PET/CT and PET/MR

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RIGSHOSPITALET
- 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

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.
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

| PET | 1950 | First Positron Imaging Device |
| 1962 | Multiple Detectors |
| 1969 | Computed Tomography |
| 1979 | Current Ring and Cylinder Devices |
| 2001 | PET/CT for commercial use |
| NM | 1958 | Gammacamera (Hal Anger) |
| 1974 | SPECT rotating gammacamera for computed tomography |
| 2004 | SPECT/CT |

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
- Ultrasound
- CT
- MR

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

> 10,000 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

Normal cells use glucose

GLU
GLU-6-phosphate
CO₂ + H₂O
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

Metabolic trapping

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-life (min)</th>
</tr>
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<tbody>
<tr>
<td>¹⁸F</td>
<td>109.8</td>
</tr>
<tr>
<td>¹¹C</td>
<td>20.4</td>
</tr>
<tr>
<td>¹³N</td>
<td>9.96</td>
</tr>
<tr>
<td>¹⁵O</td>
<td>2.05</td>
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</tbody>
</table>

FDG: F-18 fluoro-deoxy-glucose

Cyklotrons for isotope production

PET – positron emission tomografi

Radiochemistry Unit with lead hot cells
PET tracers

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>[F-18] FDG</td>
<td>Onkology</td>
</tr>
<tr>
<td>[F-18] Altanserin</td>
<td>5-HT2A receptors</td>
</tr>
<tr>
<td>[C-11] CUMI-101</td>
<td>5-HT1A receptors</td>
</tr>
<tr>
<td>[C-11] DASB</td>
<td>Serotonin transporter</td>
</tr>
<tr>
<td>[C-11] Flumazenil</td>
<td>Central benzodiazepin receptor</td>
</tr>
<tr>
<td>[C-11] FIB</td>
<td>beta-amyloid plaques</td>
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<tr>
<td>[C-11] SB207145</td>
<td>5-HT4 receptors</td>
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<tr>
<td>[O-15] H2O</td>
<td>Brain CBF</td>
</tr>
<tr>
<td>[N-13] NH3</td>
<td>Heart flow</td>
</tr>
<tr>
<td>[F-18] FLT</td>
<td>Cell proliferation</td>
</tr>
<tr>
<td>[Cu-64] ATSM</td>
<td>Hypoxia</td>
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<tr>
<td>[Ga-68] DOTATOC</td>
<td>Somatostatin receptors</td>
</tr>
<tr>
<td>[Ga-68] ABY-025</td>
<td>Affibody/HER2 expression</td>
</tr>
<tr>
<td>[F-18] FET</td>
<td>Brain tumors</td>
</tr>
</tbody>
</table>

"PET - The fastest growing medical technology ever"

Positron tracer F-18 FDG
Patient injection
PET scanning combined with CT
Interpretation by NM & radiologist

High sensitivity and specificity, and game changer for 30 %

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, pathophysiology, new drugs, new methods
- non commercial
- private-public partnership
- industry driven

PET/CT as first line imaging

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

On the basis of 12,500 publications: Loft et al 2007 Gyn Oncol,
PET/CT in cervical cancer

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

PET/CT and 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/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.

External LAP laser system.

Cervical cancer with metastases.

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 too large side-effects worse
PET and MRI to improve methodology

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".
After treatment 1. series

PET/CT for planning of radiation therapy

PET/CT radiotherapy planning of pediatric cancer

Pediatric nuclear medicine with PET/CT

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

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

3D conformal IMRT Proton therapy
PET GTV-PET Dose-plan

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.
3,000 born/yr

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.

Bevægelseskorrektion med nyudviklet, patenteret system

World’s first
- Structured light surface scanner with invisible light
- Markerless tracking for MR & PET motion correction

Bevægelseskorrektion med nyudviklet, patenteret system

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

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PET tracers

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

Molecular markers

- GLUT-1, HK1, HK2
- uPAR
- Ki67, MCM2...
- Integrin$\alpha\beta_3$, VEGF...
- Caspase-3, survivin...
- HIF-1$\alpha$, CAIX...

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$^{18}$F-FLT

- $^{18}$F-FLT
- $^{18}$F-FLT
- $^{18}$F-FLT

RIGSHOSPITALET

18F-FLT PET tracers

- $^{64}$Cu-DOTA-AE105
- $^{68}$Ga-NOTA-AE105
- $^{18}$F-Galacto-RGD
- $^{64}$Cu-ATSM
- $^{18}$F-Annexin V

120h
24h
6h
0h

Human cell lines
Imaging of invasive phenotype

PET/CT-scanning can predict whether cancer will metastasize

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.

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
PET funktion og MR anatomi i columna

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

Average 204 patients

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

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

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

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

PET/MR for diagnosis of brain damage in newborns. White matter lesions are important.

Why PET/MR in children?

- Simultaneous PET and MR
- More precise co-registration and anatomical localisation
- Simultaneously acq. of quantitative dynamic PET og 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
(SynLab, 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 life style information: "Personalised medicine"

2020 SCIENCE

"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
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.