping has been implemented in clinical routine to get the best and optimal FDG PET images for evaluation of myocardial viability. We perform 2-3 viability studies per week and many of these scans are discussed at the weekly nuclear cardiology multidisciplinary team (MDT) conference.

The role of the MDT meeting is firmly established in oncology where it underpins the decision-making process. This approach has, however, been inconsistently and variably implemented for coronary revascularization in different countries. Nuclear cardiology MDT conferences have been well established at AUH for many years. Nuclear MDT meetings are held once per week and last 1-2 hrs. Specialists from Depts. of Cardiology, Cardiothoracic & Vascular Surgery, and Nuclear Medicine & PET Centre participate in these MDT conferences. The more advanced clinical cases are discussed and relevant ^{82}Rb PET and ^{18}F-FDG viability PET scans are demonstrated and discussed, and the best and optimal treatment for each patient is decided.

^{82}Rb - PET perfusion

Static images | Polar plot

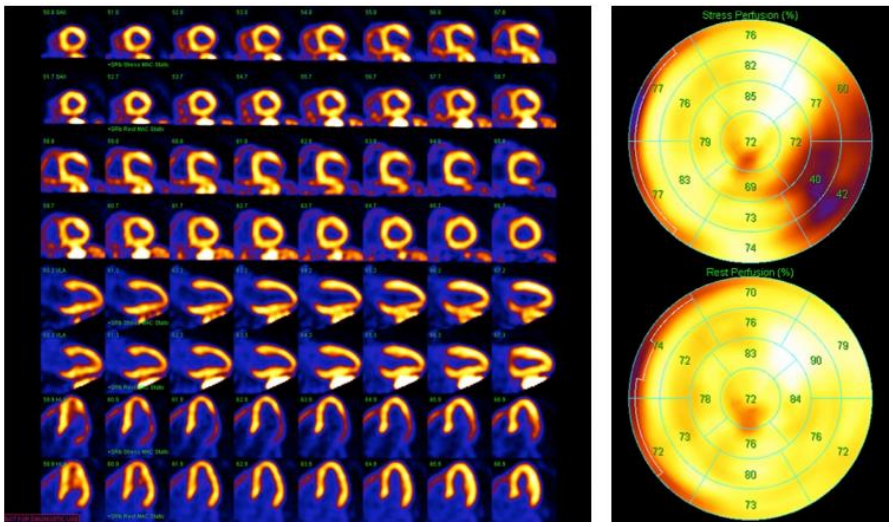
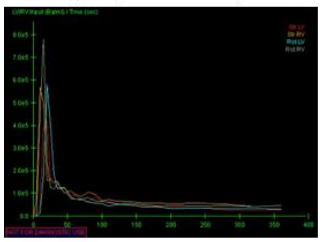
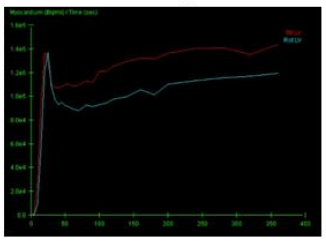


Figure 1

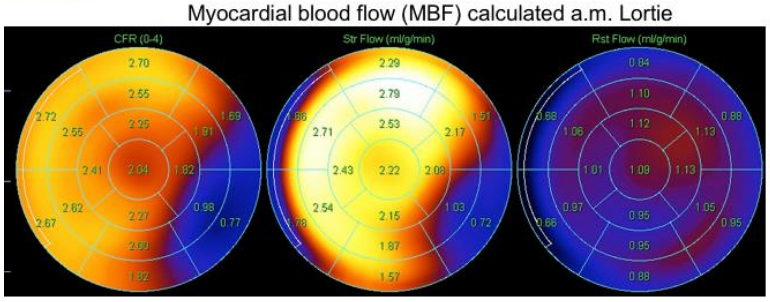
^{82}Rb - PET perfusion quantification

Input (left ventricle) | Tissue activity curve





Myocardial blood flow (MBF) calculated a.m. Lortie



Regional MBF

	Str Flow	Rst Flow	CFR	Str SF	Rst SF
APX	2.25	1.08	2.08	0.30	0.30
LAT	1.34	1.02	1.28	0.30	0.30
INF	1.79	0.90	2.02	0.30	0.29
SEP	2.31	0.90	2.58	0.33	0.30
ANT	2.49	1.00	2.49	0.31	0.30
TOT	2.00	0.98	2.06	0.31	0.30

Figure 2

Figure 1-2: A man with typical angina was referred to ^{82}Rb-PET. The scan demonstrated reversible ischemia in the Cx coronary artery both on the static image (fig. 1) and reduced absolute flow values and myocardial flow reserve in the same area (fig.2). The patient was discussed at the nuclear MDT conference and referred to invasive PCI with good effect on the symptoms.

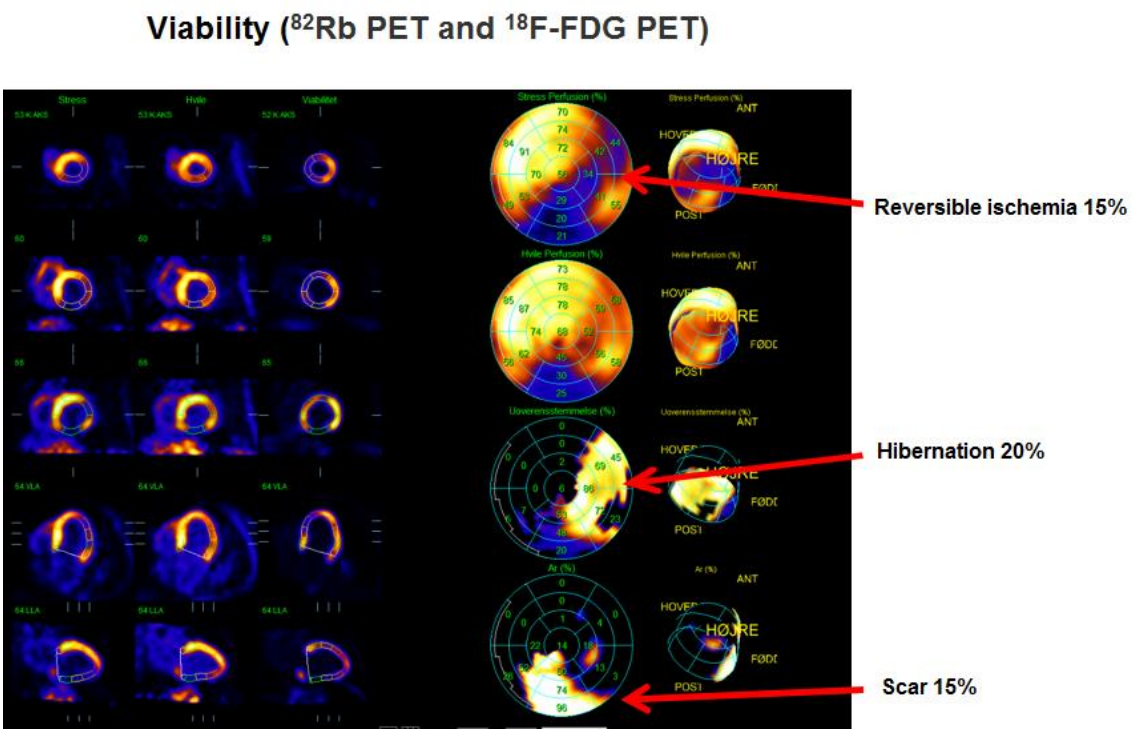


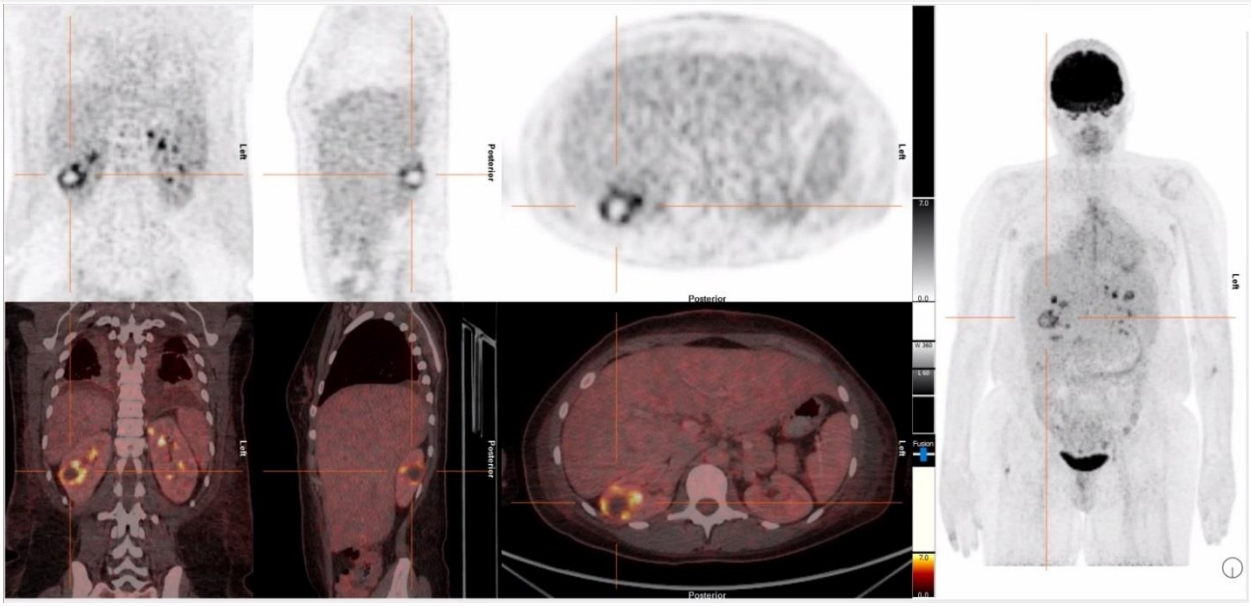
Figure 3: A man with angina, chronic occluded coronary artery on the angiogram and reduced EF was referred for viability scan. The patient underwent standard ^{82}Rb-PET and ^{18}F-FDG viability PET of the heart. The scans revealed areas with reversible ischemia, hibernation and scar tissue as shown on the figure. After discussion at the nuclear MDT conference, the patient had a PCI of the occluded Cx coronary artery.

High quality scientific research in nuclear cardiology is valuable and the aim of our cardiac research is to develop, advance and evaluate new and established nuclear cardiac imaging methods to optimize and improve the diagnosis, management and clinical outcome of patients with various cardiac diseases including, ischemic heart disease, heart failure, cardiomyopathies as well as diabetes. The Department has for a number of years conducted and published several clinical trials in collaboration with the Department of Cardiology at Aarhus University Hospital, and numerous cardiac research activities are ongoing in close collaboration with The PET Centre in Uppsala, Sweden and Boston, USA. Further information on Cardiac Research on page 61.

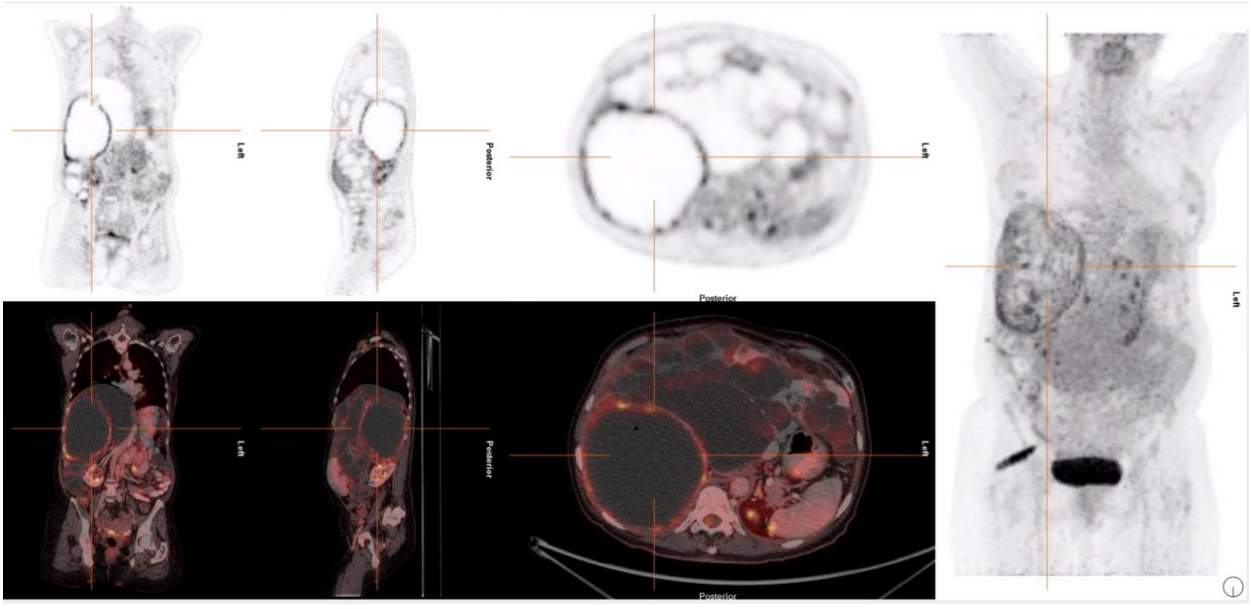
Using nuclear medicine examinations to diagnose infectious diseases

André H. Dias, Specialist Registrar, MD

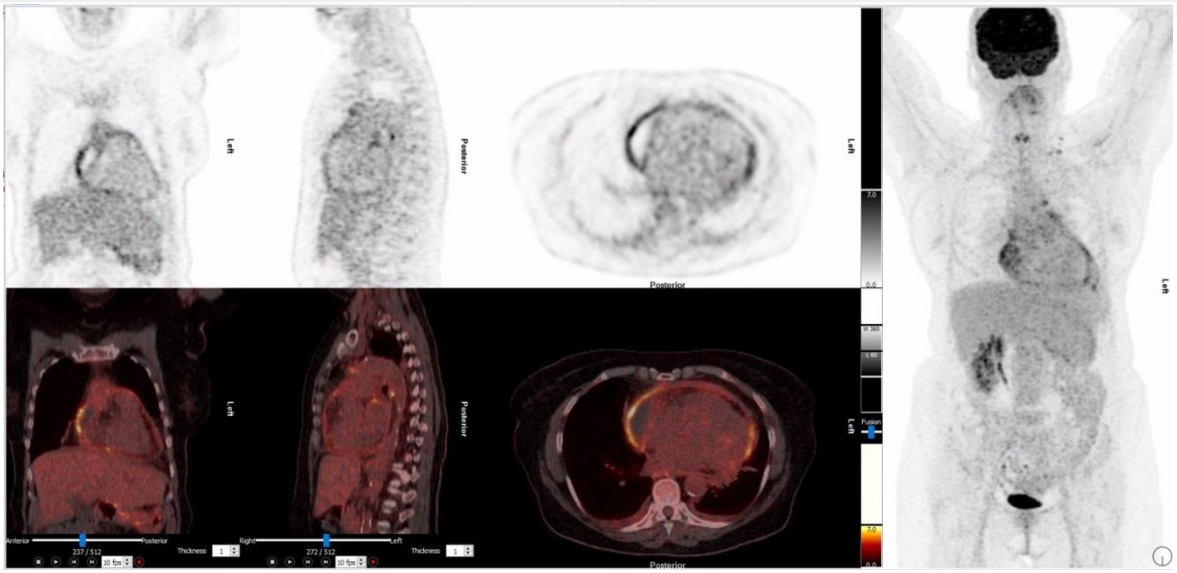
The demand for functional imaging of infectious diseases has been increasing steadily over the past decades. Labelled leukocyte imaging using 99mTc-HMPAO or 111In-oxine scintigraphy has traditionally been the radionuclide procedure of choice for diagnosing most infections, due to the ability of radiolabeled granulocytes to migrate to the foci of infection. However, these studies require extensive and time consuming laboratory preparation of the patients' blood under sterile conditions, with extraction of leukocytes that are subsequently labeled with the chosen radioactive isotope and then reinjected into the patient. In addition, an acceptable level of leukocytes has to be present in the circulation, rendering the procedure inaccessible to immunocompromised patients. Furthermore, although gamma camera scintigraphies have improved with more recent scanner generations, the images still suffer from serious problems with poor resolution. 18F-Fluorodeoxyglucose (FDG) is a PET isotope labeled radiotracer that mimics the metabolic pathway of glucose in the body. FDG thus accumulates in malignant cells as well as in the leukocytes involved in most infectious and inflammatory diseases. This non-specificity is extremely valuable in the diagnosis of fever of unknown origin (FUO), which is in most cases caused by one of these three conditions. At the Department of Nuclear Medicine & PET-Centre, we scan around 650-700 patients per year with PET/CT for infection/inflammation. Around 75% of these patients are scanned due to suspected infection with FUO as the most prevalent indication. FUO was defined in 1961 by Petersdorf and Beeson as a recurrent fever of 38.3 or higher, lasting 2-3 weeks or longer and that remains undiagnosed after 1 week of hospital evaluation. These patients often require longs periods of internment in clinical departments and per definition undergo long periods of broad spectrum antibiotic treatment without good results or resolution. In this setting, FDG PET/CT is often a valuable tool in the diagnostic arsenal of the clinician, directing the approach to e.g. biopsies as well as guiding possible treatment strategies. In the following, we present representative examples of FDG PET/CT scans in which the procedure was helpful to the referring clinician.



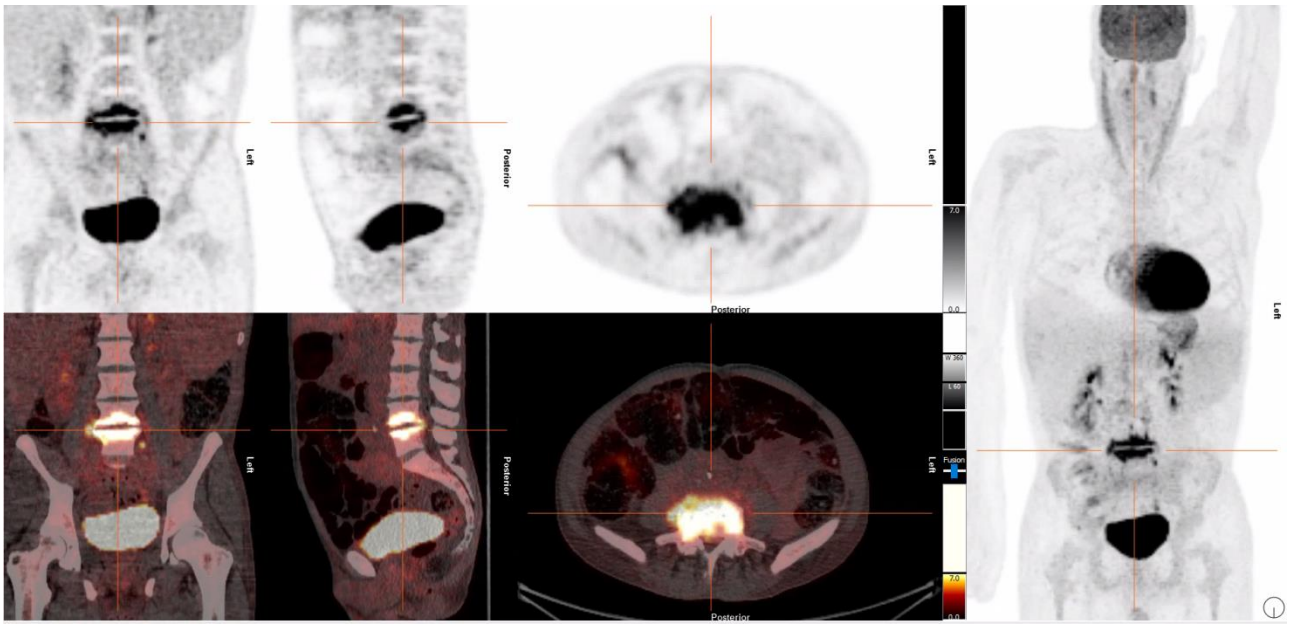
In this example a patient known to have endocarditis had persistently elevated CRP and recurrent fever after broad spectrum antibiotic treatment. FDG PET/CT showed an abscess in the right kidney, caused by septic embolization.



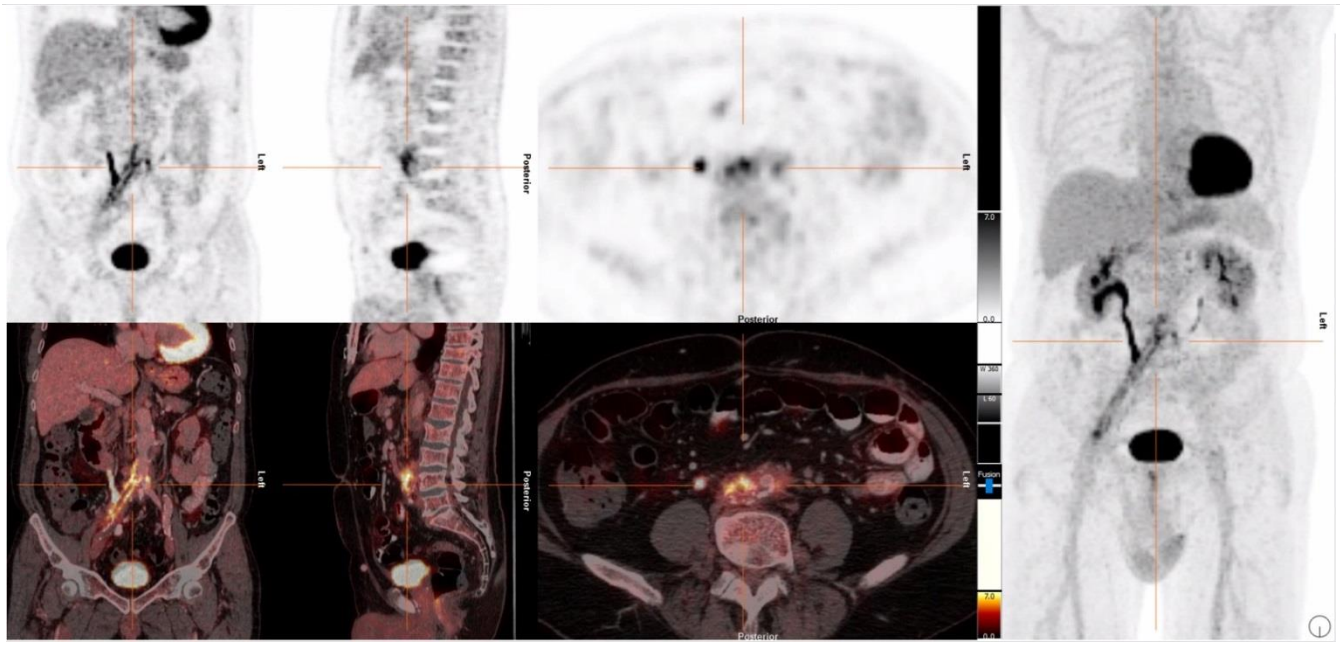
A patient with polycystic liver and kidney disease had been admitted multiple times with recurrent fever and biochemical signs of infection. FDG PET/CT convincingly revealed which of the cysts in the liver was infected, permitting adequate subsequent drainage.



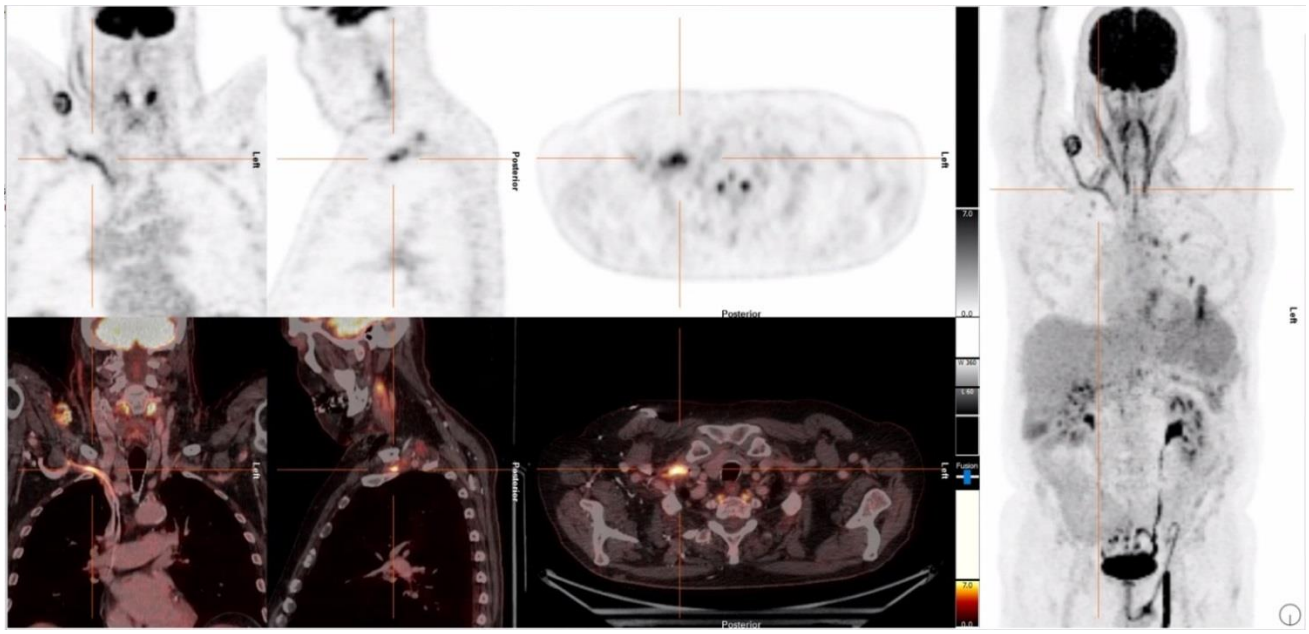
This patient was shown to have pericarditis as cause of her recurrent fever episodes.



This young patient with persistent back pain and fever was shown to have a spondylodiscitis of L4/L5.
FDG PET/CT has shown superior sensitivity regarding the diagnosis of spondylodiscitis when compared with conventional radiological techniques like CT and MRI



FDG PET/CT can also be used to visualize prosthetic material infection like in this aorto-bifemoral bypass showing infection of the right side of the prosthesis.



FDG PET showing an infection of pacemaker electrodes on the right side of the thorax.

Therapy of prostate cancer - Xofigo

Peter Iversen, Specialist Registrar, PhD

Prostate cancer (PC) is the second most common cancer form in men, except for benign skin cancer. The annual incidence in Denmark of PC is 4500 patients.

About 10-20% of patients develop castration resistant PC (mCRPC), which means that the disease no longer responds to antihormone therapy. The prognosis is poor with an overall survival rate between 1 and 2 years.

Xofigo is a bone-seeking radioactive pharmaceutical for PC patients with symptomatic bone metastasis and no disease outside the skeleton, ie. lymph node or organ metastases. In most cases Xofigo (Ra-223) is being offered as a last line therapy, or after second line chemotherapy. Since September 2017, 39 patients have been treated in the department including patients from Central Region, Denmark and referred from the Department of Urology at Aarhus University Hospital and Regional Hospital West Jutland, Holstebro.

Before referring the patient for treatment with Xofigo, a bone scan has to be performed in order to estimate the osteoblastic activity in the skeleton. The metastases from prostate cancer are normally only osteoblastic, meaning that the bone metabolism is higher in the affected/metastatic areas. Metastases outside the skeleton are evaluated by a diagnostic CT in order to exclude patients with more advanced disease from being treated with Xofigo.

In most cases, patients are eligible, but in some patients the disease in the skeleton is too extensive for successful treatment. Another success criteria is that the patient has to be physically able to tolerate treatment (performance status) making it more likely for the patient to complete the 6 treatments in a series. The treatment has a documented effect with regards to survival and pain alleviation in patients completing 5-6 treatments. It is also important that the patient has a bone marrow function close to the normal range in order to complete a full treatment cycle. Patients intensively treated with different chemotherapy regimens before being evaluated for Xofigo, are more prone to bone marrow toxicity, which is one of the main reasons for stopping the Xofigo treatment.

There are numerous safety issues when dealing with Xofigo. The patients have to be clinically evaluated before each treatment with a bone marrow status (blood samples)

as close to the next cycle as possible. In some cases the treatment will be postponed 2-4 weeks due to bone marrow suppression. There are also strict radiation safety rules for both the staff and the patients during and after administration of each treatment.

Perspectives

Xofigo is a safe treatment, and each treatment can be performed in an outpatient clinic saving the patients time and the limited resources in the nuclear medicine unit. The treatment has shortcomings, as it is limited to patients with symptomatic bone metastasis with no spread to soft tissue, and the patient has to be physically able to tolerate the treatment.

In the last decade, nuclear medicine units in Germany have offered eligible mCRPC patients a new and more targeted treatment under the 'compassionate drug use'. They have targeted the Prostate-specific membrane antigen (PSMA), which is a receptor located on the surface of prostate cancer cells. These receptors are overexpressed in a sufficient number in about 80% of mCRPC patients to allow PSMA radioligand therapy. The receptor density can be evaluated before treatment by a Gallium-68, Fluoride-18 or other PSMA PET tracers as part of the theranostic principle. It is also possible to use the same tracer for posttherapy evaluation.

Most centres have been using Lutetium-177 (Lu-177) as the radioligand for the therapy with PSMA, but case reports and small pilot studies using other radioligands such as Actinium-225 and Copper-64 in humans have been published.

From 2014 to 2015, the German Society of Nuclear Medicine conducted a multicentre study including 145 mCRPC patients, which were all treated with radioactive labelled Lu-177 PSMA (Lu-177-PSMA-617), showing a significant biochemical response, as indicated by the tumour marker, prostate specific antigen (PSA) in comparison to other third-line systemic therapies. The study also showed limited side effects. Other studies have shown similar effects.

The department is currently part of a phase 3 multicentre study using Lu-177 PSMA-617 in a selected group of mCRPC patients to evaluate the efficacy of the drug compared to a standard of care therapy. The implications of theranostics in the radiotherapy of prostate cancer are wide, and it's likely that this or other similar radioactive pharmaceuticals will be part of a future clinical setting.

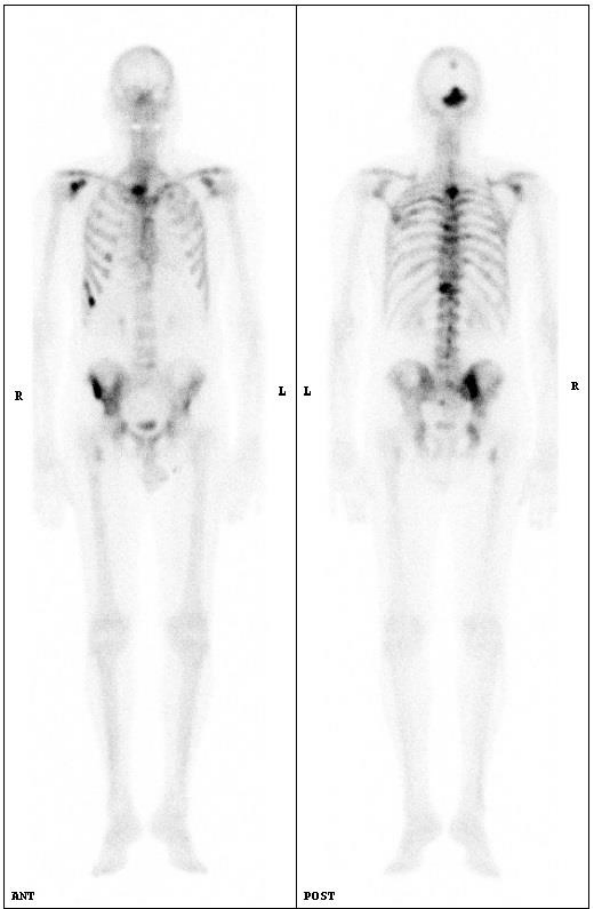


Figure 1: Shows a pretherapeutic bone scintigraphy (Tc-99m DPD). Planar images in anterior (left) and posterior (right) views showing multiple metastasis in the axial skeleton, skull, arm and legs.

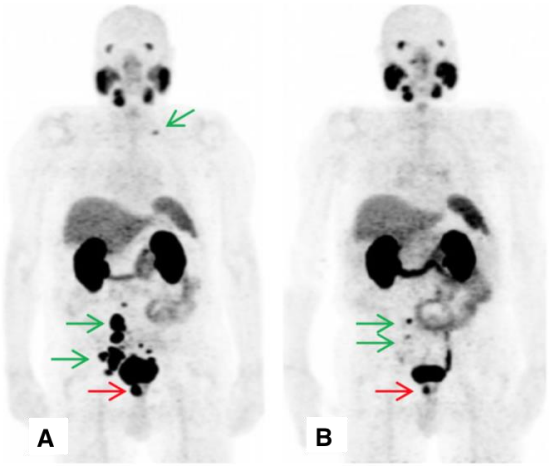


Figure 2: Ga-68 PSMA-11 PET/CT of an 80-year- old CRPC-patient before (A) and after four treatment with Lu-177 PSMA-617 (B). Notice the significant treatment response to the primary tumor (red arrow) as well as the lymph node metastases (green arrows).
From: Eur J Nucl Med Mol Imaging. 2018 Mar;45(3):471-495.

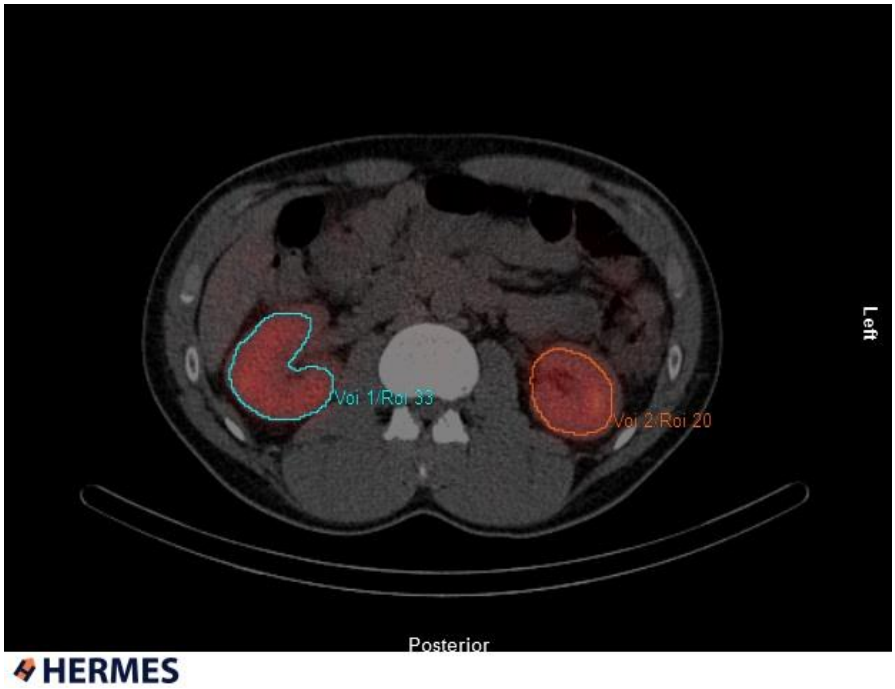
Dosimetry in radionuclide therapy of neuroendocrine tumors

Peter Frøhlich Staanum, Medical Physicist, PhD

In radionuclide therapy of cancers, cancer cells are irradiated using beta- or alpha-emitting radionuclides. The goal is to destroy all – or at least some - cancer cells in order to either cure or to reduce or stabilize the extent of the cancer. In some cases the latter alleviates symptoms and possibly downstages the disease making other treatments available such as surgical resection. The goal is best reached when a large dose of radiation can be delivered to all tumors, however, the dose cannot be increased indefinitely, because side effects due to radiation damage to healthy tissue will occur and because of the risk of developing secondary cancers.

In nuclear medicine we usually prescribe an activity (MBq or GBq) and not a physical radiation dose to the tumor(s) (Gy). In treatment of neuroendocrine tumors using peptide receptor radionuclide therapy (PRRT), a standard activity (possibly adjusted by body weight) has traditionally been prescribed. In the case of Lu-177-DOTATATE and Lu-177-DOTATOC, the standard treatment consists of 4 fractions of 7,4 GBq each.

Since the introduction of Lu-177-DOTATATE in 2015 and Lu-177-DOTATOC in 2017, we have performed post-treatment quantitative SPECT-CT scans of the abdominal region of the patients in order to determine the total radiation dose to the kidneys, which is the primary organ-at-risk for permanent damage in PRRT. After the initial treatment, patients are scanned 1, 4 and 7 days post-injection in order to determine a time-activity curve of the kidneys. The radiation dose to the kidneys can be determined from the time-activity curve, as the dose is proportional to the area under the curve (see figure 1). After the following treatments only a single scan is normally performed one day post-injection, and the excretion rate after these treatments are assumed to be identical to that of the first treatment.



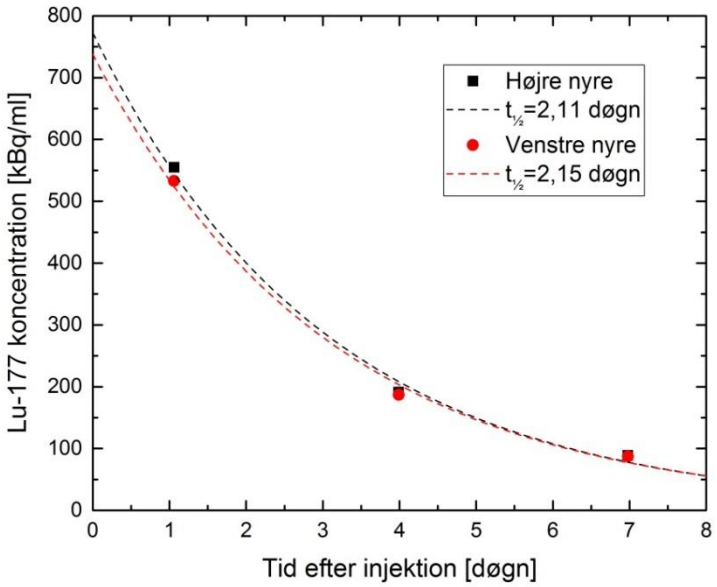


Figure 1. (a) Delineation of the kidneys in one slice of a quantitative SPECT-CT scan. (b) Time-activity curve showing the mean concentration of Lu-177 in both kidneys as a function of time after injection. For both kidneys the excretion of Lu-177 is represented by a single-exponential decay with a half life of about 2,1 days. The half life of Lu-177 is 6,647 days.

Our studies show that the radiation dose to the kidneys per injected activity (Gy/GBq) can vary by as much as a factor of 4 between individual patients. This strongly indicates that a more individualized treatment schedule would be beneficial to the patients.

The relation between the accumulated dose to the kidneys and the probability of causing chronic damage to the kidneys is not very well known. From external beam radiation therapy a limit of 23 Gy has been derived, however, this is most likely a conservative limit and in recent years the application of this limit in PRRT has been challenged. We find doses to the kidneys per injected activity in the range 0,2 to 0,8 Gy/GBq. Almost all patients can receive the standard treatment of 4x7,4 GBq, and most patients are able to get further treatments without receiving an accumulated dose of more than 23 Gy to the kidneys.

The dosimetry setup is finding increased use in a clinical setting. If indicated and recommended by the multidisciplinary tumor board, the knowledge of the radiation dose aids in judging if a patient can receive additional treatments. A number of patients have received more than 4x7,4 GBq with cumulated actitivity up to 53 GBq. The determined radiation dose is also applied to judge if a significant and rapid decline in kidney function is likely to be due to radiation damage. The latter has never been the case at our centre, which underlines that peptide receptor radionuclide therapy is a relatively safe therapy, with only limited side effects.

In the coming years we aim for individualized dosimetry in all patients referred for PRRT, with a much stronger guidance of the treatment schedule from knowledge of the radiation dose to the kidneys as well as larger tumors.

In the future, similar methods and strategies are also likely to find use in other radionuclide therapies like Lu-177-PSMA therapy of prostate cancer metastases.

PET - Radiochemistry

Chief-chemist Dirk Bender, PhD.

In 2018 a new state of the art GMP laboratory, new cyclotron and QC laboratory were installed at Palle Juul-Jensens Boulevard 165. Complete installation was delayed several times due to general hospital construction delays. As a result, the laboratory approval process which was scheduled for June 2018, could first be started in late December 2018. Likewise it was necessary to postpone inspections of the new facilities by the Danish Medicines Agency in order to obtain the § 39 production licence.
Considerable resources were assigned to completing the installation. This caused a reduction in production capacity at Nørrebrogade 44 several times within 2018.

Final approval of the laboratories is expected by the end of January 2019 with a production licence shortly after. This will allow production to be closed down at Nørrebrogade 44 in the first quarter 2019 and the relocation of heavy equipment such as cyclotrons and hot cells to start shortly after.
Relocation and reinstallation is expected to be finalized by the end of 2019 thereby reassuring full production capacity. In terms of tracer productions, PET tracers were again supplied every working day, meaning no down-time was observed. The centre's 7 PET radiochemists, 3 PET radiochemistry technologists and 4 other technologists, responsible for the FDG morning production, performed almost 1500 PET tracer productions, dedicated for use in patients and healthy control subjects. The radiotracer portfolio of tracers produced within delivery permits or marketing authorization increased to 44 compounds in 2018. From this radiotracer portfolio 23 different tracers were used in 2018. This is remarkable taking into account the additional workload due to the relocation of the facility to Palle Juul-Jensens Boulevard.

FDG was the dominating PET tracer in 2018 with 10977 doses (67.6%). Besides the generator-based Rb-82 (2348 doses, 14.4%), all other tracer productions varied from a few produced doses to several hundred. In 2018 we observed a drastic increase in deliveries of F-18 NaF, mainly to Vejle.

As for the Ga-68 labelled tracers the demand for Ga-68 PSMA was still somewhat increasing in 2018. It is planned to substitute Ga-68 PSMA with an F-18 PSMA variant in 2019. F-18 PSMA may be produced in much

larger quantities and covers the unmet demand for examinations using PSMA.

In 2018 three new tracers were included in the pipeline for tracer development for human use:
The dopamine transporter ligand F-18 PE2I, C-11 UCB-J for imaging the Synaptic Vesicle Glycoprotein 2A in the brain and F-18 PSMA-1007 for prostate cancer imaging and F-18 FEOBV. F-18 PE2I PET imaging is intended to replace the costly SPECT scanning procedure by applying the commercially available DaTscan™ which will help to compensate for budget reductions. C-11 UCB-J, developed at Yale University, is probably the most promising PET tracer for PET neuroimaging in years and several projects aimed at imaging synapses in neurological disease are already lined up. F-18 PSMA-1007 is meant to be a replacement for the above -mentioned Ga-68 PSMA. Besides the considerably higher resolution due to the better PET properties of F-18, the availability of the generator-based Ga-68 PSMA is a considerable limitation for covering the demand of PSMA examinations. The aim is to have these three tracers available for studies in humans in 2018.

In 2018 the department continued to supply radiotracers out-of-house to up to 8 different user sites. The total number of radiotracer deliveries was 1141, an increase of approximately 10%. The main out-of-house user sites in 2018 were Aalborg University Hospital, Aarhus University Hospital Department of Nuclear Medicine at Skejby, Aarhus University Hospital Department of Oncology at Skejby and the Regional Hospital in Herning with more than 200 deliveries per year to each site. In 2018 the total number of delivered doses was 6773.

The main challenge for 2019 will be the establishment of the department's new facilities at the New Aarhus University Hospital in Skejby and to obtain a production licence for this new site and at the same time continue production activities at the existing site at Nørrebrogade. The aim is to have a production licence for the new facility and start production of F-18 tracers by the end of the first quarter 2019. Upon availability of production and PET scanning capacity at Skejby, relocation of the existing two cyclotrons and hot cell equipment will be started. However, it is not likely that relocation will be finished before the end of 2019/start 2020.

In terms of research activities the PET centre's radiochemistry continues its program for the development of new labelling techniques and tracer development. These research activities are performed in department internal collaborations, AUH internal collaborations, joint projects with Aarhus University departments and other universities in Denmark and Europe, here besides others partner in EU FP 7 initiative targeting tracers for alpha synuclein aggregates. Besides scientific collaborations, collaborations with industry (currently Novo Nordisk, Lundbeck, Ferring and Ipsen/Octreopham) continued as well in 2018.

Concerning the departments teaching obligations, the PhD course, "Introduction to GMP", introduced in 2016, was held in 2018. This course was a success and will be available again in September 2019

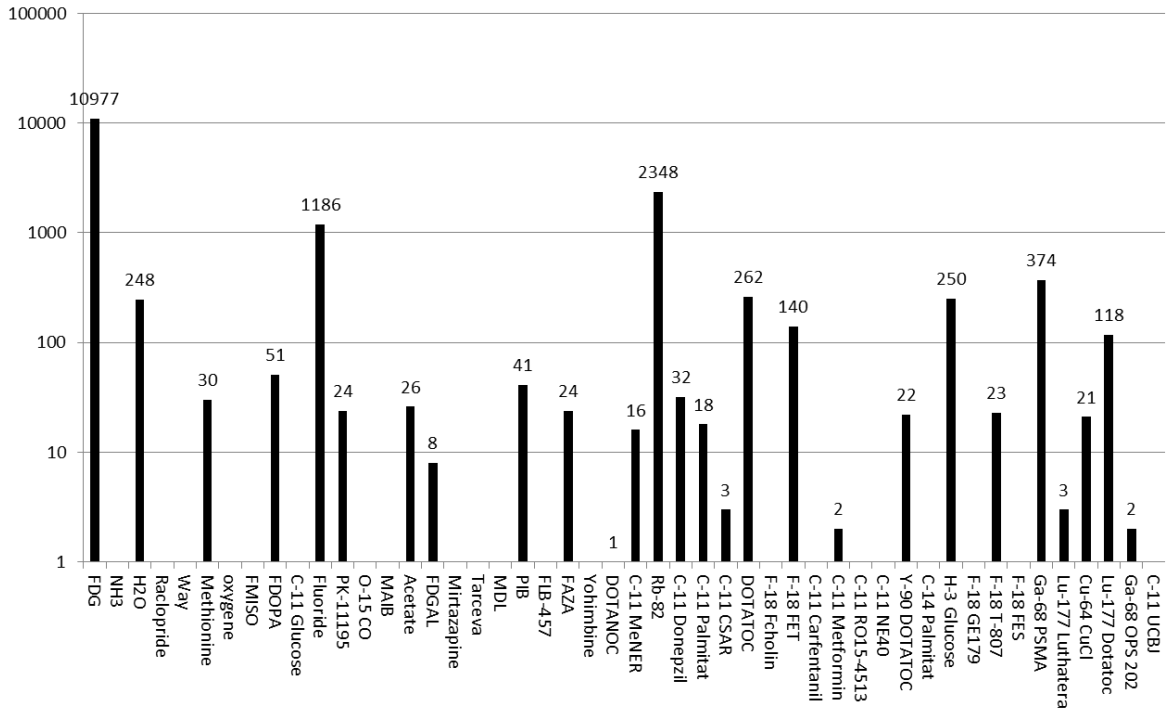


Figure 1: Portfolio of radiotracers produced for human use, both under marketing authorization and within compassionate delivery permits (GMP tracers) in 2018 including number of doses.

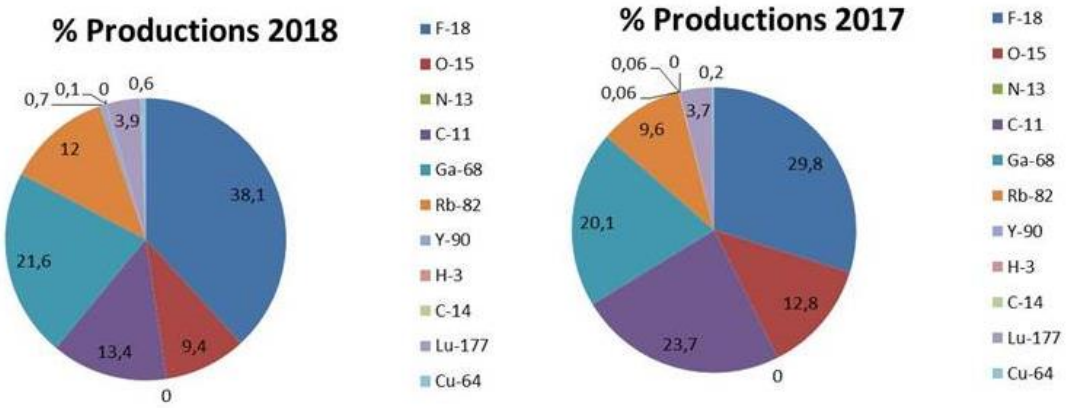


Figure 2: GMP productions: Distribution per radioisotope for 2017 and 2018

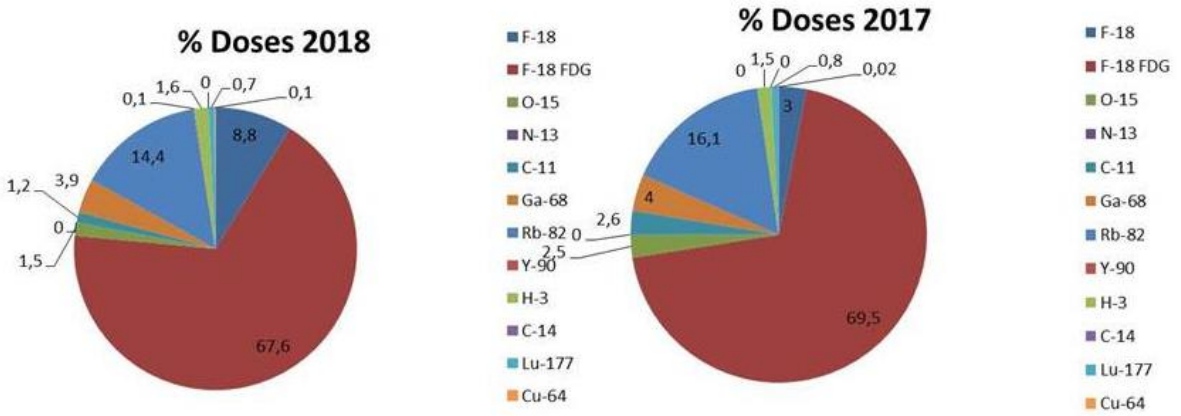


Figure 3: GMP produced doses: Distribution per radioisotope for 2017 and 2018

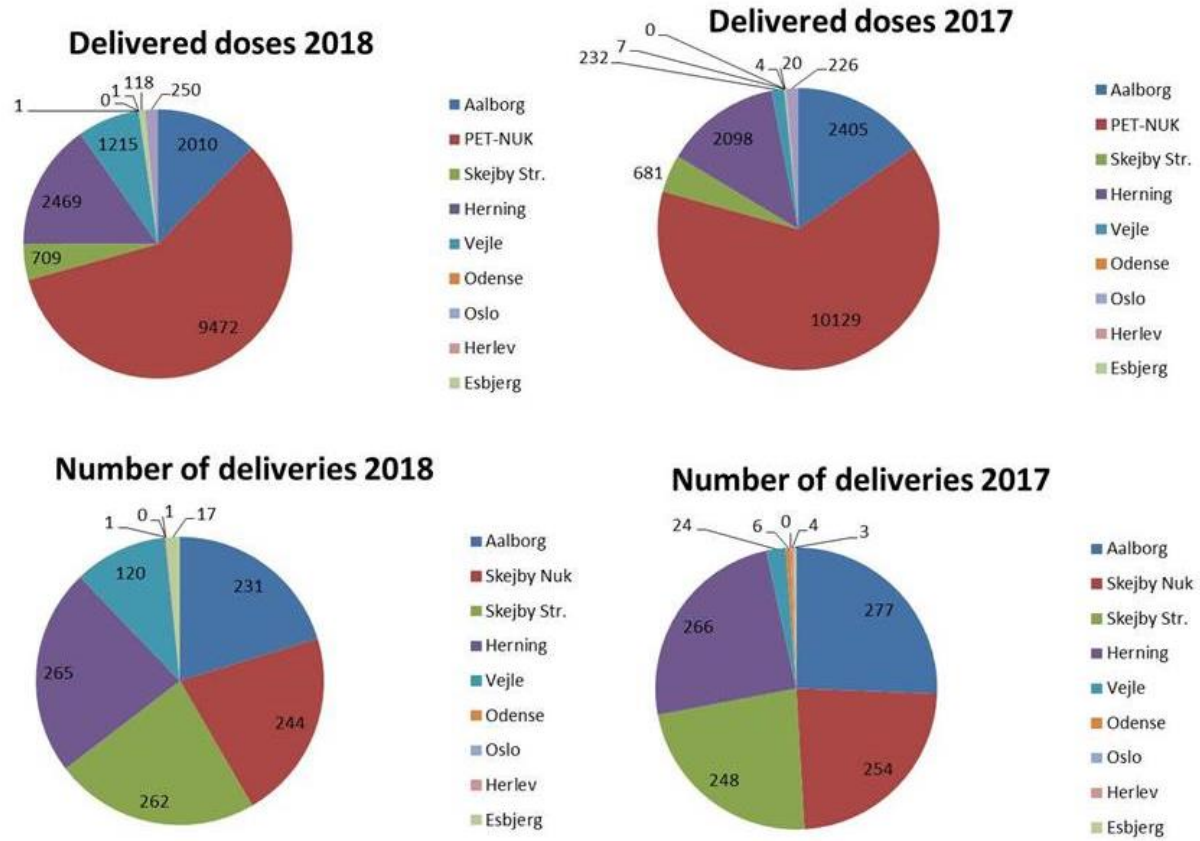


Figure 4: Doses delivered and number of deliveries for out of house users for 2015 and 2016

Research in the origins of Parkinson's disease

Per Borghammer, Clinical Professor, MD, PhD, DMSc.

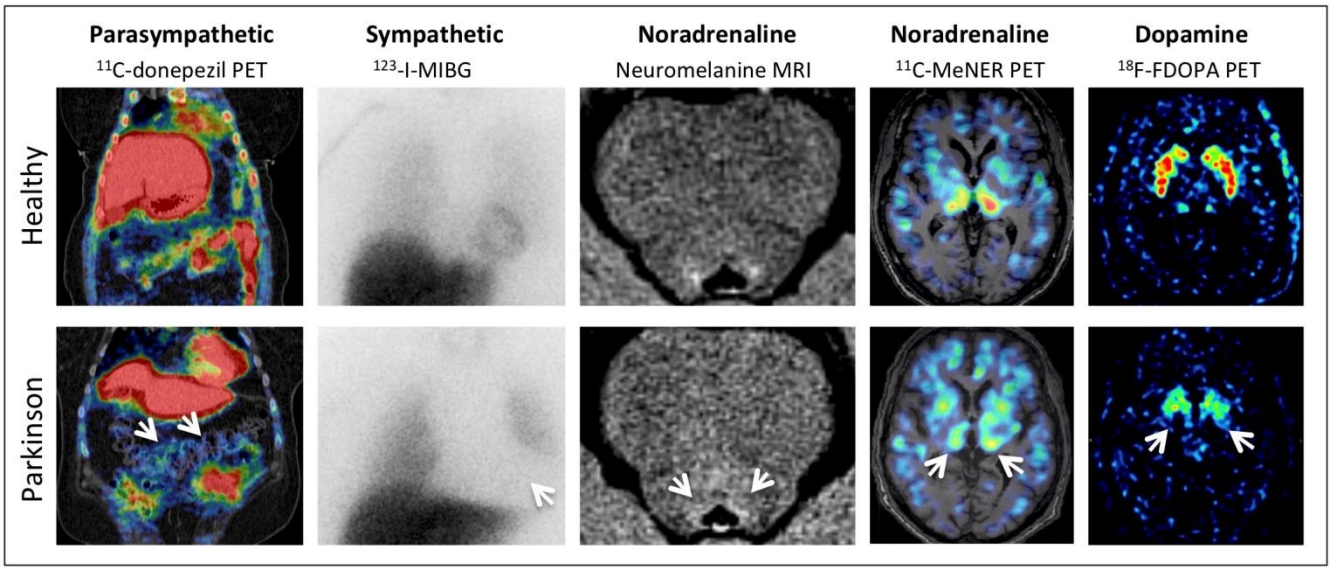


Figure 1 . Using five different imaging modalities, extensive neuronal damage can be visualized in Parkinson patients in the parasympathetic, sympathetic, noradrenergic, and dopaminergic neuronal systems. Arrows indicate visually apparent loss of tracer accumulation in the patients.

The department runs an extensive research program within Parkinson's disease (PD) including advanced imaging studies of prodromal, early-stage and late-stage patients to understand how various neuronal systems undergo degeneration as the disease progresses, but also how these systems are differentially affected in different subtypes of PD. Patients undergo PET, SPECT, CT, and MR imaging in addition to ultrasonographical examinations allowing a detailed *in vivo* quantification of dysfunction in peripheral and central neuronal populations (figure 1). Using this approach, we recently showed that those 30% of PD patients, who develop a particular sleep disturbance during the prodromal phase, exhibit early, severe destruction of the peripheral autonomic nervous system years before they are diagnosed with the disorder (Knudsen et al., Lancet Neurology 2018). This striking observation supports the

growing suspicion that PD in some cases originates in the gut. This "body-first" hypothesis is further explored in studies of archived tissue from PD patients in collaboration with the department of pathology, in transgenic models of PD, and in epidemiological studies in collaboration with the department of clinical epidemiology.

During the past 5 years, Borghammer's team has developed the first PET imaging method, 11C-donepezil PET, which allows quantification of reduced parasympathetic innervation in the peripheral organs (Gjerløff et al., Brain 2015, Fedorova et al., Neurology 2017, Knudsen et al., Lancet Neurology 2018). A 2. generation PET ligand for this purpose is now being developed and tested at the department, which may allow even more accurate assessment of the parasympathetic system. In parallel studies, we utilize novel PET tracers, including 11C-UCB-J and 18F-FEOBV, to assess whether the overall loss of cortical synapses or the specific loss of cholinergic neurons contribute to the development of dementia in Parkinson's disease and the related disorder, Dementia with Lewy bodies.

Early markers of parkinsonian disorders

Nicola Pavese, Associate Professor, MD, PhD, FRCP, FEAN

In vivo functional imaging with PET in patients with Parkinson's and related disorders has significantly increased our understanding of the extent and rate of progression of dopaminergic and non-dopaminergic degeneration in these conditions. It has also helped understand the role of possible molecular mechanisms, such as neuroinflammation (microglia activation). However, the majority of studies has been performed in patients with well-established disease and, therefore, do not provide information on the earliest pathological brain changes which could be potential targets for future disease modifying drugs.

Our research, which is funded by the Independent Research Fund Denmark and the Danish Parkinson's Association, aims to use neuroimaging techniques, including PET and MRI to investigate the earliest pathological abnormalities in the brain of patients at high risk of developing Parkinson's and related conditions. Hopefully, this knowledge will help identify areas in the brain that could be targets for future drug research. Additionally, it will allow an early diagnosis of these conditions, possibly when the pathological process is still confined.

This is an international programme, which involves Aarhus University, Barcelona University, Newcastle University, and University College London.

We have been the first team to report increased levels of neuroinflammation (microglia activation), as measured by ^{11}C-PK11195 PET, in patients with idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD), a strong prodromal marker of Parkinsonian disorders [*Stokholm et al., Lancet Neurology, 2017*]. We are currently performing the longitudinal clinical and imaging follow-up of this cohort of patients to investigate the temporal relationship among microglia activation, nigrostriatal dysfunction, and clinical onset of Parkinsonism.

We have also detected the presence of neuroinflammation (microglial activation) in brain regions susceptible to Lewy body formation in asymptomatic carriers of genetic mutations linked to Parkinson's (*GBA1* and *LRRK2* mutations) (Figure 1). Interestingly, microglial activation in the substantia nigra of carriers of Glucocerebrosidase mutation (*GBA1)* correlates with hyposmia and seems to precede the loss of striatal dopaminergic

terminals measured with ^{18}F-DOPA PET [*Mullin & Stokholm et al., Lancet Neurology, submitted*]. Since a significant number of patients with iRBD develop Dementia with Lewy Bodies, we have used PET with ^{11}C-Donepezil PET, a tracer for visualization of acetylcholinesterase, to explore changes of brain cholinergic function in these patients.

We found that iRBD patients had cholinergic denervation in several cortical areas, including bilateral superior temporal cortex, occipital cortex, posterior and anterior cingulate cortex and dorsolateral prefrontal cortex. This cortical cholinergic dysfunction could be important for the development of future cognitive impairment/dementia in these subjects (Figure 2). [*Stokholm et al. 2019, submitted to European Journal of Neurology*].

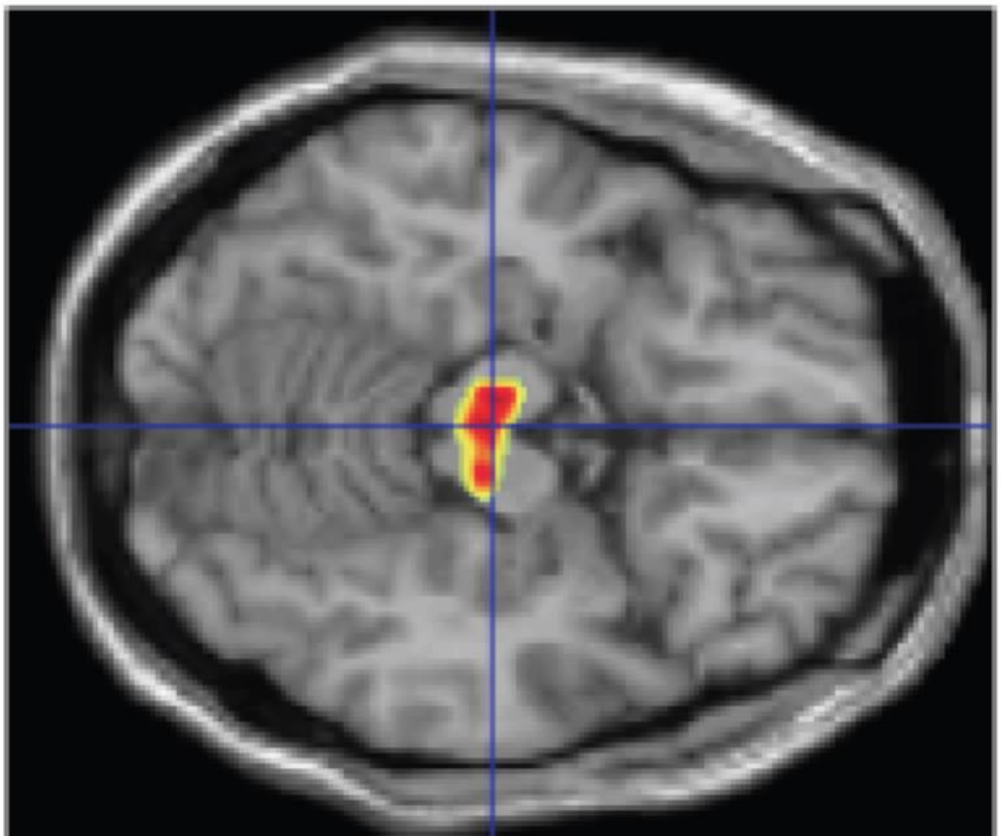


Figure 1: Clusters of significantly increased ^{11}C PK11195 binding potential (BP_{ND}) in the brainstem region of *GBA1* carriers compared to control subjects.

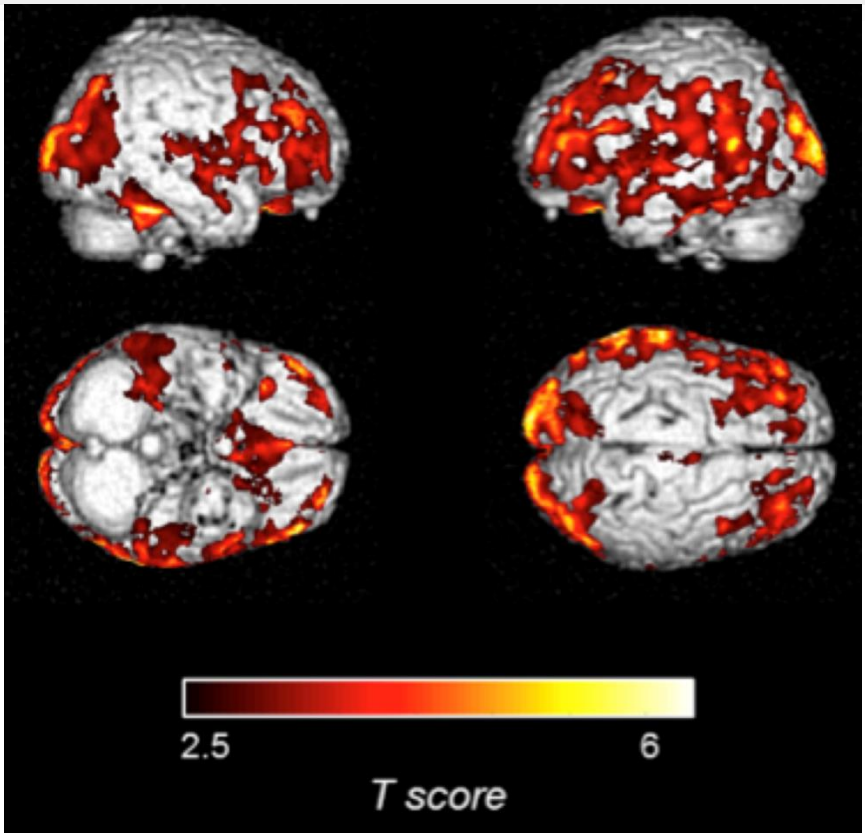


Figure 2: Reductions in cortical ^{11}C-donepezil binding potentials in iRBD compared to controls

More recently, we have observed that the cortical cholinergic dysfunction observed in these patients could be related to an increased load of neuroinflammation (microglial activation) in the Substantia Innominata, the major source of cholinergic input to the cortex [*Stær et al. 2019, in preparation*]. The longitudinal clinical and imaging follow-up of this cohort, funded by the Danish Parkinson's Association, will help clarify if these changes could contribute to the development of cognitive impairment and if ^{11}C-Donepezil PET can be used to predict the onset of dementia in these patients.

Finally, using MRI in collaboration with Associate Professor Simon Fristed Eskildsen and Professor Leif Østergaard, we have found changes in brain microvascular cerebral blood flow in iRBD patients compared to controls. These changes could contribute to the development of neurodegenerative processes in these patients and potentially provide a predictive biomarker for disease progression to Parkinsonism and/or cognitive impairment [*Fristed Eskildsen et al. 2019, in preparation*].

Research in Alzheimer's disease

David J Brooks, Professor, MD DSc FRCP(UK) FMedSci(UK) FEAN

Our programme is designed to determine how molecular and structural imaging can be best used to support diagnoses of clinical, prodromal, and preclinical Alzhiemer's disease (AD) and to examine the temporal and spatial inter-relationships between the characteristic pathologies - β-amyloid plaques, intraneuronal tau tangles, inflammation in the form of microglial activation, and changes in the microcirculation. It is generally believed that β-amyloid plaques formation preceeds tau tangle formation and it is the latter that leads to nerve death and cognitive dysfunction. The time courses of inflammation and circulatory changes are less clear. We are studying β-amyloid fibril load with ^{11}C-PiB PET, tau tangle load with ^{18}F-flortaucipir (AV1451) PET, inflammation with ^{11}C-PK11195 PET and microcirculation changes with Gd contrast enhanced MRI. Healthy subjects carrying the ApoE4 gene and at increased risk of Alzheimer's disease are being recruited along with subjects with isolated memory impairment (mild cognitive impairment – MCI), and early Alzheimer disease (AD).

To date, we have found that two thirds of our MCI cases show evidence of amyloid deposition and 80% of these have associated areas of brain inflammation. Levels of cortical inflammation β-amyloid are correlated in some regions and inflammation, but not β-amyloid levels, correlate with cognitive deficit. This work has been reported (P Parbo et al. Brain 2017; 140: 2002-2011). The relationship between β-amyloid plaques and tau tangles is more complex. Amyloid plaques can be seen without tau tangles in MCI but all our cases with cortical tau also showed cortical amyloid. Tau tangles target mesial temporal cortex while amyloid plaques target frontal and cingulate areas. We have seen no clear correlation between levels of tau and inflammation in our series but tau levels correlate with cognitive decline. These findings have been recently reported (P Parbo et al. Neurobiology of Disease 2018; 117: 211-216). Additionally, an inverse correlation between levels of microglial activation and plasma neurofilament light (NfL), a marker of axonal damage, was seen suggesting inflammation may initially be protective in MCI. This work was funded by the Thon foundation in collaboration with Henrik Zetterburg in Gothenburg.

A cohort of MCI cases has now been followed for two years and repeat PET and MRI performed – see figure. Interestingly, while

amyloid load remains stable the level of inflammation falls significantly while tau tangle load rises. This also suggests that inflammation is initially protective in early Alzheimer's disease but this declines over time. Correlations of our longitudinal imaging findings with the cognitive status of the MCI cases are currently being interrogated.

We have been funded by Horizon 2020 and Eurostar grants to study the prevalence of amyloid deposition in elderly healthy controls who carry the ApoE4 gene. Those amyloid positive healthy subjects, who represent preclinical Alzheimer's disease, will be asked to undergo cognitive testing with the Brain+ computer programme to determine whether subtle cognitive deficits are present. The presence of imflammation, tau, and microcirculatory changes will also be examined with PET in these cases. We have already determined that β-amyloid can be detected in the absence of inflammation (F Husum Mårup – unpblished data). It is eventually intended to test cognitive rehabilitation paradigms in healthy controls who have amyloid pathology and show subtle deficits on Brain+.

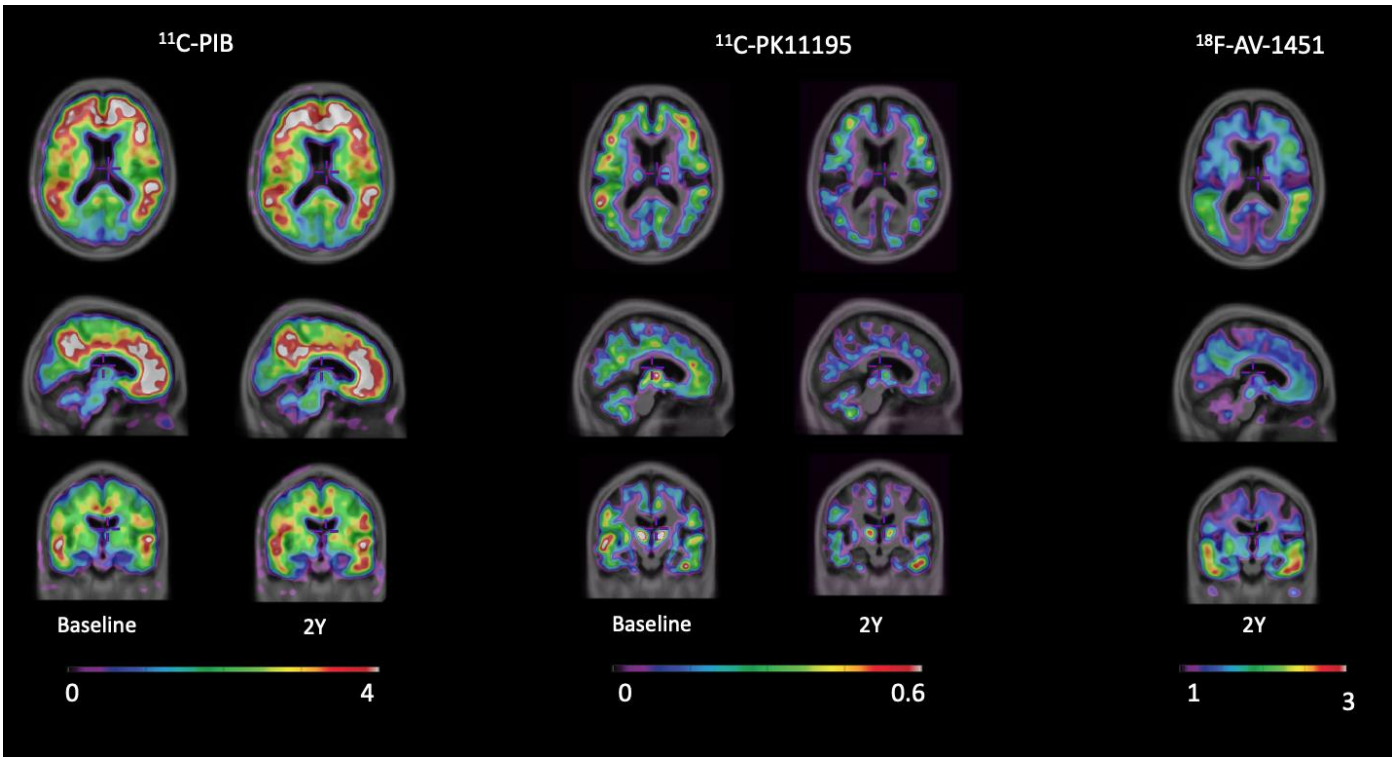


Figure 1: Amyloid load (^{11}C-PIB), inflammation (^{11}C-PK11195) and tau load (^{18}F-flortaucipir/AV1451) changes measured with PET over two years in an MCI patient.

Preclinical Imaging of Pathophysiology, Pharmacodynamics and Phamacokinetics

Mikkel Holm Vendelbo, Associate Professor, MD, PhD

A combined position with both the Department of Biomedicine, Aarhus University, and the Department of Nuclear Medicine and PET Center, Aarhus University Hospital, creates great opportunities for collaborations between the researchers at Aarhus University and at the University Hospital. The joint venture promotes basic research with state of the art in vivo imaging techniques, using molecular biology and molecular imaging we provide a platform to: examine physiological and pathophysiological mechanisms, identify pharmacological target tissues, provide tissue specific pharmacokinetic information and evaluate treatment response.

Growth factor receptors are highly involved in cell growth and proliferation in both normal physiology and in cancer development. We therefore have a special focus on visualizing growth factor receptors. Expression levels and body distribution of these receptors can be quantified *in vivo* by molecular imaging techniques and this will be of major importance in the decision of specific targeted treatment for cancer patients in future. The possibility of choosing a targeted treatment from full body imaging will improve medicine precision to each individual patient, a cornerstone in personalized medicine.

In collaboration with research groups from Aarhus University, who has developed new disease models with e.g. CRISPR/CAS9 technique, we identify cancer and quantify disease burden in rodents with PET/MRI. The specific mutations induced with molecular biology techniques cause spontaneous cancer in targeted tissues. The imaging technique supersedes sacrificing animals and enables *in vivo* monitoring of disease progression, pathophysiological characteristics and treatment response. Insulin- and IGF-I receptors are classified as Tyrosine Kinase Receptor Class II receptors, due to extensive homology, and are often overexpressed in various cancers. The receptors are central regulators of tumor growth and regulate protein synthesis through the Akt/mTOR pathway. IGF-I receptor inhibition significantly reduce Akt/mTOR pathway activation in several cancer cell lines and significantly reduce ^{18}F-FDG uptake. We have therefore labeled antibodies with ^{89}Zirconium to visualize

tumors expressing the IGF-I receptor in a preclinical rodent model.

Molecular imaging of growth factor receptors hold promise for proper patient identification in the future and we, therefore, also focus on imaging other growth factor receptors as HER2 and Somatostatin Receptors in humans.

PET scans are in addition well suited for detection of tissue specific uptake of radiolabeled pharmacological compounds in order to identify target tissues and pharmacokinetics in vivo. We are engaged in several preclinical studies exploring biodistribution of newly developed pharmacological compounds.

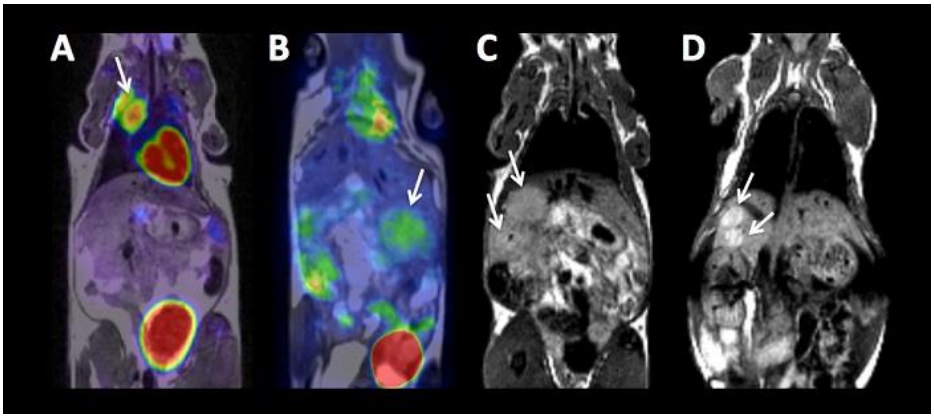


Figure 1: It is possible to identify cancer in preclinical animal models with PET/MR. Panel A illustrates a CRISPR/CAS9 genetic modified mouse with FDG uptake in a lung cancer (indicated with arrow). In panel B, the arrow indicates an FDG avid liver cancer in a mouse, and the MR scans in panel C and D shows the liver tumor size regression during one month of experimental immunomodulating therapy.

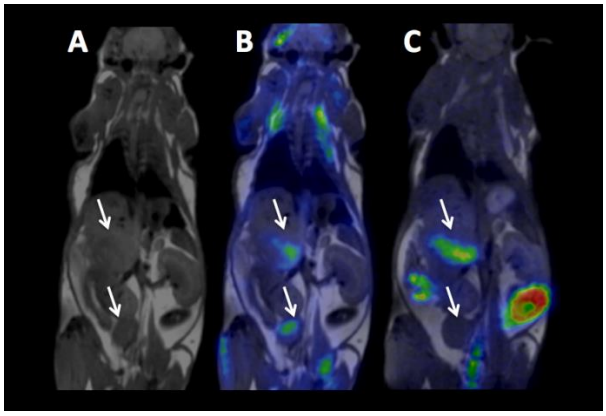


Figure 2: Using several different PET-tracers makes it possible to visualize tumor characteristics in vivo. Two abdominal cancers are seen in a CRISPR/CAS9 genetic modified mouse on the MR scan in panel A, see arrows. The two tumors are metabolically active, as indicated on the FDG-PET scan in panel B, while the FAZA PET scan (Panel C) reveals that only the most cranial tumor is hypoxic.

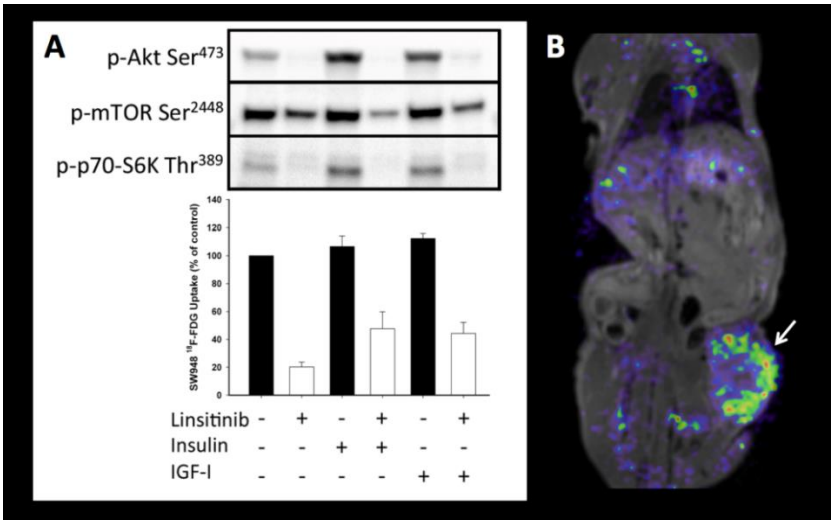


Figure 3: Using molecular biology techniques, we have identified cell lines sensible to inhibition of insulin- and IGF-I receptors and used a xenograft model to validate radioligands against the receptors. Panel A illustrates that the insulin- and IGF-I receptor antagonist, Linistinib, reduces growth signaling and reduces FDG uptake in a colorectal cancer cell line. Panel B shows uptake of a radiolabeled antibody against the IGF-I receptor in a xenograft mouse model.

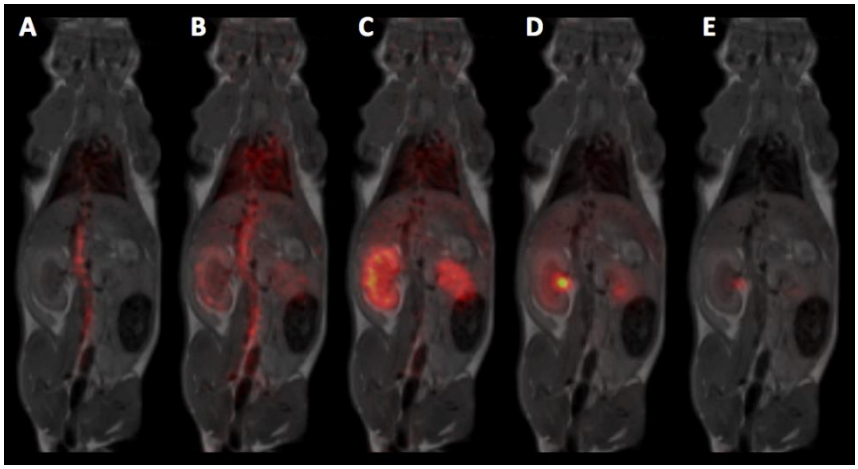


Figure 4: Radiolabeling of pharmacological compounds enables visualization of tissue biodistribution and pharmacokinetics. Panel A to E show representative images from a dynamic PET scan in chronological order and visualize distribution of a newly developed experimental drug in a mouse. It is seen that the compound after intra venous injection is taken up and excreted from the kidneys and that there is a transient accumulation in the liver tissue.

FDG PET/CT in inflammatory diseases – current research

Lars Christian Gormsen, Clinical Associate Professor

Inflammatory diseases are characterized by often transitory changes in the volume and activity of energy consuming white blood cells and are therefore exceptionally well suited for functional imaging by 18F-FDG PET/CT. As a consequence, an increasing body of litterature advocates using FDG PET/CT in the diagnostic work-up of patients with large vessel vasculitis (LVV) and polymyalgia rheumatica (PMR). However, low-grade inflammation as seen in the aging patient and in patients with degenerative diseases of the musculoskeletal system often affect the same bursae, tendons and vessel walls that are affected in LVV and PMR. In addition, the treating rheumatologists will often institute prompt treatment with glucocorticoids in order to avoid inflammation related vascular events (stroke and blindness). Glucocorticoid treatment promptly suppresses white blood cell activity and therefore also FDG uptake rendering correct interpretation of FDG PET/CT's difficult. Reading inflammation FDG PET/CT's is therefore an increasingly challenging task that requires extensive knowledge of concurrent diseases and medication. We have therefore in collaboration with the Department of Rheumatology undertaken a series of studies in patients with suspected LVV to establish:

1. Whether three or ten days of treatment with glucocorticoids significantly reduces the diagnostic accuracy of FDG PET/CT to diagnose LVV
2. Whether cranial artery vasculitis (temporal, maxillary and occipital arteries) can be diagnosed using conventional whole body FDG PET/CT reconstruction protocols
3. Whether ultrasound (US) can replace FDG PET/CT as a first-line imaging technique in patients with LVV

In the first study [1], we enrolled 24 patients with LVV diagnosed by pre-therapy FDG PET/CT and the ACR criteria for Giant Cell Arteritis (GCA). Patients were divided into two groups and had an additional in-therapy FDG PET/CT performed after either 3 or 10 days of glucocorticoid therapy (60 mg prednisolone). All patients responded well to treatment as judged by biochemistry (CRP) and subjective symptoms (headache, claudication and general malaise). The main finding of the study was that PET/CT was still able to accurately diagnose LVV after three days glucocorticoid treatment

whereas this was not the case after ten days (figure 1). This observation is now a part of the european guideline for FDG PET in inflammatory diseases.

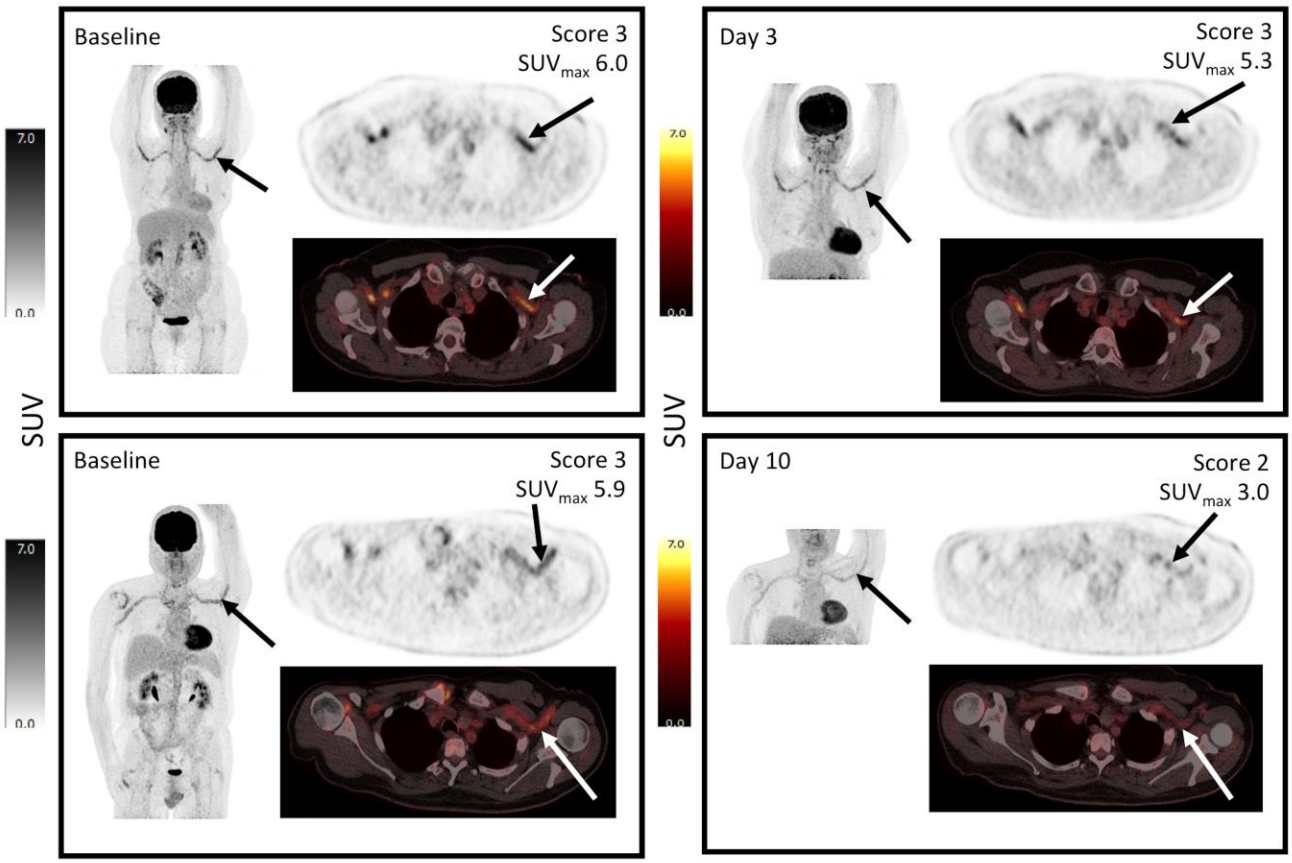


Figure 1

In the second study[2], we retrospectively reviewed FDG PET/CT scans of 44 patients with LVV to observe whether we could identify pathological FDG uptake in the cranial arteries. As a control group, we also reviewed 44 patients undergoing routine surveillance FDG PET/CT (malignant melanoma patients). Four nuclear medicine physicians were trained for 30 minutes on a training set of five patients with cranial artery vasculitis and subsequently reviewed FDG PET scans cropped to include only the head and neck. Their diagnostic accuracy turned out to be quite excellent, since the consensus specificity was 100 % and sensitivity 83 %. In practice, any FDG uptake in cranial vessels should therefore be considered indicative of LVV.

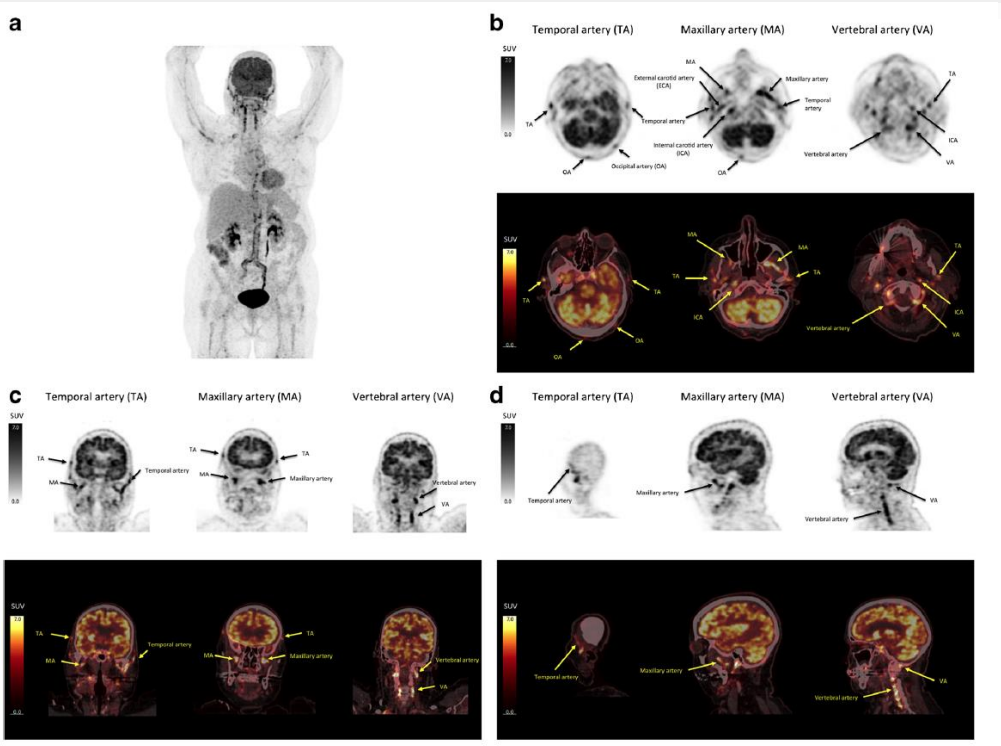


Figure 2

In the third study, a cohort of patients (N=102) with suspected LVV who underwent FDG PET/CT as part of their diagnostic work-up were US scanned in the axillary and temporal arteries. Using FDG PET/CT as the reference standard for LVV, US had a specificity of 97 % and a sensitivity of 93 %, which implies that US in the hands of the experienced user may replace FDG PET/CT as a first-line imaging tool (figure 3).

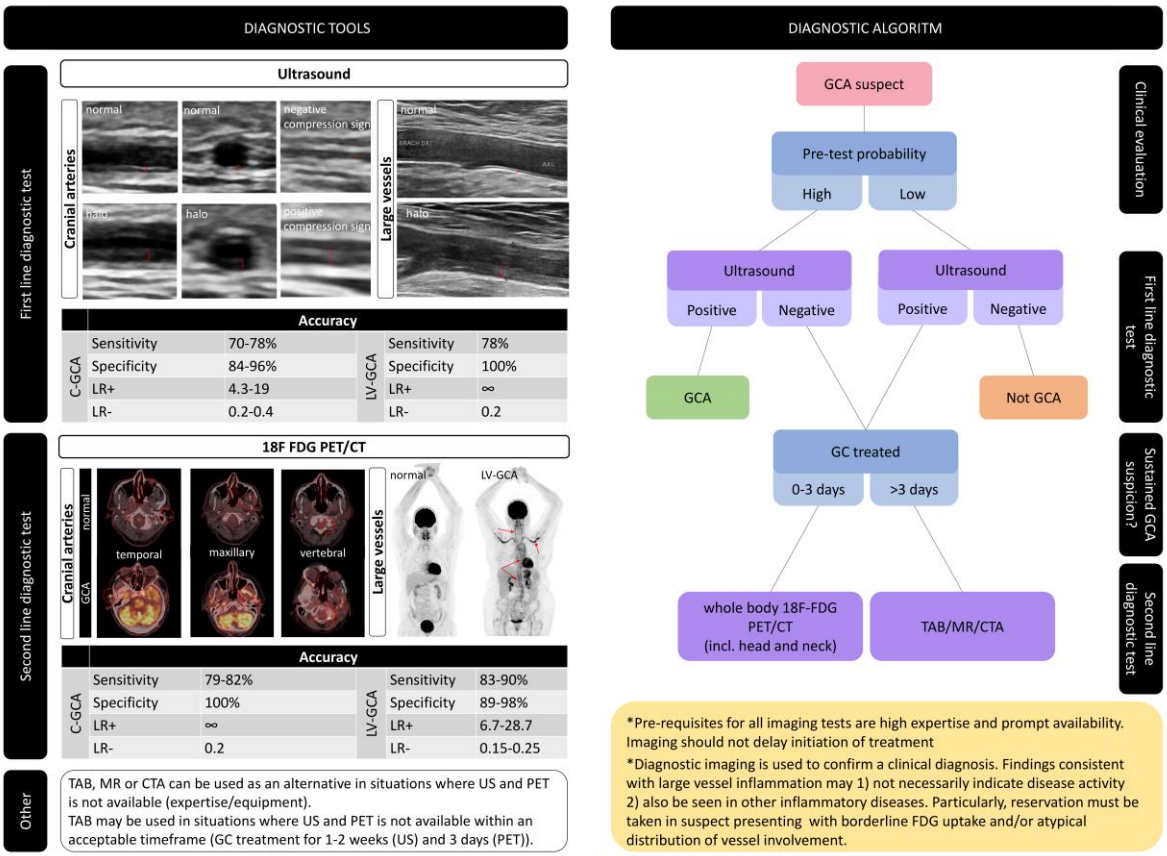


Figure 3

In the coming years, we will prospectively enroll patients with suspected PMR and will investigate whether cessation of glucocorticoid therapy for fourteen days enables certain diagnosis of PMR by FDG PET/CT. In addition, we will investigate whether glucocorticoid therapy may be tapered according to the results of a FDG PET/CT performed after 8 weeks of therapy. It is our belief that the results of these studies will further aid our clinical interpretation of the increasing volume of non-oncology FDG PET/CT's.

1. Nielsen BD, Gormsen LC, Hansen IT, Keller KK, Therkildsen P, Hauge EM: Three days of high dose glucocorticoid treatment attenuates large-vessel 18F FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. *European journal of nuclear medicine and molecular imaging* 2018, 45(7):1119-1128.
2. Nielsen BD, Hansen IT, Kramer S, Haraldsen A, Hjorthaug K, Bogsrud TV, Ejlersen JA, Stolle LB, Keller KK, Therkildsen P *et al*: Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. *European journal of nuclear medicine and molecular imaging* 2018

Tumor Perfusion Imaging in Prostate Cancer

Mads Ryø Jochumsen, MD, Ph.D.-Student

Angiogenesis is one of the fundamental hallmarks of cancer. Unregulated angiogenesis can lead to increased blood flow in the tumor, which is important as proliferating tissues require excess supplies. Tumor blood flow (TBF) imaging has therefore been studied as a potential method for characterization and for evaluation of treatment-response in multiple cancers. We have validated ^{82}Rb PET as a new method for quantitative measurement of TBF in prostate cancer by showing that ^{82}Rb PET TBF were highly correlated with the gold standard ^{15}O-H_2O PET TBF. We also found that ^{82}Rb TBF in prostate cancer tissue was significantly higher than blood flow in assumed healthy prostate tissue of a control group.

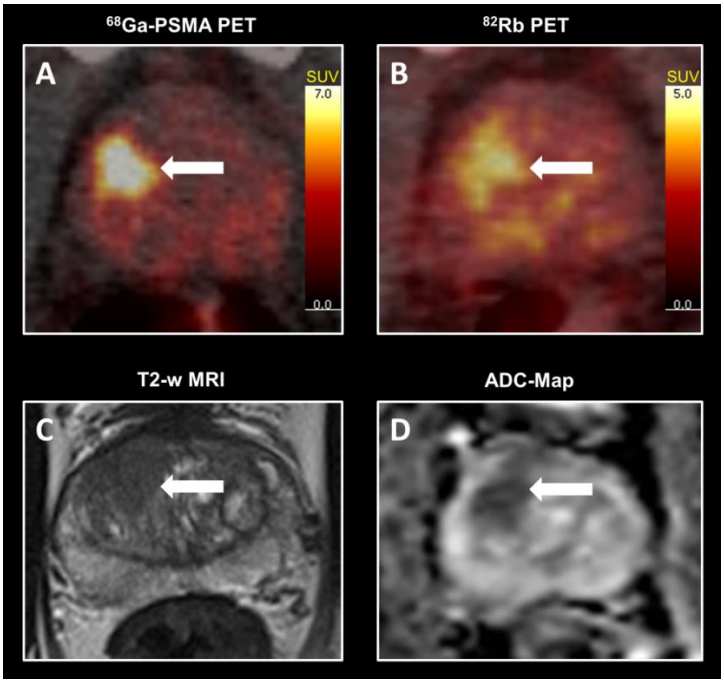


Figure 1: An example of a primary prostate tumor with highly increased blood flow. ^{68}Ga-PSMA PET/CT (A), ^{82}Rb PET/CT (B), T2-w MRI (C) and ADC-map (D).

In the past year we have studied the repeatability of both static and dynamic ^{82}Rb PET TBF in prostate cancer. This information is important in order to evaluate the potential usefulness of the method. We found that dynamic ^{82}Rb PET K1 has a repeatability of 32% in prostate cancer, and that the corresponding repeatability of static ^{82}Rb standardized uptake value (SUV) max was 51%. These data mean that dynamic ^{82}Rb PET can detect an actual change in blood flow between repeated measurements of more than 32%, whereas static ^{82}Rb PET can detect changes in blood flow between repeated measurements of more than 51%. Dynamic ^{82}Rb PET could be consistent enough to draw conclusions in individual patients, whereas static ^{82}Rb PET probably is more suited for studying a population.

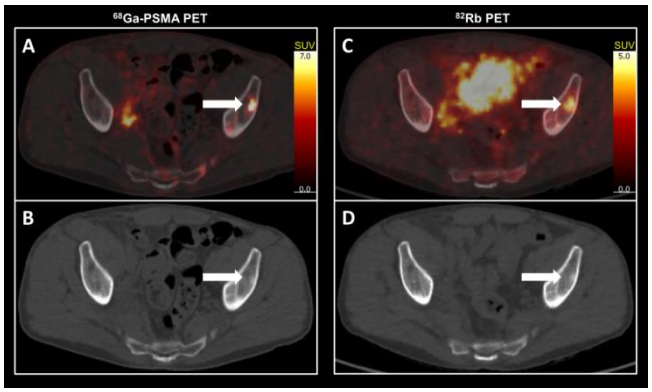


Figure 2: Bone metastases have increased blood flow as well. ^{68}Ga-PSMA PET/CT to the left (A and B) and corresponding ^{82}Rb PET/CT to the right (C and D).

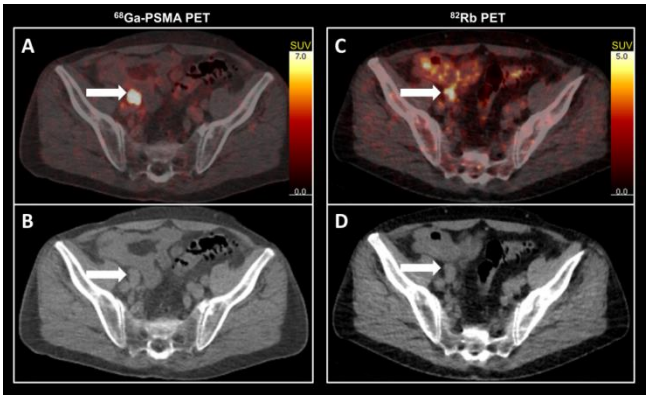


Figure 3: Lymph node metastases also have increased blood flow. ^{68}Ga-PSMA PET/CT to the left (A and B) and ^{82}Rb PET/CT to the right (C and D).

Furthermore, our studies showed a correlation between TBF and postprostatectomy Gleason Grade Group, which is equivalent with prostate cancer aggressiveness. We are currently studying this relationship in a larger population. If TBF correlates with prostate cancer aggressiveness, there may be a potential for using ^{82}Rb PET/CT in risk stratification of prostate cancer patients.

Furthermore, we plan to study whether the initial response in TBF after start of treatment, is associated with long-term treatment response. If so, TBF measurement could be a potential tool for early treatment-response evaluation in prostate cancer and may contribute to a more personalized medicine.

Improving the identification of Breast cancer subtypes

Mette Abildgaard Pedersen, MD, PhD Student

Breast cancer (BC) is the most prevalent cancer diagnosis among women. Accurate staging is important for treatment decisions and prognosis in patients with newly diagnosed BC. ^{18}F-Flurodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) scans are a well-established imaging modality to visualize metastatic cancer disease. However, the recommendations for the use of FDG PET/CT in breast cancer patients vary among guidelines and it remains a matter of debate which BC patients will benefit from the scans. Furthermore, tumour metabolic heterogeneity addressed with FDG is not well described in the literature. A new project will examine BC staging and tumour heterogeneity by FDG PET/CT.

In addition to stage, histopathological biomarkers are also used to determine treatment. The estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) are all used to identify BC subtypes and determine targeted therapy. It is recognized that HER2 positive subtypes are among the most aggressive and treatment with anti-HER2 monoclonal antibodies has improved survival in up to 20% of these patients. It is therefore apparent that identification of high HER2 expression in the primary tumour and/or in metastatic lesions is crucial for effective targeted therapy. Currently, HER2 expression is characterized by histopathological tests done on material obtained from invasive biopsy procedures. Intratumoural heterogeneity and small sample size limit the accuracy of the invasive methods and it has been reported that up to 20% of the HER2 results are inaccurate in BC. For the patient, the invasive procedures to obtain tumour tissue for HER2 analyses, may be associated with pain, especially so when targeting metastatic lesions in visceral organs. Using specific anti-HER2 radiopharmaceuticals it is possible to quantify HER2 expression with *in vivo* PET-scans. A few anti-HER2 probes have been developed and used for detection of HER2 expression in humans. In patients with biopsy proven HER2-negative primary BC has this method been used to detect HER2-positive metastatic disease, identifying patients who could benefit from targeted therapy. Most of the probes are radiolabeled monoclonal antibodies. However, major drawbacks with antibody imaging are a very high radiation dose to the liver and that optimal images only can be obtained 4 to 7 days after injection. In order to improve upon

antibody imaging, an Anti-HER2 affibody has been developed. Affibodies are medium sized peptides and ^{68}Ga-ABY-025 has been proven to detect HER2 positive disease in small-scale human studies, as seen in **figure 1.** The possibility of heterogeneity of HER2 expression both within primary tumours and between primary and metastatic disease sites demonstrates a need for accurate whole body assessment of HER2 status, and an imaging biomarker used to predict HER2 overexpression in tumours would be a welcome tool. HER2-targeted PET imaging with ^{68}Ga-ABY-025 has the potential to become a clinically valuable tool in the care of patients with BC.

In collaboration with centers in Sweden and Finland we will engage in a prospective, multicenter, open-label, phase II/III, diagnostic trial to evaluate ^{68}Ga-ABY-025 PET/CT (ABY-PET/CT) for non-invasive quantification of HER2-expression in advanced breast cancer.

In the future, the use of this method may be expanded to other types of cancer disease where HER-expression is relevant e.g. gastroesophageal cancer.

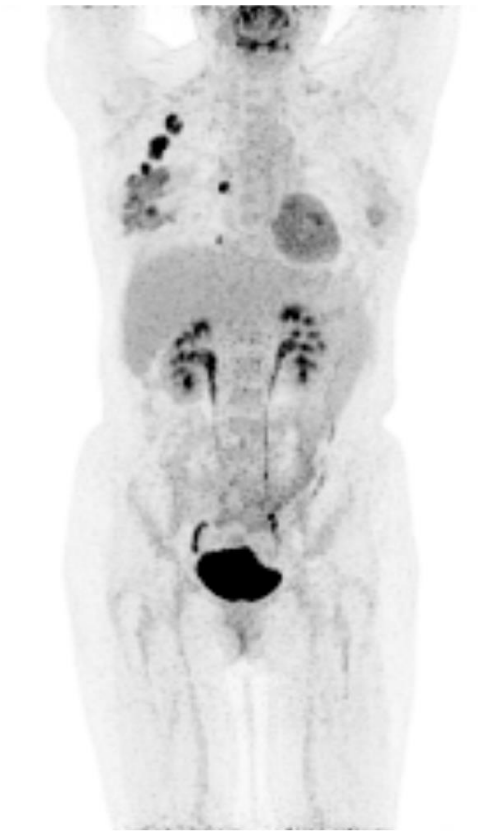


Figure 1.

Research in Cardiac PET

Lars Poulsen Tolbod, Medical Physicist, PhD

Lars Christian Gormsen, Clinical Associate Professor

Jens Sørensen, Professor, MD, DMSc

The information available from dynamic cardiac PET scans is not limited to either perfusion or metabolism. In fact, there is a wealth of hemodynamic information to be obtained from the same data. Since 2013, researchers from Dept. Nuclear Medicine & PET, Aarhus University Hospital, and the Uppsala Clinical Research Center, Uppsala University, have worked on the automation of cardiac PET analysis, including the segmentation of the chambers of the heart and the lung circulation. Together with local cardiologists, these tools have been applied in a variety of diseases.

Preload and extravascular lung water from standard 15O-water Cardiac PET

In a recent publication in European Heart Journal – Cardiovascular Imaging, the work of Roni Nielsen, Hans Harms and co-workers showed that applying simple indicator-dilution principles and the automated segmentation methods to the first passage of 15O-water can be used as a non-invasive method for pulmonary congestion (extravascular lung water) and preload in heart failure patients [1]. The hypothesis was initially tested in an animal-model and then applied to a cohort of heart failure patients and healthy volunteers.

Oxygen consumption and myocardial efficiency.

11C-acetate is multifaceted tracer; it is taken up by the myocardium at a rate corresponding to the myocardial blood flow and washed out at a rate reflecting to the oxygen consumption of the heart. The ability to measure oxygen consumption, and thus energy use of the heart, has previously been used to quantify how much the consumed energy is used for the work performed by the heart when pumping blood forward in the circulation. This is known as the myocardial external efficiency (MEE). The mechanical work of the heart has previously been

estimated by anatomical imaging modalities such as MRI and echocardiography, thus, requiring two imaging sessions. However, in two back-to-back publications in Journal of Nuclear Cardiology, Hans Harms, Henrik Hansson and colleagues showed that this can be done in a single session with both oxygen consumption and mechanical work obtained from the same dynamic 11C-acetate PET-scan with excellent reproducibility [2, 3].

Ketone Bodies help Chronic Heart Failure patients

Ketonic diets are all over the internet and the recent paper in Circulation on cardiovascular effects of ketone bodies is probably the most talked about paper by this department on SoMe this year [4]. Using the single session MEE method described above, ketone bodies were shown by Roni Nielsen, Lars Gormsen and co-workers to increase cardiac output in heart failure patients without affecting the MEE suggestion that ketone bodies can be used for treatment.

Myocardial oxygen metabolism and external efficiency in Cardiac Amyloidosis

Cardiac Amyloidosis is a disease in which abnormal proteins, amyloids, are deposited in the cardiac muscle leading to stiffness and, eventually, failure of the heart. The disease is related to certain types of dementia, where amyloids are deposited in the brain, and dementia PET tracers, like 11C-PiB, are useful for diagnosis of both types of diseases. Again using the single session MEE 11C-acetate method, Tor Clemmensen and co-workers showed that the total energy consumption of the amyloidosis patients' hearts was increased, but the stiff and enlarged hearts were not very efficient in using this energy to pump the blood and the MEE was reduced to almost the half that of a healthy person [5].

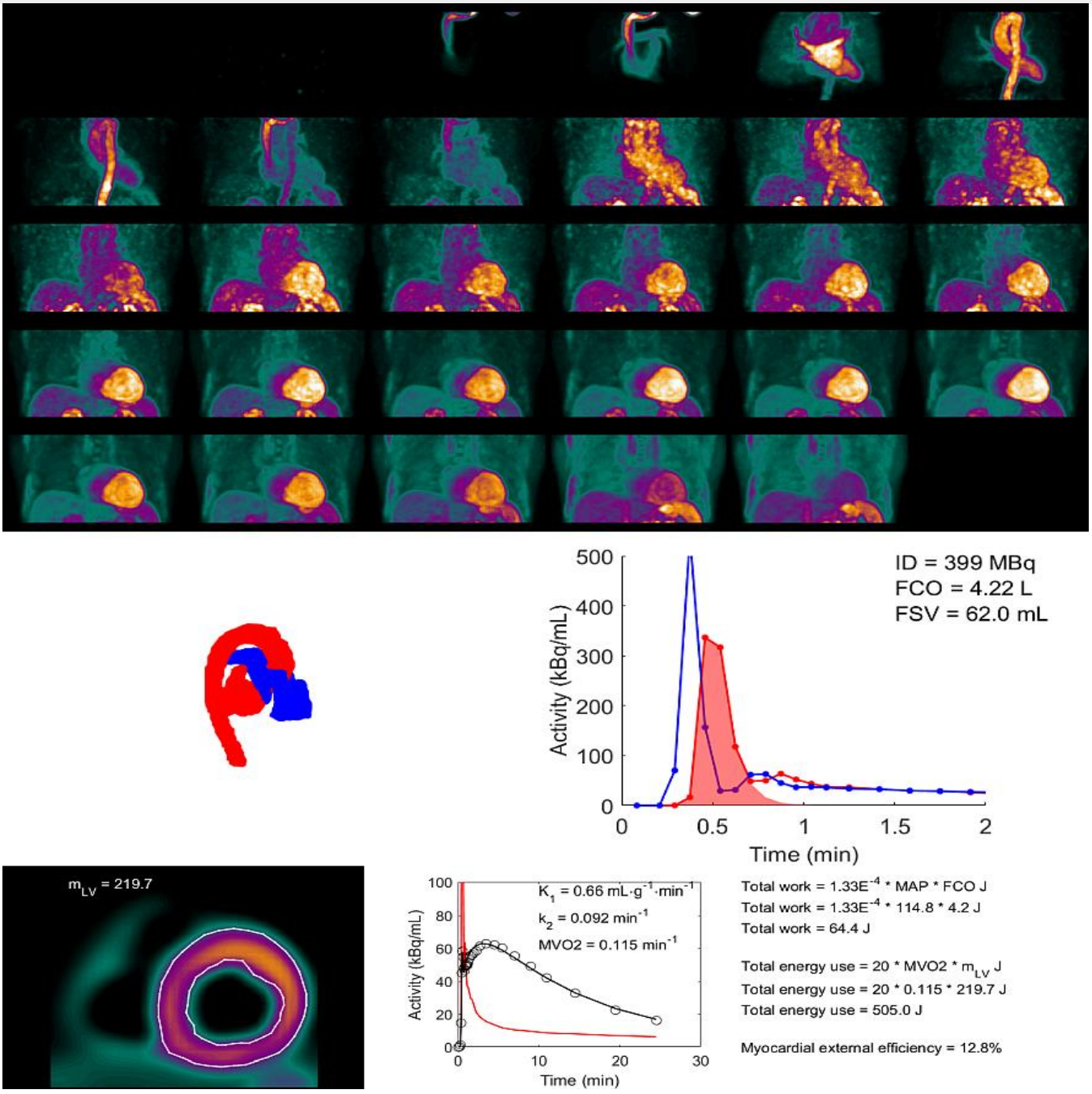


Figure 1: The principles behind measuring MEE with a single dynamic 11C-acetate scan. The forward stroke volume is obtained from the first pass the tracer, the left ventricle mass is obtained from segmentation of parametric images and finally the oxygen consumption is obtained from kinetic modelling. A patient with aortic valve stenosis and low MEE is shown.

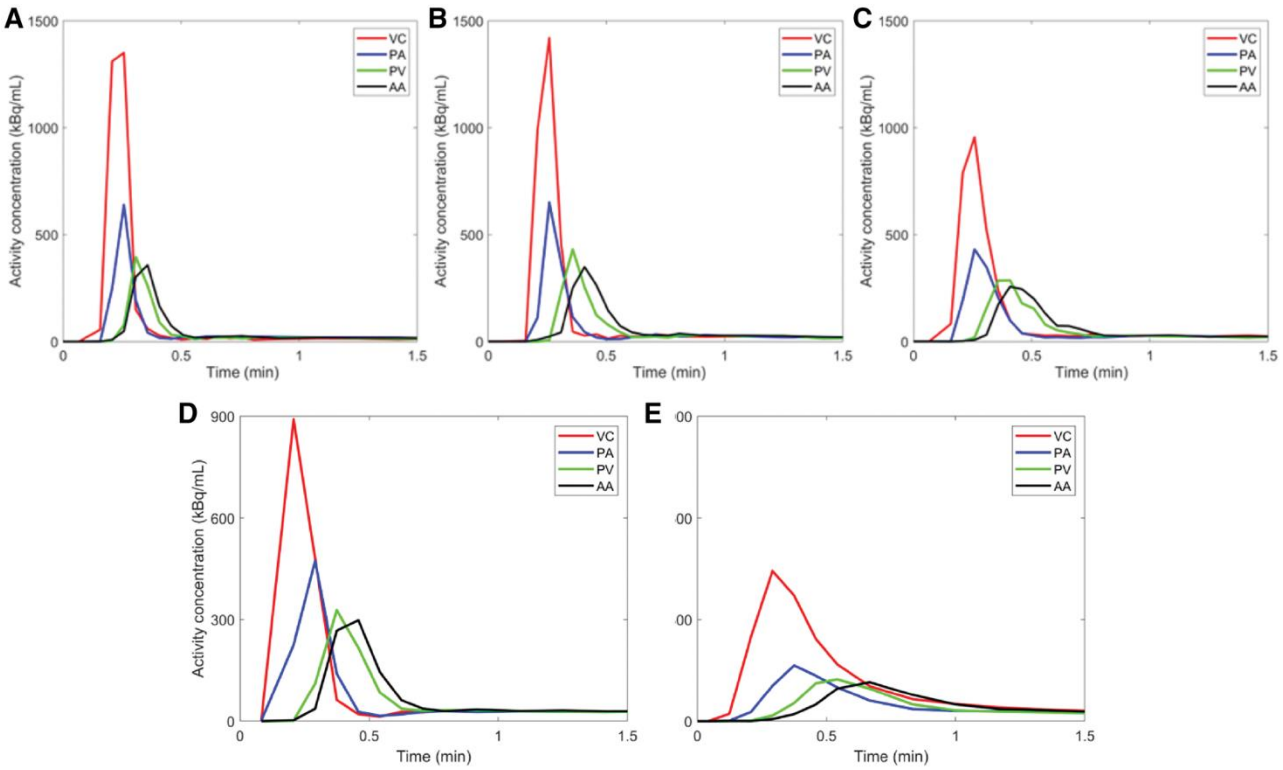


Figure. 2: Characteristics of 15O-water time-activity curves. . A-C: Pig at various stages of induced pulmonary congestions. D: Healthy volunteer. E: Heart Failure patient. Curves are from vena cava (VC); pulmonary artery (PA); pulmonary veins (PV); ascending aorta (AA).

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Animal experimentation in Nuclear Medicine and PET

Aage Kristian Olsen Alstrup, DVM, PhD

Preclinical research

Our department's pre-clinical research focuses on the development of new tracers, and the use of existing tracers and scanning techniques in the study of experimental animal models. For this purpose, primarily mice, rats and pigs are used, but occasionally other experimental animals such as chinchillas are also used.

Development of new PET tracers

PhD student Majken Borup Thomsen has worked towards validation of [11C]UCB-J PET as a measure of synaptic function in rodent and pig brain, and has compared PET and molecular biology results. She has applied this tracer to models of Parkinson's and Huntington's disease, and PhD student Simone Larsen Bærentzen joins the team at Nuclear Medicine & PET-Centre and also at the Translational Neuropsychiatry Unit to study synaptic function with [11C]UCB-J PET in models of depression and antidepressant therapies.

In another project, performed in collaboration with Kim Frisch, Susanne Keiding, Michael Sørensen and others, a bile acid tracer, [18F]FBCGly, was evaluated in rats and pigs. The studies showed that there is tracer uptake in the liver which is then excreted into the small intestine, where it is subsequently re-absorbed and returned to the liver via portal circulation (enterohepatic recirculation). It is advantageous to have access to both the µPET/MRI scanner and the PET/CT clinical scanner at same time, since this can provide insight into tracer characteristics in two different animal species (rodent and non-rodent).

Parkinson´s disease

The preclinical research was in 2018 working intensively with Parkinson's disease. In collaboration with Nathalie Van Den Berge, Per Borghammer and others, animal studies have been performed to clarify whether Parkinson's disease may start in the gut and from there spread to the brain. Alpha-synuclein fibrils have been surgically placed into the intestine of rats. The preliminary results indicate a trans-synaptic and bidirectional spread of pathology from gut-to-brain and back again via the vagus nerve within 2-4 months post-injection. Additionally, spread of pathology to the heart was observed. These findings support the dual-hit hypothesis in Parkinson's disease. The validation of animal models of Parkinson's disease, for studies of disease

mechanisms, novel PET tracer development and testing of therapeutics, has been a main focus of our research led by Annie Landau. Thanks to close and fruitful collaboration with Professor Jens Christian Sørensen and the CENSE group, as well as international collaborators, we finalized and published three manuscripts in 2018 on the development of models of Parkinson's disease in minipigs. This line of research began in Annie Landaus group in 2010 and for the past 3 years has been driven by Thea Pinholt Lillethorup, forming the basis of her PhD thesis, which was successfully defended in June 2018. Similar studies performed in rodents, in close collaboration with Associate Professor Marina Romero-Ramos at the Department of Biomedicine, are currently in the final stages and formed the basis for Kathrine Stockholm's Master's thesis, also successfully defended in June 2018.

Over the last few years, our group has had the opportunity to collaborate with Professor Malin Parmar and her team at Lund University, world leading experts in stem cell therapy for PD. In 2018, working closely with the CENSE group, we continued to collect neuroimaging and histology data in minipigs injected with human embryonic stem cells engineered to produce dopamine in order to determine whether these cells can survive and form functional dopamine synapses, thereby providing a dopamine-replacement therapy for PD. Data are encouraging and this promising therapy in the minipig will be an important part of our research in the coming years, as a prelude to future studies in humans.

monitored mouse and pig cancer models,

Liver Radiation

As a research year project, Kristoffer Kjærgaard investigated the liver's functional response to radiation injury. Healthy minipigs were subjected to whole liver irradiation and were investigated by liver PET/CT five weeks later. The pigs did not develop hepatic fibrosis, but [18F]FDGal and [11C]CSar PET showed that hepatic metabolic function and hepatobiliary secretion were increased by the radiation injury.

Oncology research

In collaboration with Morten Busk from the Department of Oncology, we have conducted research in mice bearing conventional tumor xenografts and tumours established directly from patient biopsies. Special focus has been on unravelling the relationship between different imaging tracers, such as methionine, acetate, FDG (glucose use) and FAZA (hypoxia) using PET, but also dual-tracer autoradiography. The overall aims of the research were to (1) refine disease characterization, including assessment of the aberrant energy metabolism and hypoxia, which are features linked to treatment failure, and (2) assess the usefulness of PET for treatment guidance and for early treatment efficacy monitoring.

Transgenic techniques

Our department works with transgenic experimental animals, which are scanned in collaboration with other research teams. In co-operation with Martin Kristian Thomsen's group, Mikkel Vendelbo and others have which have been locally deployed with

oncogenes by using the CRISPR technique, in order to develop e.g. lung cancer or prostate cancer. Here it is an advantage that these valuable animals can be monitored using microPET/MRI or PET/CT without killing them, whereby progressions of diseases can be followed in the individual animal. A similar model for glioblastoma is planned.

Aage Kristian Olsen Alstrup is the first veterinarian in Denmark to have obtained authorisation as a veterinarian specialist in Experimental Animal Medicine from the Ministry of the Environment and Food in Denmark.

Veterinary specialist recognition was established in 2017. Veterinarians can now obtain specialist recognition just as medical doctors have been able to obtain specialist recognition for many years. The appointment of a veterinarian specialist fulfills the EU requirements as major research institutions and companies must have a veterinary specialist attached.

Aage Kristian Olsen Alstrup became a veterinarian in 1997, earned his PhD in Laboratory Animal Science in 2002 where he has been employed at the PET Center ever since. Aage is also an associate professor in veterinary science at the Department of Clinical Medicine, Aarhus University.

Medical Laboratory Technologists and radiography

Christian Juhl, Medical Laboratory Technologist

The department plays an important role in the education and training of medical laboratory technologists. The students come from VIA University College, Aarhus at different stages in their training. In 2018, there were 26 students who undertook a placement in the department. The placements lasted between 3 to 14 weeks. Of these 26 students, 18 completed their training at the department, followed by a clinical exam.

In 2016 the course underwent a comprehensive overhaul. One of the many positive effects of this is a longer and more coherent clinical training period for the students. The education and the clinical training is now more concentrated on the patient, the development of generic skills and a closer relationship between theory and practice. All these new changes give good meaning and all contribute to a new and modern health care system. The changes were started in the autumn of 2016 and are expected to be implemented fully in 2019.

Throughout the last few years, both the number of students allocated to the department and the number of ECT points for medical laboratory technologists and radiography students that the department handles has increased steadily. This is due to a larger intake of students from VIA University College, Aarhus and fewer training departments in the Central Denmark Region as well as an exciting collaboration with the radiography course at University College of Northern Denmark, Aalborg (UCN). In 2018, there were 18 radiography students on a clinical placement at the department.

Christian Juhl is the medical laboratory technologist who has the administrative responsibility and is responsible for the clinical training courses for the medical laboratory technologists and radiography students. He also has various supervisory tasks and teaching assignments in connection with the department's contribution to the training of future medical laboratory technologists and radiography students. Annette Dysterdich also has diverse supervisory tasks and is responsible for teaching. Furthermore, the department has three clinical supervisors, Rikke Bertelsen, Maiken Nybo and Gitte Kodahl. Their role in the department's educational practice is essential as they facilitate and support the important learning space in the clinic.

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.
The department has three external examiners in the Danish National Censor Corps.

Three in one! Education and training of medical doctors/specialists

Anne Arveschoug, MD, Senior Consultant

An entirely new department - New work flows and daily routines - New faces – all at once! Or three former department locations finally together as one!

The 3 in 1 concept can be expressed in many ways, but the main focus of 2018 (and continuing in 2019) has been and will be the merger of three former subunits into one entity at PJJB.

Routines and work flows from three different subunits must be merged and aligned. This also includes the training of medical students/doctors and specialists again naturally integrated into the department's daily clinical program. Routines must be reevaluated and new work flows for supervision and feedback included with respect to productivity.

Camilla Molich Hoff, MD, PhD, Specialist Registrar

The ideas were already reviewed in the 3-hour meeting in 2017, where worries and ideas were discussed, and an ongoing working group of all the junior doctors and more formal junior doctor internal conferences have already been established.

In 2018 the 3-hour meeting focus points were the inclusion of junior doctors at both internal and external conferences, visualization of feedback situation and senior doctors' responsibility for training in different subspecialties. Focus points that earlier were naturally included in the smaller subunits must now be re-addressed and formalized in a larger group setting.

The new department has two floors, an on-call room, situated on the second floor, where the on-call team of the day is situated. It usually consists of two doctors, one in

early training and one in main or late specialist training. The resident in main training serves as a backup and supervisor for the resident in early training, as well as for the medical students responsible for the nuclear cardiology patients that day. Both of the residents in charge have a specialist in nuclear medicine as back-up, one specialist for the nuclear medicine patients and one for the nuclear cardiology patients.

In order to maintain the interdisciplinary cooperation between the doctors and technologists, the examinations of the day are divided among the residents at work. In the distribution of the studies, the development of competences is also taken into account. This breakdown of examinations was implemented as the junior doctors report a great proportion of the examinations performed in the new department.

Maintaining the supervision and feedback, which is so important in workplace-based education has been attempted this way. This came naturally in small subunits but is very time-consuming when the number of examinations has been tripled – however still of utmost importance for fast work progression, discussions and reflection of one's own practice.

On the bottom floor, 3 large rooms for reporting nuclear medicine examinations are concentrated, both the dual viewing of the PET/CT and the viewing and reporting of nuclear medicine studies. The proximity of all the doctors involved in the reporting of all the nuclear medicine examinations offers a unique opportunity to learn and to be supervised.

In 2018 there were three junior doctors in early training and four in late specialist training. Medical doctors in specialist training in other specialties, especially urology, internal medicine and endocrinology visit the department on focused educational stays. In 2018 an IMCC student from Turkey also paid a visit to the department.

Medical students are introduced to the department and the work of a specialist in clinical physiology and nuclear medicine through lectures in medical school and visits, both short and long, can be arranged at the department. Our team of medical students participating in nuclear cardiology examinations is a great advantage and they are very well integrated, being of great benefit to the students and the young doctors in training who act as their supervisor during the day. Many of the medical students have gained an interest in our specialty and have been included in research projects.

Monitoring of competence achievement and learning progression is important in a time of change, so the department has continued the scheduled meetings for all specialist and main supervisors every second month. The aim is to optimize the training for the individual doctors in all aspects of the medical training program.

The junior doctors are involved in administrative tasks at the department, they are themselves responsible for the weekly presentations of clinical cases, facilitated and supplemented by specialists. The weekly

case is now timetabled as the teaching of the staff by the junior doctors, which take place each month.

Teaching in major theoretical topics takes place for all doctors and academics in the department. These educational sessions are usually with guest-specialists from collaborating departments. These sessions take place approximately once a month.

Updating of training programs will be on the agenda in 2019 as the work continues with the postgraduate medical education in the department.

Medical physicists

Peter Frøhlich Staanum, Medical Physicist, PhD

In 2018 medical physics came on the curriculum in danish high school physics. For the next three years medical physics is a compulsory theme in A-level physics classes (the highest level) in high school.

In this context the book "Hospitalsfysik - stråleterapi og nuklearmedicin", co-authored by Peter Frøhlich Staanum, was published in order to support the teaching. A two-day course for about 70 high school teachers was held at Aarhus University as preparation for their teaching in medical physics, and at this course the book authors lectured amongst other topics on nuclear medicine imaging and radionuclide therapy. In the evening the participants went on a tour to our new facilities at Palle Juul-Jensens Boulevard and followed it with great enthusiasm.

In 2018 Søren Baarsgard Hansen lectured on Radionuclide Imaging at the MS program in biomedical engineering at Aarhus University. He also lectured abroad in Radionuclide imaging and PET instrumentation as part of the neuroscience and neuroimaging program at the Sino-Danish Center for Education and Research, Beijing.

Radiochemists

Anders Floor Frellsen, Chemist, PhD

Chemists at the department are trained in specialized work techniques for handling radioisotopes by apprenticeship. The chief chemist arranges an individualized package of courses for new chemists at the department regarding radiopharmacy, radiochemistry, and radioprotection – *e.g.* participation in the European Radiopharmacy Course at Eidgenössische Technische Hochschule (ETH) Zürich. If no previous radioprotection training has been performed the locally taught Isotope course for medical laboratory technologists is also part of the training of chemist at the department.

Medical Secretaries

Stine Mark Nielsen Gunni, Medical Secretary, Supervisor for secretary pupils

Each year 25-40 medical secretary students complete their training in Aarhus University Hospital. At the Department of Nuclear Medicine and PET-Centre, Stine Mark Nielsen Gunni is responsible for the training of medical secretary students. Together with the department's other medical secretaries she ensures that the students receive the appropriate training throughout their stay. Students also participate in the clinic. 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 program are also taken into account. In 2018, there were three medical secretary students on an 8-month stay in the department.

In 2018 Stine Mark Nielsen Gunni graduated as Supervisor for secretary pupils.

Total activity	2017	2018
Number of examinations	22580	23091
Total value of examinations mill. Dkr	107	114

Referring hospital	2017	2018
Aarhus University Hospital	17260	16535
Regional Hospital Horsens	1476	1575
Regional Hospital Randers	1650	2455
General Practice	1635	995
Regional Hospital of Viborg, Skive and Silkeborg	1292	1026
Regional Hospital of West Jutland	327	321
Private Hospitals	9	55
The North Denmark Region	145	65
Region of Southern Denmark	28	29
Capital Region of Denmark	11	8
Psychiatry Central Denmark Region	27	27

Radiotherapy planning	2017	2018
Radiotherapy planning delineation, PET/CT	556	576

PET research scanning	2017	2018
Human research scans, PET/CT	794	735
Pig research scans, PET/CT	61	60

CT examinations	2017	2018
In total	*3069*	*3254*
CT WholeBody PET/CT	3068	3254
CT WholeBody on SPECT/CT	1	0

Blood and lymph system	2017	2018
In total	*264*	*294*
Bone marrow scintigraphy	4	3
Spleen scintigraphy, Tc-99-erythrocyte, heated	3	6
Sentinel node scintigraphy, tumour drainage, c. mammae	4	4
Sentinel node scintigraphy, tumour drainage, c. vulva	22	18
Sentinel node scintigraphy, tumour drainage, c. penis	39	40
Sentinel node scintigraphy, tumour drainage, MM	192	223

CNS og peripheral nervous system	2017	2018
In total	*1042*	*1044*
Regional cerebral receptor, F-18-DOPA	0	1
Regional cerebral receptor, C-11-PIB	31	28
Regional cerebrale blood flow, pharm. prov., O-15-H2O	36	27
Regional cerebrale blood flow, physiol. prov., O-15-H2O	15	9
Regional cerebrale metabolism, F-18-FDG	541	582
Cisternography, In-111-DTPA	2	1
Regional cerebral receptor, F-18-FET	90	80
Regional Dopamine Transporter Receptor Imaging, I-123-FP-CIT (DAT-Scan)	327	316

Bone and Joint	2017	2018
In total	*668*	*825*
Bone Scintigraphy, multi phased	22	25
Bone Scintigraphy, whole body, static	45	87
Bone Scintigraphy, SPECT	621	713

Other diagnostic procedures	2017	2018
In total	*5816*	*5936*
White blood cell scintigraphy, In-111-leuco	5	4
PET infection scanning, F-18-FDG	425	667
Neuro endocrine receptor scanning, F-18-DOPA	11	27
Tumourscintigraphy, I-131-jodid	196	148
Whole body scintigraphy following Lu-177-therapy	121	104
PET tumour scanning, F-18-FDG	4359	4302
PET tumour scanning, GA-68-DOTATOC	251	258

PET tumour scanning, GA-68-PSMA	357	375
PET tumour scanning following Y-90-SIRT therapy	13	7
Tumourscintigraphy, I-123-jodid	22	25
Intraarteriel tumour-/shunt scintigraphy, Tc-99m	16	13
Tumourscintigraphy following Y-90-SIRT therapy	13	6

Gastrin intestinal tract, liver, biliary tract and pancreas	**2017**	**2018**
In total	*216*	*240*
Meckels diverticulum scintigraphy, Tc-99m-pertechnetat	4	5
Gastric emptying scintigraphy, solid food, Tc-99m	52	52
Liver metabolisme, F-18-FDGal	7	5
Gall bladder scintigraphy, Tc-99m-Mebrofenin	32	18
Biliary tract scintigraphy, Tc-99m-Mebrofenin	31	27
Bile acid turnover, Se-75-SeHCAT	89	132
Bleeding scintigraphy, abdomen, Tc-88-erythrocyte	1	1

Heart and cardiovascular system	**2017**	**2018**
In total	*3531*	*4140*
Hyperinsulinemic euglycemic clamp	79	85
Isotope cardiography, LVEF, Tc-99m-HSA	854	941
Myocardiel perfusion, Rb-82, pharm. stress	1162	1439
Myocardiel perfusion, O-15, pharm. stress	0	2
Myocardiel perfusion, Rb- 82, rest	1166	1440
Myocardiel metabolisme, F-18-FDG	79	85
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, adenosine	77	66
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, physiol. stress	22	13
Myocardiel perfusion scintigraphy, Tc-99m-MIBI, pharm. stress, dobu	14	9
Myocardiel perfusion scintigraphy, Tc-99m-MIBI,rest	74	55
Myocardiel sympaticus activity, I-123-MIBG	4	5

Respiratory organs	**2017**	**2018**
In total	*1066*	*1015*
Lung perfusion scintigraphy, regional, Tc-99m-MAA	199	200
Lung ventilation scintigraphy, regional, Tc-99m-MAA	39	33
Lung function test, spirometry	224	282
Lung perfusion scintigraphy, SPECT, Tc-99m-MAA	303	250
Lung ventilation scintigraphy, SPECT, Tc-99m-technegas	301	250

Peripheral vessels	**2017**	**2018**
In total	*657*	*644*
Systolic blood pressure, fingers	1	2
Skin perfusion pressure measurement	16	24
Systolic blood pressure, ancle and toes	640	618

Endocrine organs	**2017**	**2018**
In total	*2146*	*1807*
Thyroid scintigraphy, Tc-99-Pertechnatet	1530	1058
Thyroid scintigraphy, SPECT, Tc-99-Pertechnatet	71	358
Iodine uptake test, I-131-Iodide	241	168
Parathyreoid scintigraphy, Tc-99m-MIBI	304	221
Adrenocortical scintigraphy, I-131-norcholesterol	0	2

Kidneys and urinary tract	**2017**	**2018**
In total	*3001*	*2815*
Renography, Tc-99m-MAG3, diuresis	579	611

Renography, Tc-99m-MAG3	97	76
Renography, Tc-99m-DTPA, ACE-inhibitor	95	39
Renography, Tc-99m-MAG3, ACE-inhibitor	0	41
Renography, Tc-99m-DTPA	18	10
Renal scintigraphy, Tc-99m-DMSA	122	106
Glomerular filtration, Cr-51-EDTA, multi samples	321	318
Glomerular filtration, Cr-51-EDTA, single sample	1715	1564
Micturition cystourethrography scintigraphy, Tc99m-MAG3	53	50

Radioisotope therapy	**2017**	**2018**
In total	*528*	*501*
Isotope therapy with Lu-177-DOTATOC	123	99
Isotope therapy with Lu-177-DOTATATE		4
Isotope therapy with Y-90-DOTATOC	1	22
Isotope treatment with I-131, benign	237	164
Isotope treatment with I-131, malignant	121	88
Selective internal radiotherapy with Y-90-SIRTEX	12	7
Isotope therapy with Ra-223	34	117

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Department adresses in 2018

Department of Nuclear Medicin
& PET-Centre
Aarhus University Hospital
Nørrebrogade 44, building 3,
2nd floor
DK-8000 Aarhus C

Department of Nuclear Medicin
& PET-Centre
Aarhus University Hospital
Nørrebrogade 44, building 10,
6th floor
DK-8000 Aarhus C

Department of Nuclear Medicin
& PET-Centre
Aarhus University Hospital
Palle Juul-Jensens Boulevard 99
DK-8200 Aarhus N

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