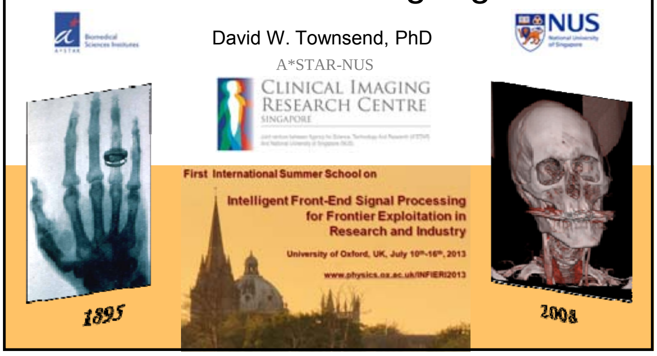
# Future Trends in Medical Imaging

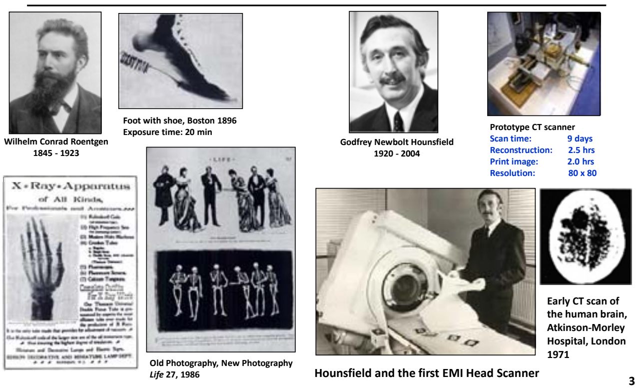



## Topics

- Where have we come from: early days of medical imaging
- The (EM) spectrum of medical imaging modalities
- A focus on Positron Emission Tomography (PET)
- Image fusion and the birth of hybrid imaging
- The road from PET/CT to ….PET/MR…. and beyond

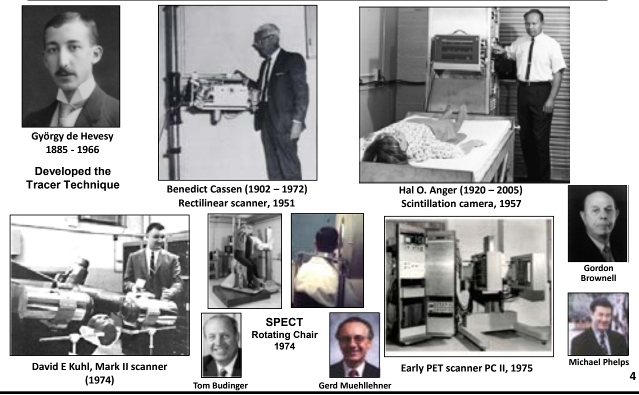


## Milestones in Radiology: from 1895



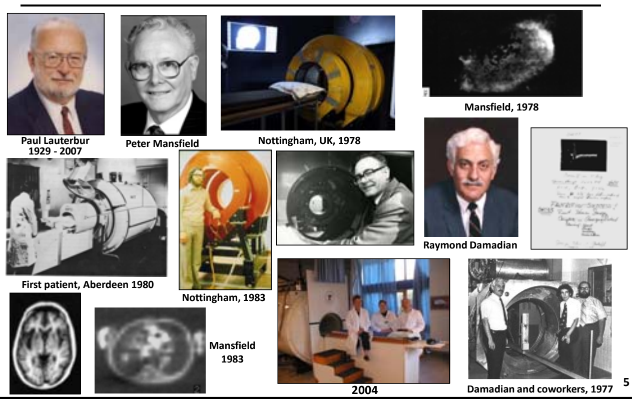



## Milestones in Nuclear Medicine: from 1950



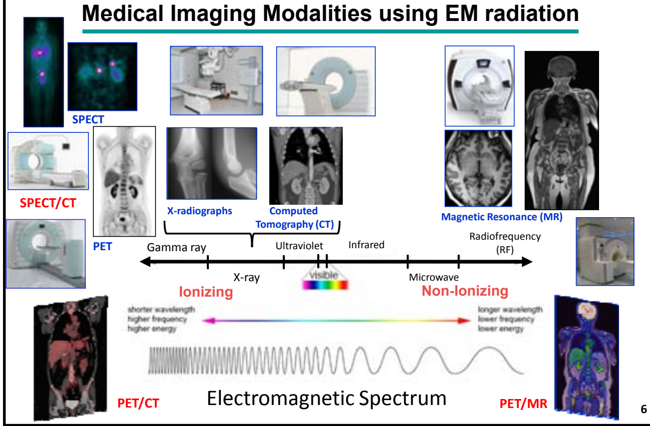



## Milestones in Magnetic Resonance Imaging: from 1980

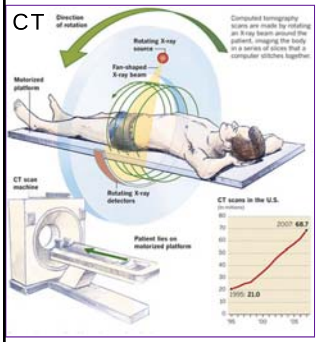


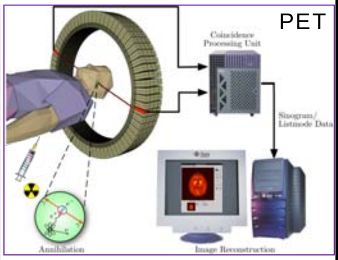



## Medical Imaging Modalities using EM radiation



## Ionizing: Transmission and emission imaging




**Emission tomography**

Use of ionizing radiation for passive (transmission) and active (emission) imaging. In passive imaging, the radiation source is external whereas in active imaging the source is injected into the patient.

**Transmission tomography**



## Sensitivity of imaging modalities

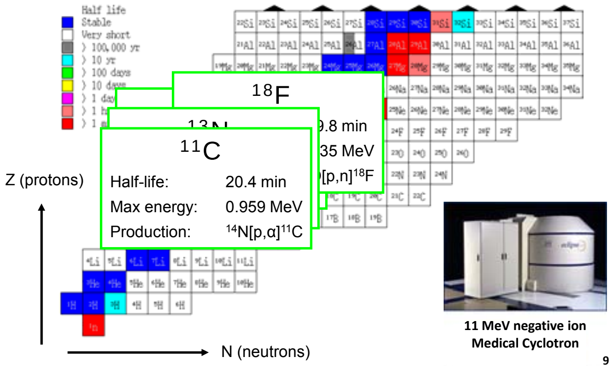
| Imaging Modality | Spatial Resolution (mm) | Acquisition time per frame(s) | Molecular probe mass required (ng) | Molecular sensitivity (mol/L) | Tissue penetration depth (mm) | Signal quantification capabilities |
|---|---|---|---|---|---|---|
| **PET** | 1-2 (animal)<br>6-10 (clinical) | 1-300 | 1-100 | $10^{-11}$-$10^{-12}$ | >300 | High |
| **SPECT** | 0.5-2 (animal)<br>7-15 (clinical) | 60-2000 | 1-100 | $10^{-10}$-$10^{-11}$ | >300 | Medium-High |
| **Optical** | 2-5 (visible to IR) | 10-2000 | $10^{3}$-$10^{6}$ | $10^{-9}$-$10^{-11}$ | 1-20 | Low |
| **MRI** | 0.025-0.1 (animal)<br>0.2 (clinical) | 0.1-100 | $10^{3}$-$10^{6}$ | $10^{-3}$-$10^{-5}$ | >300 | High |
| **US** | 0.05-0.5 (animal)<br>0.1-1 (clinical) | 0.1-100 | $10^{3}$-$10^{6}$ | Not well characterized | 1-300 | Low |
| **CT** | 0.03-0.4 (animal)<br>0.5-1 (clinical) | 1-300 | NA | Not well characterized | >300 | Medium-High |

From Craig S Levin. Eur J Nucl Med & Mol Imag. 2005, 32(14), S-325-45.



## Chart of nuclides

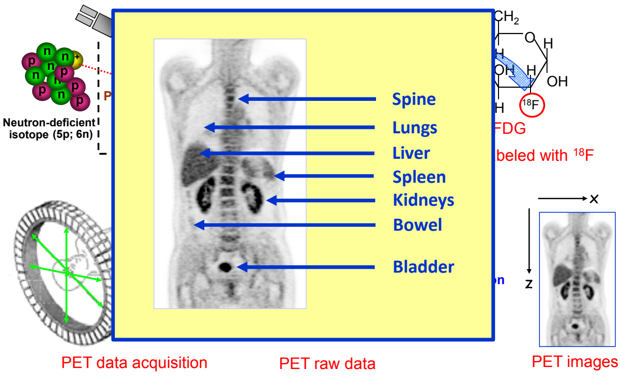
*Korea Atomic Energy Research Lab*




11 MeV negative ion Medical Cyclotron

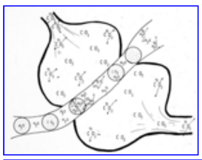


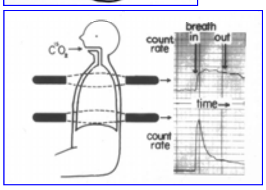
## Positron Emission Tomography: how it works






## PET instrumentation in 1958……Hammersmith Hospital, UK






Dyson NA. The Annihilation Coincidence Method of Localizing Positron-emitting Isotopes, and a Comparison with Parallel Counting. *Phys Med Biol.* 1960;4:376-390.



## PET instrumentation in the 1970s

- **Boston (MGH): Gordon Brownell group, with Charlie Burnham and David Chesler and others**
- **St Louis: Michael Ter-Pogossian group, with Mike Phelps, Ed Hoffman and others**
- **Los Angeles (UCLA) with Z.H. Cho, Lars Eriksson and others who developed a 64 crystal ring scanner**
- **Montreal, Canada: L. Yamamoto, C. Thompson, E. Meyer with a 32 crystal scanner in Montreal in 1976, originally from Brookhaven**
- **Lawrence Berkeley Laboratory, California: Thomas Budinger, Steve Derenzo, Ron Huesman and others developed a 280 crystal PET ring**
- **CERN, Geneva, Switzerland: Alan Jeavons, David Townsend with Dual HIDAC detectors employing lead convertors**
- **UCSF and LBL: Lim, Chu, Kaufman and Perez-Mendez with Multiwire Proportional Chambers (MWPC)**
- **NIRS, Chiba, Japan: E. Tanaka and others**

## PET instrumentation in the 1970s……St Louis

**Mike Phelps, Ed Hoffman, Michael Ter-Pogossian**

PETT II: First coincidence detection version of PETT design. Phantom studies: Jan 74

PETT II 1/2: Computer controlled scanning Phantom and animal studies : Feb 74

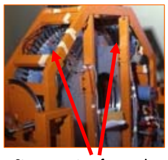

First PET images of the human brain acquired on the PETT III scanner built at Washington University in St Louis in 1976 using $^{11}$C-D-Glucose

PETT III: Whole body clinical system Human and animal studies: Dec 74

ORTEC ECAT II: First commercial PET scanner at UCLA: Dec 76; based on PETT III



## PET instrumentation in 1978……Karolinska, Sweden



Stepper motors for x and y motion (wobble)

PC-95 at the Karolinska Hospital (in operation 1978-1981) demonstrated by Mats Bergström

PC-95, a first generation PET scanner at the Karolinska Institutet in 1976-1978
A 95 NaI(Tl) detector ring system (8 x 20 x 50 mm$^3$)
(L. Widen, T. Greitz, L. Eriksson, C. Bohm and others)

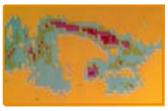
$^{68}$Ga-EDTA images from a study showing rupture of blood brain barrier in study acquired on PC-95

L. Widén and L. Eriksson



## The HIDAC Camera Project, 1977-1982 CERN, Geneva

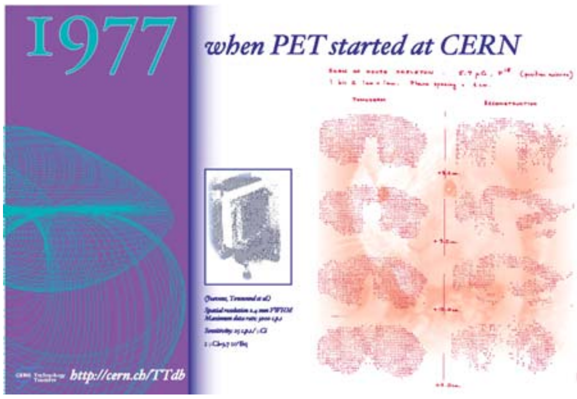
**1978 CERN**

First mouse imaged at CERN with $^{18}$F transported by air from Hammersmith Hospital in London

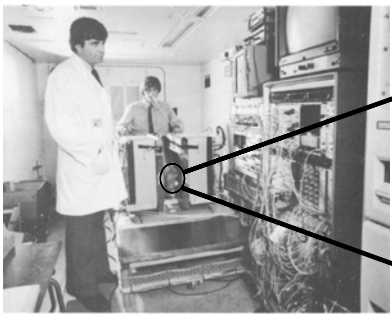
**HIDAC prototype in Geneva University Hospital**





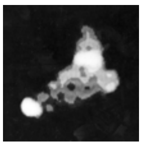



## Multi-wire chambers at Hammersmith 1981



*Mr Terry Jones observing a positron camera produced image of the circulation of blood to the left foot of a subject.*

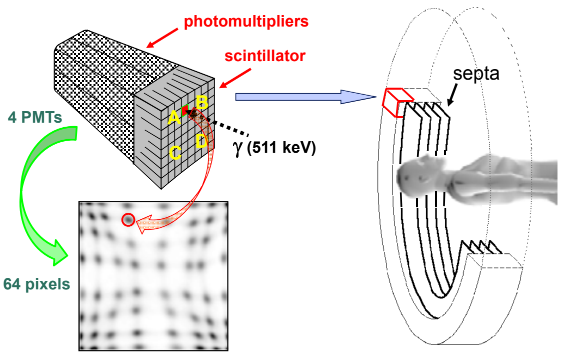
$C^{15}O_2$ : blood flow



**Bulletin** *7 Sept 1981*



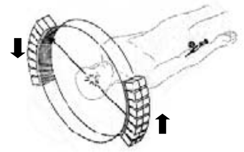
## The block detector 1984 Casey and Nutt, 1986




Scintillator pixel map

Multi-ring scanner

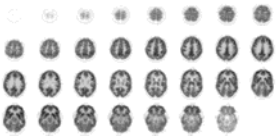
## The PRT Camera Project 1990 - 1992



PRT-1
Dual rotating arrays


Caméra ultraprécise à l'Hôpital cantonal universitaire

Nouveau Quotidien July 19, 1992



First FDG brain study on PRT-1, May 1991

*Financially supported by the CERS*

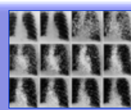
19

## Early fusion imaging: from analogue to software

**1960**

Manual contouring and image overlay

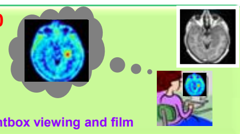
**1970**



Inhalation of $C^{15}O_2$

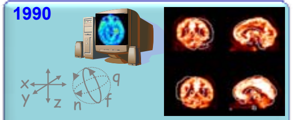
Image overlay: PET and radiograph

**1980**



Lightbox viewing and film

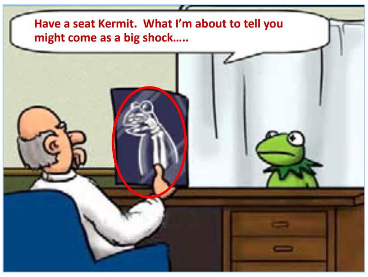
**1990**

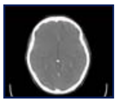


Software-based fusion (semi-automated)

20

## A clinical diagnosis from imaging

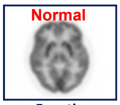


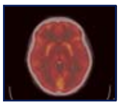
Anatomy (CT)

Dead

Function (PET)




Function (PET)



Anatomy + Function (PET/CT)

*Diagnosis from anatomy.....* *Diagnosis from function..*

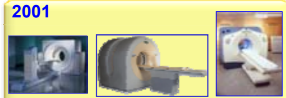
21

## More recent fusion imaging: hardware

**1993 - 1998**


Hardware-based fusion: Prototype designs

**2001**



Hardware-based fusion: Commercial PET/CT

**2004**

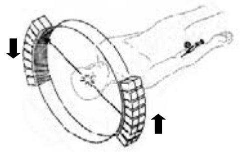
Hardware-based fusion: Commercial SPECT/CT

**2010**

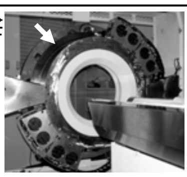
Hardware-based fusion: Commercial PET/MR

22

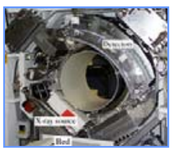
## The concept of PET/CT: 1991



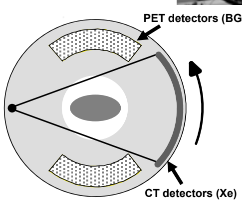
The Geneva PRT-1



PRT-1
The device



CT




PET/CT: artist's impression

PET

23

## Where in the world is.....the lesion?

*P. Brueghel*

**X-ray CT: anatomy** **PET: function**

**CT + PET: anatomy + function**

*The best of both worlds!*

24

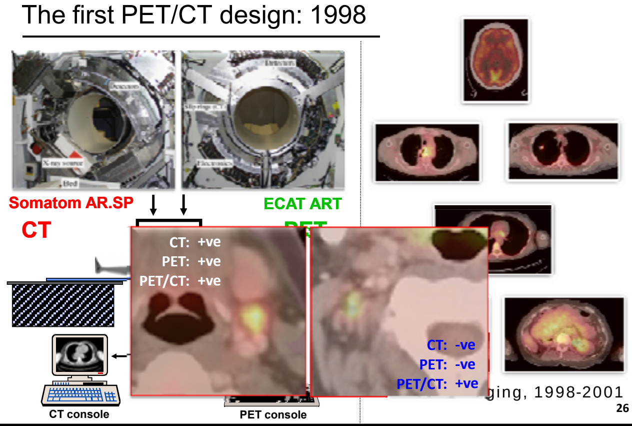
## The importance of imaging both structure and function

*"Structure without function is a corpse;*
*function without structure is a ghost"*

-- Steven Wainwright

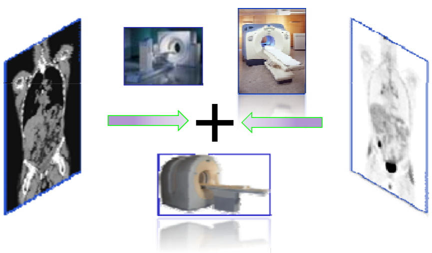


## The first PET/CT design: 1998

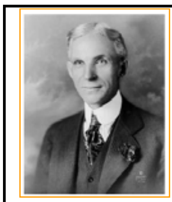





## 2001: Commercial PET/CT







## Henry Ford

***If I had asked my customers what they wanted, they would have said faster horses.***



## Comments from our potential "customers"

*JNM, October 1999*

"I think fusion is overblown in reputation. Good nuclear physicians can correlate just as well using internal landmarks."

"As one user of PET, I'm strongly willing to use the PET/CT fused imaging system. However, I have concern that the issue of sectionalism between radiologists and nuclear medicine physicians would prevent development of this special system."

"I hate to say it, but radiologist and nuclear medicine docs don't work as a team now most of the time, and getting the two types of images from one device won't change this characteristic."

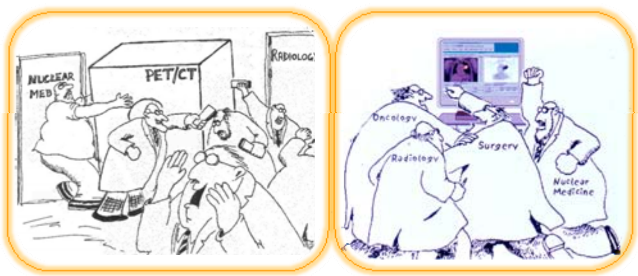
"The PET business will go to the radiologist who will in fact own / control the CT."

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 40 • No. 9 • October 1999



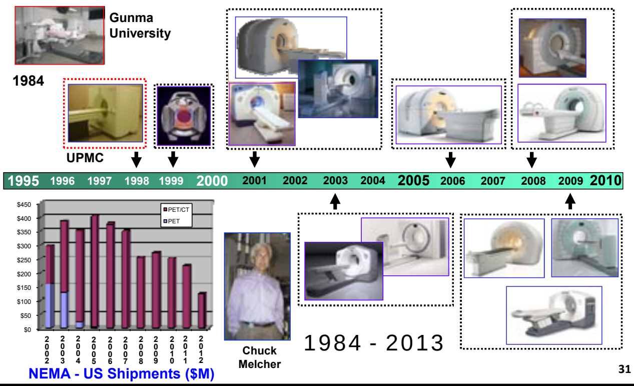
## The introduction of PET/CT into the clinic….

**2001**




**Ownership of the PET/CT** | **Reading the PET/CT images**

## The evolution of PET/CT






## Technical advances in PET and CT

PET

| | | |
|---|---|---|
| Smaller scintillator crystals | → | Higher spatial resolution |
| Extended axial field-of-view | → | Increased sensitivity |
| Time-of-flight (TOF) | → | Improved SNR |
| Respiration gating | → | Motion correction |
| Model-based reconstruction | → | Improved CNR |

CT

| | | |
|---|---|---|
| Increased detector rows | → | Fast, high-resolution coverage |
| Increased x-ray tube power | → | Short cooling periods, stability |
| Light-weight x-ray tube | → | Faster rotation times |
| Increased computer capacity | → | Fast processing |
| Iterative reconstruction | → | Reduce radiation dose |
| Better use of x-radiation | → | High-quality images |



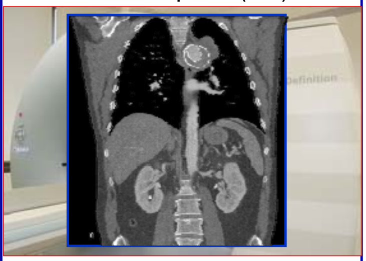
## Progress in CT

**Over 40+ years of development**

**EMI parallel beam scanner (1972)**


180 views per rotation in 300 s
2×160 positions per view
113 kB data

**Siemens 128-slice Dual source spiral CT (2005)**

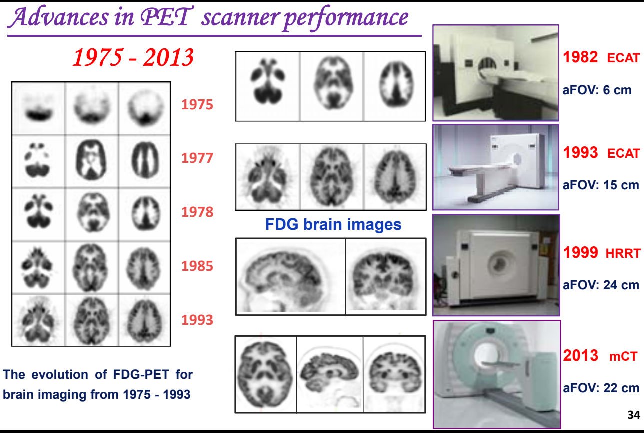


1536 views per rotation in 0.33 s
2·32×(672+352) 2-byte channels per view
600 MB/s data transfer rate
5 GB data size typical



## *Advances in PET scanner performance*

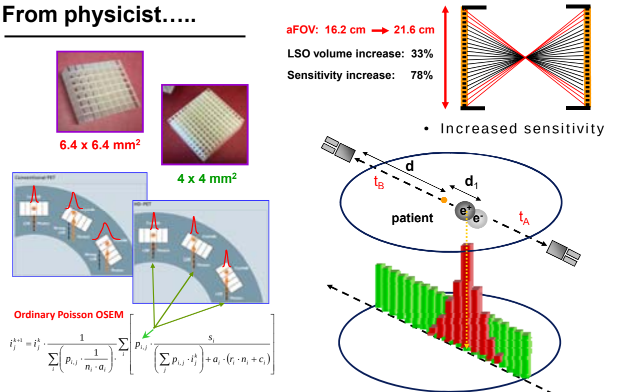
*1975 - 2013*




The evolution of FDG-PET for brain imaging from 1975 - 1993



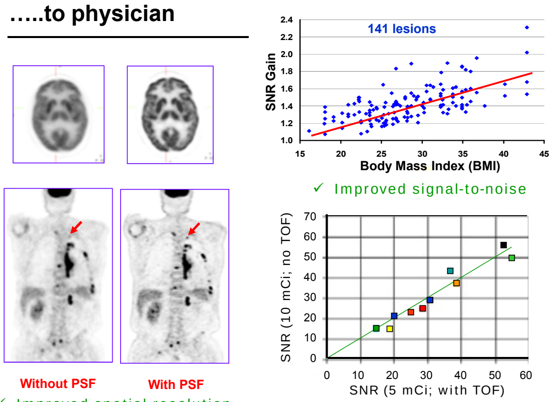
## From physicist.....




- Increased sensitivity
- Improved spatial resolution
- Improved signal-to-noise



## .....to physician




✓ Improved signal-to-noise

✓ Improved spatial resolution

✓ Reduced radiation dose

## Molecular Imaging


**And we've had PET/CT for over a decade!**

*D. Karantis et al,* ... 053 authors of papers in major oncology journals ... onse rate

66% felt consultation with imag... ...re a scan to be useful

96% felt interaction between referring ... physicians good for patients

39% reported frequent necessity for discussion ... xpert

61% always read entire PET/CT report

30% reported ambiguity, poor explanation or lack of familiarity ...

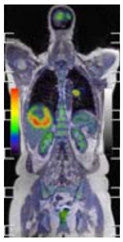
85% expressed desire for access to PET/CT images

47% raised concerns about high cost of PET/CT scans

41% has concerns about over-interpretation of imaging findings

37

## 2010: and now…PET/MR

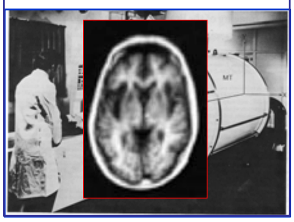



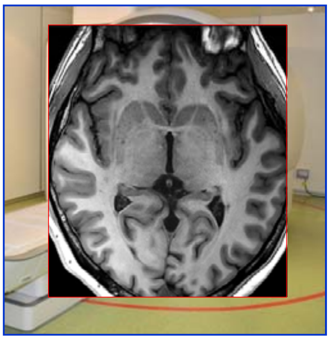
38

## Advances in MR

Over 30+ years of development

First patient on Aberdeen MRI (1980)

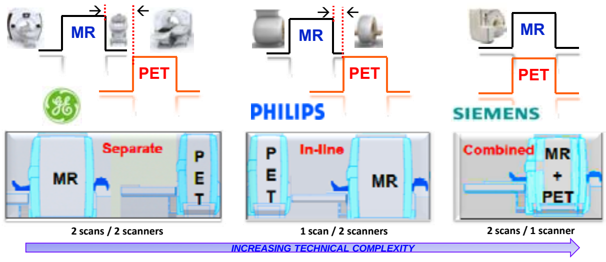




SIEMENS Skyra MRI scanner (2013)

39

## PET/MR: clinical system designs




| | | |
|---|---|---|
| straightforward design | whole-body scanning | whole-body scanning |
| whole-body scanning | fairly straightforward | simultaneous imaging |
| easily upgradable | potentially upgradable | challenging to upgrade |
| sequential imaging | sequential imaging | cross-talk possibility |
| large footprint | medium footprint | servicability issues |
| Utility Factor = 1 | Utility Factor = 0.5 | Utility Factor = 2 |

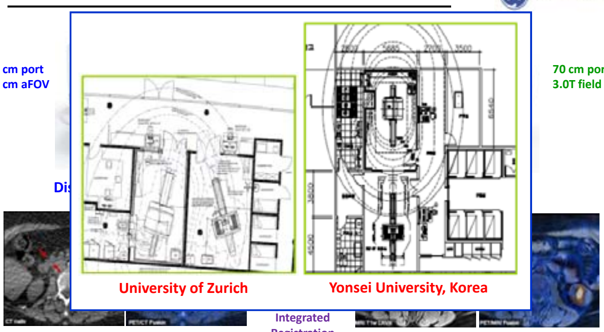
40

## Tri-modality PET/CT + MR

imagination at work

70 cm port
16 cm aFOV

70 cm port
3.0T field




CT identifies pathology

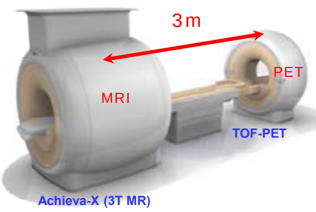
PET/CT confirms functional abnormality

MR differentiates soft tissues

PET/MR localizes lesion to pancreatic head

41

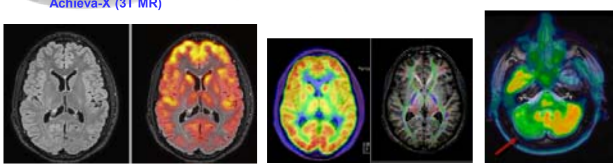
## Ingenuity TF PET/MR PHILIPS




HUG

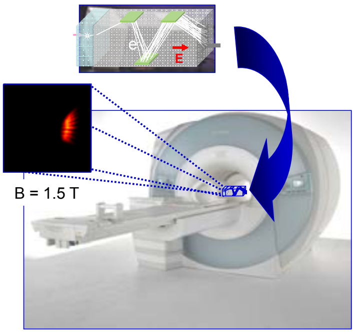
**Osman Ratib, MD, PhD**

Div of Nuclear Medicine
Dept. of Medical Imaging and Information Sciences
University Hospital of Geneva

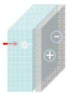


42

## Detectors for integrated MR/PET



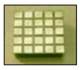

**Avalanche Photodiodes**



APD-based PET detector

- compact
- high quantum efficiency
- low bias voltage
- magnetic field insensitive
- lower gain
- limited time resolution

**SiPM or G-APD**



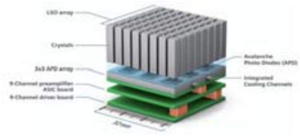
SiPM-based PET detector

- high gain
- low bias voltage
- compact
- magnetic field insensitive
- very fast
- low cost CMOS process

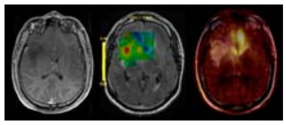


## SIEMENS mMR


- LSO crystal material + APDs
- 4 x 4 x 20 mm crystal elements
- 26 cm axial coverage
- ≤ 4.7 mm spatial resolution @ 1 cm
- ≥ 12 kcps sensitivity
- ≥ 155 kcps peak NECR (@ 21.8 kBq/cc)

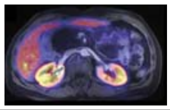


MR-compatible PET detector



MR | MRI + MRS | MRI + $^{11}$C-MET

UKT, Tübingen, Germany



Somatostatin receptors imaged with PET/MR

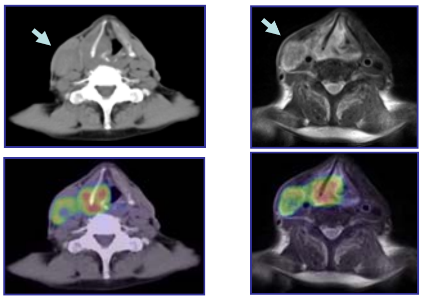
From: N. Schwenzer et al.: *Whole-body MR/PET: Applications in abdominal imaging*; (2011)



## Nasopharyngeal cancer on mMR @ CIRC

CLINICAL IMAGING RESEARCH CENTRE SINGAPORE

Improved soft-tissue contrast



PET/CT: 1 min/position | PET/MR (T2): 4 min/position

PET/CT

PET/MR

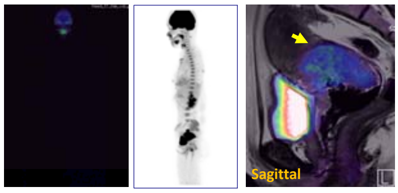
71 year-old male patient with nasopharyngeal cancer

Time between scans: 60 min



## Patient studies on mMR @ CIRC

CLINICAL IMAGING RESEARCH CENTRE SINGAPORE

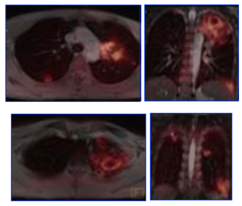



Frontal sections | PET MIP | PET/MR fusion

55 year-old female with recently-diagnosed ovarian cancer. Patient has been undergoing chemotherapy. The PET/MR scan demonstrates a very large mass in the pelvis with the involvement of at least one lymph node (white arrow).

**Ovarian cancer**

PET/MRI matches PET/CT for gynecological malignancies
By Wayne Forrest, AuntMinnie.com staff writer



**Tuberculosis**

FDG-PET/MR in patient under-going treatment for tuberculosis. No longer infectious at scan time

WB radiation dose: ~ 3mSv



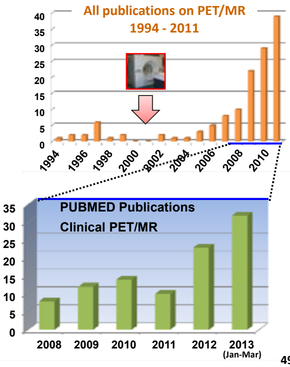
## PET/MR: worldwide distribution up to March 2013




## Where will PET/MR make a difference?

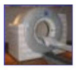
- ✓ CNS disease: dementia, tumours, epilepsy
- ✓ Chronic degenerative diseases in joints
- ✓ Oncology: prostate (not FDG), liver, H & N
- ✓ Cardiology and cerebrovascular disease
- ✓ Pediatric and young adult diseases
- ✓ Non-malignant diseases (TB, infections)
- ✓ Metabolic diseases (diabetes, obesity)
- ✓ "One stop shop" for MR and PET study

- Multi-parametric image analysis, display
- Metabolomics: fat metabolism, β cell mass
- Early therapy response assessment in RT

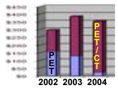





## PET/CT: A technical *evolution* and an imaging *revolution*



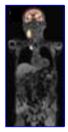
(**2002 – 2004:** *Units shipped in USA: 360*)




## PET/MR: A technical *revolution* and an imaging *evolution*

(**2010 – 2012:** *Units shipped in USA: 14*)

*Johannes Czernin*
*Director of Nuclear Medicine, UCLA*





## Australia's Productivity Loss

Population Growth | Ageing Population | Obesity

Diabetes | Mental Illness | Cardiovascular Disease | Cancer | Joint Disorders

**Expenditure**

| Diabetes | Mental Illness | Cardiovascular Disease | Cancer | Joint Disorders |
|---|---|---|---|---|
| ⬆520% | ⬆342% | ⬆142% | ⬆190% | ⬆223% |

Source Goss, J., 2008, projection of Australia's healthcare expenditure by disease, 2003 to 2033



## The cost of neurological disease in Europe:

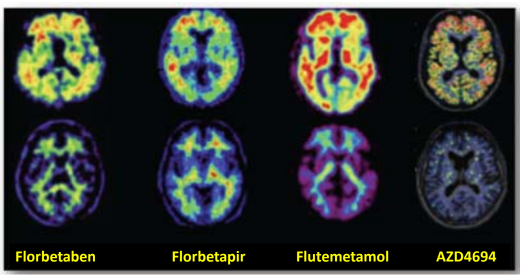

**800 B € per year**

- Dementia 105B €
- Schizophrenia 94B €
- Epilepsy 14B €
- Depression 113B €
- Brain Tumours 5B €
- Anxiety 74B €
- Addiction 65B €
- Cerebral Vascular Disease 64B €
- Movement Disorders 14B €

*Gustavsson et al., 2011*



## [18]F-labeled amyloid imaging agents for AD



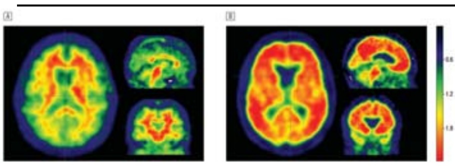

| Florbetaben | Florbetapir | Flutemetamol | AZD4694 |
|---|---|---|---|
| Piramal (Bayer) | Lilly/AVID (AV-45: Amyvid) | GE (FPIB) | Astrazeneca |

*David J Brooks, MD*

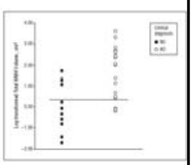


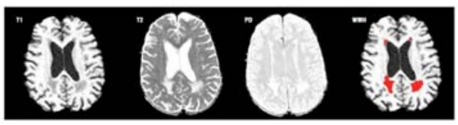
## White Matter Hyperintensities and Cerebral Amyloidosis

*JAMA Neurology 2013*




[11]C-PIB negative scan    [11]C-PIB positive scan



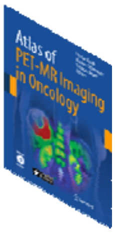


WMH volume for a group of PIB positive patients and a group of normal controls. At the cutoff, sensitivity is 83% and specificity is 64% for a diagnostic classification.

WMH: White matter hyperintensity (segmented) for AD patient

## Summary:

- Both PET and MR are complex imaging modalities
- PET/MR will not replace PET/CT in the medium term
- Complex protocols to be defined (oncology)
- Cost and efficient time usage of both modalities
- Patient comfort and acceptance to be established
- Accurate MR-based attenuation correction needed




Clinical evidence of real benefit?

- ✓ PET/CT over PET and CT separately
- ✓ SPECT/CT over SPECT and CT separately
- ✓ PET/MR over PET(/CT) and MR - for specific indications (TBD)



## Biomarkers and modalities for imaging

Courtesy Simon Cherry PhD

| Imaging agent | Imaging modality | Molecular weight (Daltons) | Comments |
|---|---|---|---|
| **Small molecule** | PET and SPECT | 1 - $10^2$ | Receptor ligands, enzyme substrates, many drugs. No change in biological function |
| **Macromolecules** | PET and SPECT, MR, Optical | $10^2$ - $10^4$ | Engineered molecules with labeling flexibility to image receptors and enzymes |
| **Peptides** | PET and SPECT, MR, Optical | $10^3$ - $10^4$ | Small chains of labeled amino acids used to target cell surface receptors. Immune response problem |
| **Antibodies** | PET and SPECT, MR, Optical | $10^5$ - $10^6$ | Large labeled proteins used to target cell surface receptors. Engineered fragments clear faster |
| **Particles** (nanoparticles, microbubbles, quantum dots) | PET and SPECT, MR, Optical, Ultrasound | > $10^3$ | Particles used for intra-vascular targets; exterior of particle coated with targeting molecules (peptide) |

PET and SPECT | Magnetic Resonance (MR) | Optical | Ultrasound



## The Biomarker Challenge

GMP production and regulatory approval

Cyclotron

Radiochemistry and hot cells

- $^{18}$F-NaF
- $^{18}$F-FLT
- $^{18}$F-FAZA
- $^{18}$F-FMISO
- $^{18}$F-FPPRGD2
- $^{18}$F-FHBG
- $^{18}$F-choline
- $^{18}$F-FES
- $^{18}$F-FET
- $^{11}$C-choline
- $^{11}$C-methionine
- $^{11}$C-acetate
- $^{82}$Rb-chloride

- glucose utilization
- tumor hypoxia
- tumor blood flow
- angiogenesis
- amino acid synthesis
- cell proliferation
- apoptosis, cell death
- somatastin receptors
- estrogen receptors
- fluoride bone imaging
- cardiac perfusion

- cerebral blood flow
- cerebral blood volume
- β-amyloid plaques
- tau protein levels
- amino acid synthesis
- dopamine transporter
- D2/D3 receptors
- TSPO in inflammation
- GABA-A receptors
- activated microglia
- serotonin receptors

- $^{18}$F-FDG
- $^{18}$F-dopa
- $^{11}$C-raclopride
- $^{18}$F-fallypride
- $^{11}$C-McN5652
- $^{11}$C-DASB
- $^{18}$F-altanserin
- $^{11}$C-flumazenil
- $^{11}$C-diprenorphine
- $^{11}$C-carfentanil
- $^{11}$C-PIB
- $^{18}$F-Flutametamol
- $^{18}$F-Florbetapir
- $^{18}$F-AZD4694

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