PET/CT and PET/MR

Prof. Liselotte Højgaard
Clinical Physiology, Nuclear Medicine & PET
Rigshospitalet, University of Copenhagen & Technical University of Denmark
Chair Danish National Research Foundation
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- International university hospital for highly specialized treatment
- 2000 peer review papers per year
- 12,700 staff
- The first hospital in the Nordic countries with research - from 1757

- 115,000 patient investigations per year
- 10,000 PET + 1,000 for RTP
- 160 peer review publicationer
- Staff 200 + 30 PhD students
- 2 cyclotrons & radiochemistry
- 5 PET/CT, 1 PET/HRRT and 1 PET/MR
- PET/CT & PET/MR for animals
- Research funding 50 mio DKK / year
- Budget 130 mio DKK / year

X-rays were described for the first time by Wilhelm Conrad Röntgen, Würzburg, in 1895.
1044 papers about X-rays in medicine were published in 1896.

The first X-ray machine Copenhagen 1896
Nuclear Medicine was born in Copenhagen

Nuclear Medicine was developed in Copenhagen by Georg de Hevesy & Niels Bohr and published in 1935.

Hevesy won the Nobel Prize in 1943 for the tracer technique.

History of Nuclear medicine

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1950</td>
<td>First Positron Imaging Device</td>
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<tr>
<td>1962</td>
<td>Multiple Detectors</td>
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<tr>
<td>1969</td>
<td>Computed Tomography</td>
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<tr>
<td>1979</td>
<td>Current Ring and Cylinder Devices</td>
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<tr>
<td>2001</td>
<td>PET/CT for commercial use</td>
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<tr>
<td>1958</td>
<td>Gammacamera (Hal Anger)</td>
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<tr>
<td>1974</td>
<td>SPECT rotating gammacamera for computed tomography</td>
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<tr>
<td>2004</td>
<td>SPECT/CT</td>
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PET/CT December 2001

PET positron emissions tomography
CT computer tomography

F-18 FDG: FDG fluoro-deoxyglucose for PET glucose metabolism. Cancer cells have high glucose metabolism. F-18 decays with positrons.
Diagnostic imaging in cancer

PET/CT

Diagnosis
Staging – how widespread is the disease?
Treatment effect
Relapse – has the disease reappeared
Planning of surgery and radiation therapy

Many diseases, many methods, which to choose?

PET/CT

Diagnostic accuracy – sensitivity and specificity
Prize
Side effects
Availability
Cost effectiveness
> 20,000 articles

The rapid spread of PET/CT

2001 first PET/CT scanners
2002 first abstracts
2004 first JNM supplement
2008 5,000 papers on PET in oncology
2009 first randomized paper PET/CT
2011 first PET/MRI
2014 PET/MRI with spin lab
2016 PET/MRI routine for patients with brain cancer and dementia
2017 PET/MRI attenuation problem solved

Normal cells use glucose

GLU → GLU → GLU-6-phosphate + CO₂ + H₂O
hexokinase
FDG → FDG → FDG-6-phosphate
Glut1 &3
FDG fluoro-deoxy-glucose
Cancer cells use a lot of glucose

GLU → GLU-6-phosphate → CO₂ + H₂O

FDG → FDG-6-phosphate

Glut1 & 3

Metabolic trapping

FDG: F-18 fluoro-deoxy-glucose

Radioisotope Half-life (min)

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-life (min)</th>
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<tbody>
<tr>
<td>F</td>
<td>109.8</td>
</tr>
<tr>
<td>C</td>
<td>20.4</td>
</tr>
<tr>
<td>N</td>
<td>9.96</td>
</tr>
<tr>
<td>O</td>
<td>2.05</td>
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</tbody>
</table>

Cyklotrons for isotope production

PET – positron emission tomografi

Radiochemistry Unit with lead hot cells
### PET Tracers

- **[F-18] FDG**: Use: Onkology, 5-HT2A receptors, 5-HT1A receptors, Serotonin transporter, Central benzodiazepin receptor, beta-amyloid plaques, 5-HT4 receptors, Brain CBF, Cell proliferation, Hypoxia, Somatostatin receptors, Affibody/HER2 expression, Brain tumors.
- **[C-11] Flumazenil**: Use: Central benzodiazepin receptor.
- **[O-15] H2O**: Use: Brain CBF.
- **[N-13] NH3**: Use: Heart flow.
- **[F-18] FLT**: Use: Cell proliferation.
- **[Cu-64] ATSM**: Use: Hypoxia.
- **[Ga-68] DOTATOC**: Use: Somatostatin receptors.
- **[Ga-68] ABY-025**: Use: Affibody/HER2 expression.

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### PET Research

**Basic Research** – cyclotron isotopes, radiochemistry tracers, scanner hardware and new math algorithms

**Translational** – from lab to clinical patients in animal and man

**Clinical Research** – diagnosis, treatment evaluation, relapse, radiation therapy planning

- New isotopes, new tracers, new hardware & software, physiology, patophysiology, new drugs, new methods
  - non commercial
  - private-public partnership
  - industry driven

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### PET/CT as First Line Imaging

- PET/CT with FDG is integrated in Danish routine patient work up “Kraftpakkerne”
  - Lung cancer
  - Cervical and ovarian cancer
  - Lymphoma
  - Head & Neck
  - Malignant melanoma

PET/CT in cervical cancer

Metastatic lymph nodes:
- Pelvis
- Para-aortal
- Inguinal
- Mediastinum
- Neck
- Omentum

PET/CT in lung cancer

Preoperative staging of lung cancer with combined PET/CT. Randomized study on PET/CT and lung cancer staging, N=189, Conventional or same + PET/CT. Relative risk reduction for a futile thoracotomy 51%.

Cost effectiveness analysis:
Full health care sector perspective by Health Economist
Outcome parameter: Numbers needed to treat (PET/CT scans) to avoid futile operation = 5.
Excluding costs due to co-morbidity PET/CT was cost effective with savings 900 € per patient.
With full analysis incremental cost 4,000 € for patients in PET/CT group, as 4 patients in PET group were extremely expensive.
So, dependent on which model you use results can either be a bargain or very expensive.

Method problems:
- Models have assumptions
- They may be wrong
- Could change conclusion to the opposite
- Systems are dynamic
- Costs and gains may change

PET the first diagnostic imaging method evaluated so meticulously
PET/CT scans are interpreted by a nuclear medicine specialist and a radiologist together—also for radiotherapy planning. N = 1,000 per year as part of clinical routine.

Always whole-body examinations for radiotherapy.

Cervical cancer with metastases.

External LAP laser system.

Cervical cancer for IMRT - Size of lymph nodes?
With PET/CT the definition is more precise!

Radiotherapy and imaging

Radiotherapy planned by CT
- If tumor is drawn too small possibilities for cure smaller
- If tumor is drawn to large side-effects worse
PET and MRI to improve methodology

PET and MRI to improve methodology

Advance PET scanner 1995

Dose painting from FDG-PET

Head & neck cancer: Preliminary results show that relapse is seen in the original PET+ part of the tumor, so that part should have higher dose

Lena Specht & Anne Due et al., work in progress

PET+ part given higher dose without increase in harmful dose to healthy tissue.

PET+ part tailor made therapy using local voxel intensity values: "Dose painting by numbers"
12 year old boy with Hodgkin’s lymphoma - before treatment

PET/CT for planning of radiation therapy

Pediatric nuclear medicine with PET/CT

- Protocols Nordic and European, EORTC
- PET/CT for Radiation therapy planning

PET/CT radiotherapy planning of pediatric cancer

PET/CT for Radiotherapy planning of paediatric haematological- and solid tumours. Experiences from Copenhagen L. Borgwardt et al. Presented at 7th ESOPNM Scientific Committee Award for Poster with Highest Clinical Relevance

Impact of the use of PET guided radiation therapy planning of paediatric cancer
Comparison of 3D conformal, IMRT and Proton therapy with or without PET. Tumour control and long-term toxicity

Supported by funding from the Danish Childhood Cancer Foundation.
PET HRRT brain scanner with 120,000 crystals
Resolution 1.2 mm

Structured Light System
New tracking system for motion correction in brain imaging

System:
One miniaturized DLP projector and two CCD cameras
Capturing: 15 fps captured with two cameras → tracking with 3-4 Hz

Oline Vinter Olesen, PhD M.Sc. Medicine & Technology, RH, DTU, Yale, Siemens
NIR Structured Light System

Results: The system has been tested on human faces with similar results as the visible system.

A modified system where the visible light source has been replaced with a near infrared light diode.

Cluster for molecular imaging

Development of new tracers.

Early evaluation of new drugs for cancer treatment with molecular imaging using animal studies with PET/CT and PET/MR.

Translational from use in animal to man.
Tissue characteristics

- Glycolytic activity
- Invasive phenotype
- Cell proliferation
- Angiogenesis
- Hypoxia
- Apoptosis

Molecular markers

- GLUT-1, HK1, HK2
- uPAR
- Ki67, MCM2
- Integrin\(\alpha_\beta_3\), VEGF
- HIF-1\(\alpha\), CAIX
- Caspase-3, survivin

PET tracers

- \(^{18}\text{F}-\text{FDG}\)
- \(^{64}\text{Cu-DOTA-AE105}\)
- \(^{68}\text{Ga-NOTA-AE105}\)
- \(^{18}\text{F}-\text{FLT}\)
- \(^{18}\text{F}-\text{Galacto-RGD}\)
- \(^{64}\text{Cu-ATSM}\)
- \(^{18}\text{F-Annexin V}\)

\(^{18}\text{F-FLT}\)

- Human cell lines
Imaging of invasive phenotype

PET/CT-scanning can predict whether cancer will metastasise

This patient’s tumor will spread - uPAR is high. Cu-64 uPAR tracer is the isotope Cu-64 with the urokinase-receptor demonstrating invasiveness.

Professor Andreas Kjaer

Treatment of cancer with radioactive medicines

Ra-223 for prostate cancer with bone metastasis and severe pain.

Lu-177 PSMA for prostate cancer,
F-18 PSMA for diagnosis

Neuroendocrine tumors treated with Lu-177 Dotatate.
Neuroendocrine tumours

Old tracer

New tracer including treatment

Biograph mMR – the world’s first simultaneous whole-body molecular MR

Copenhagen PET/MRI

- Simultaneous PET and MRI
- From December 2011

PET specifications
- LSO crystals: 4 x 4 x 20 mm
- 4.7 mm transverse spatial resolution
- ≥12 cps/kBq sensitivity
- 25.8 cm FoV in z-direction

MR specifications
- Magnet: 3 Tesla
- Axial/transaxial FOV: 45/50 cm
3 Tesla MR with coils for simultaneous exams

Head/Neck, A Tim coil
Spine, A Tim coil
Body, A Tim coil
4-channel flex coil, large and small

Morphology, physiology & molecular imaging
...in the same scanner ...at the same time
Absorption of x-rays 
Radioactive PET tracer Leading to 2 gamma photons 
magnetic resonance with radiofrequency

**Method problem PET/MR**

When PET is attenuation corrected via MR in the new scanner bone is estimated too low. Difference 15 % compared to CT-based correction.

New optimization of PET/MR: RESOLUTE

- **Error:** Scanner
- **Error:** Our method

- **CSF**
- **Brain**
- **Air**
- **Bone**
- **Volume**

**Average 204 patients**

New technique for PET/MR adjusts the reconstruction error. Also usable in children. Error now <1 % on PET-signal using RESOLUTE

Claes Ladefoged, cand.scient., ph.d.-student

**PET/MR Hippocampus-volume in dementia**

- 400 patients per year
- PET/MR scanning in one investigation
- Hippocampus-volumetry

Multi-center evaluation of 11 PET/MR-correction methods

**Navigation-related structural change in the hippocampi of taxi drivers**

MR-study London 2000

London taxi drivers have a bigger posterior hippocampus than controls.

The more driving experience the bigger.

Hippocampus stores spatial information and grows in persons using navigation. The changes are reversible.

PNAS 2000, Maguire EA, Frackowiak R, Frith C.
Metod for brain CBF in newborn babies with PET/MR

Method developed in piglets

Minimal invasive and very low radiation dose. Can measure regional CBF via data from the heart during a dynamic scanning.

Why PET/MR in children?

• Simultaneous PET and MR
• More precise co-registration and anatomical localisation
• Simultaneously acquired quantitative dynamic PET and MR with tracers and I.V. contrast
• MR-based motion-correction
• Shorter time in scanner – perhaps less sedation

Potential indications

• Lymphoma
• Neuroblastoma
• Liver tumors
• Pelvic tumors and musculoskeletal tumors
• Brain tumors
• Epilepsy
• Head-neck tumors
• Neurofibromatosis
• Multiple inherited osteochondromas
Pediatric PTLD - post transplantation lymphoma

11 y/o female with PTLD. PET/CT and PET/MRI shows residual metabolically active mass centrally in the abdomen. PET/MRI can discriminate the pathological area in the intestines. More information and less radiation.

Combined PET and hyperpolarized $^{13}$C - MR (‘HyperPET’)

Hyperpolarizer
(SpinLab, GE Healthcare)

Combined PET/MR
(mMR Biograph, Siemens)

MR polarization = 100,000 in $[^{1-13}C]$Pyruvate

Simultaneous in vivo $^{13}$C-MRI and FDG-PET

- Generation of $[^{1-13}C]$Lactate and uptake of FDG in tumor
- Increased $^{13}$C-lactate production in tumor compared to muscle:
  - $^{13}$C-lactate/$^{13}$C-pyruvate ratio tumor: 0.29
  - $^{13}$C-lactate/$^{13}$C-pyruvate ratio muscle: 0.085

H.B. Gutte, A.E. Hansen et al.; to be presented at EANM 2014
PET/MR and PET/CT and genes and epigenetics and clinical and lifestyle information: "Personalised medicine"

"If this does not help, please come again, and we find something else"

"Couldn’t I get the something else right away?"

Personalized Medicine

Paradigm shift with tailored prevention, early diagnosis, treatment based on genes and epigenetics – AND – all the rest.

4P medicine – cheaper

USA NIH and FDA have teamed up

NIH 4P medicine: predictive, personalized, preemptive and participatory
Conclusion

PET/CT-scanning for the diagnosis of cancer is a powerful tool with high accuracy and it is "game changer" for 30% of patients. PET/MR for brain.

Research with molecular imaging with new tracers to improve diagnosis and thereby patient treatment.

Interdisciplinarity and convergence between research areas.