Accelerators for Medical and Industrial Applications

JUAS
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Organization of the lecture

- Intro: About IBA
- Part 1: Radioisotopes for medical applications
  a. Diagnosis and molecular imaging
  b. Radioisotopes for cancer therapy
- Part 2: Cyclotrons for Isotope production
- Part 3: Particle therapy of cancer
- Part 4: The ProteusOne and S2C2 project
- Part 5: Industrial applications of electron beam technology

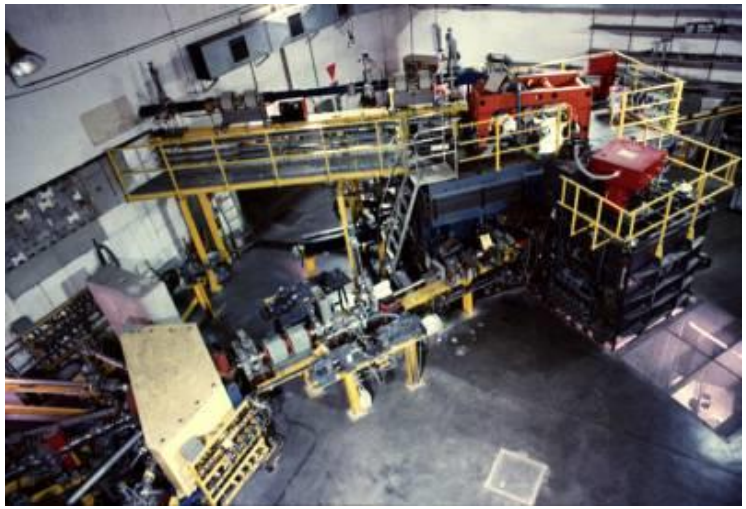
Foreword

- In this lecture, I cannot present an exhaustive overview of all possible applications of accelerators
- I will mainly limit myself to subjects where IBA has first hand experience

Belgium has a tradition and important know how in civil nuclear applications

- Belgium is one of the first European countries to install a cyclotron in 1947
- SCK/CEN Research centre for nuclear energy (MOL), founded in 1952
- Cyclotron Centre at LLN was started in 1970

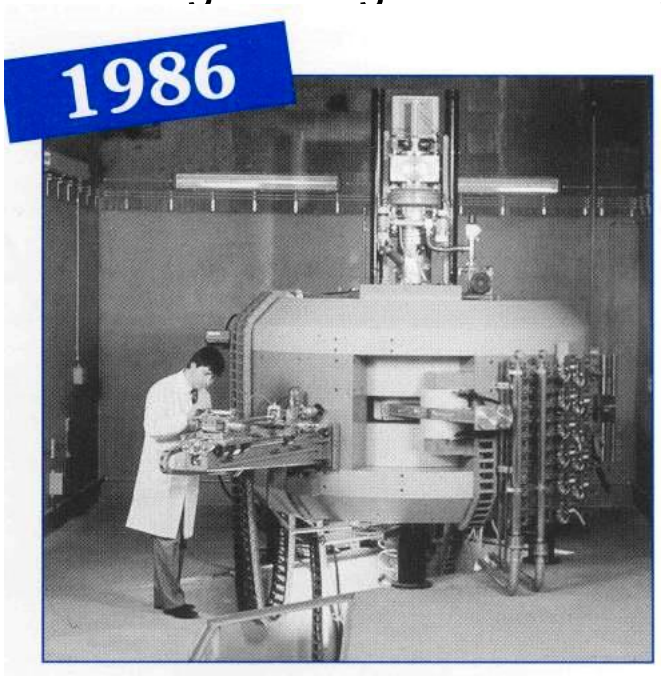
Yoke of first cyclotron in Belgium



CRC CYCLONE-110
Thomson-CSF
p 65 MeV, d 50 MeV, α 110 MeV

Foundation of IBA

- 1986 => spinoff from the CRC at UCL (Catholic University of LLN)
- Start of IBA => Cyclone 30: a revolutionary cyclotron for medical isotopes => 5 x more output and 3 x less power consumption
- Founder Yves Jongen currently IBA Chief Research Officer and recognized global leading accelerator expert

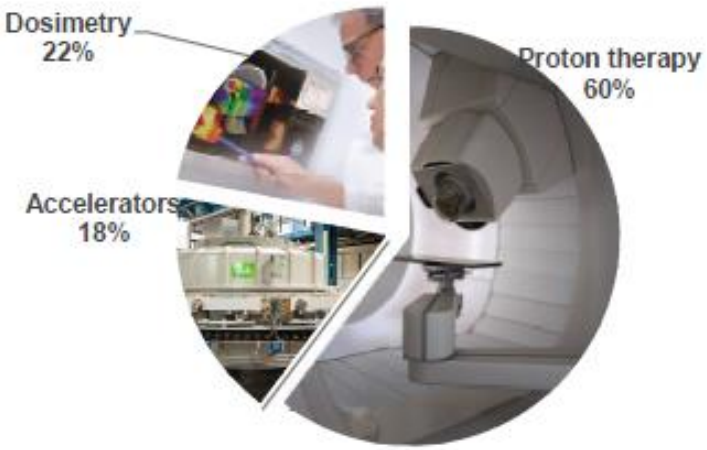


The origins of IBA

- The initial company ambitions in 1986 were modest:
  - Build one cyclotron per year
  - Maximum 15 employees
  - Business of 1.5 to 2 M€ per year
  - Getting rich was not part of the initial objectives, but having fun clearly was…
  - …and in this respect, we were quite successful !

The IBA Group in 2014

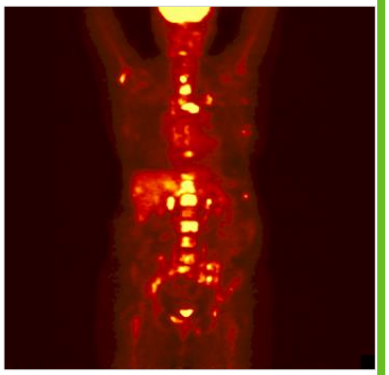
- 1200 employees worlwide
- Turnover > 220 M€ and growing steadily every year
- More than 300 systems (200 Cyclotrons) installed
- Not anymore just a cyclotron company, but a company focused on medical technology for the fight against cancer:
  - Cancer diagnostic: molecular imaging
  - Cancer treatment: Particle therapy & dosimetry
- More than 400 patents in use
- Listed on Euronext Brussels
- http://www.iba-worldwide.com



IBA Today: Centering on the fight against cancer

Pharmaceuticals

Radiopharmaceuticals
- Molecular Imaging
- Nuclear Medicine (diagnostics & therapy)

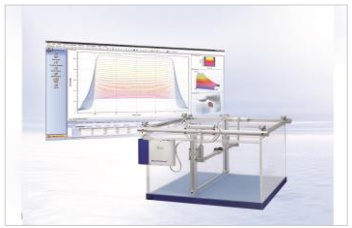


Particle Therapy

Proton Therapy is increasingly considered as the ultimate radiotherapy for cancer due to its superior dose distribution

Dosimetry

Dosimetry equipment
to measure and calibrate radiation dose for
- Radiotherapy
- Radiodiagnostics



Accelerators

Cyclotrons
- To produces Radioisotopes

E-beam / X-rays
- To irradiate / treat many industrial products

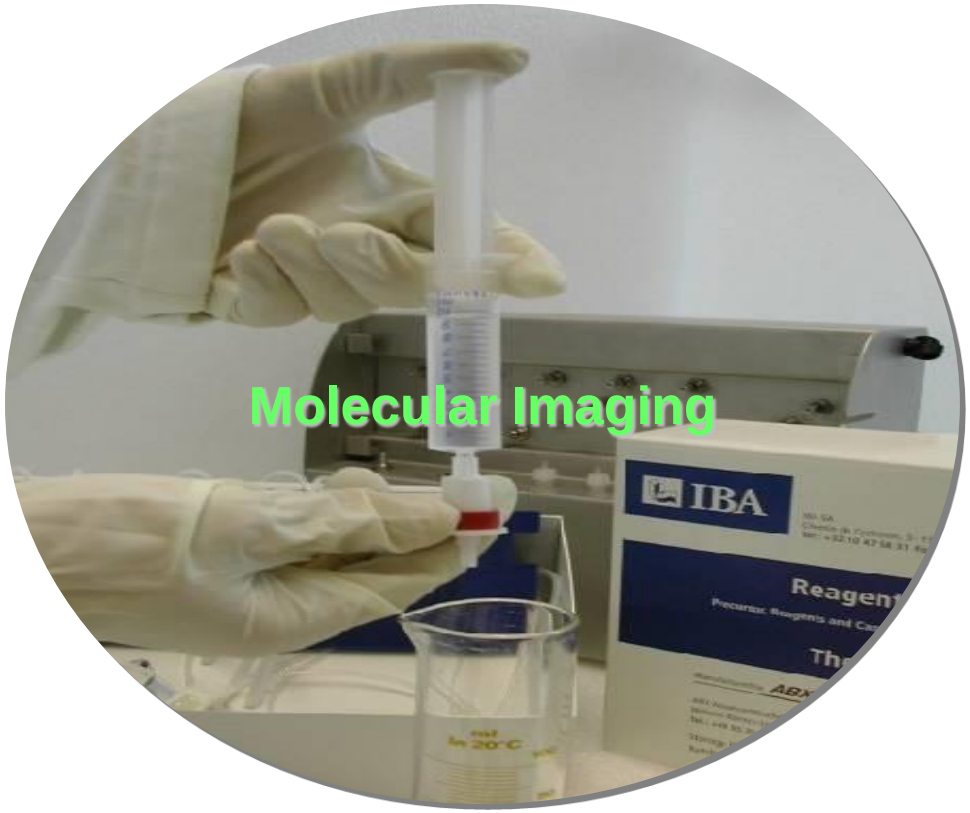
PART I:

Radioisotopes for Medical Applications

Part I-A: radio-isotopes for medical diagnosis

SPECT: Single Photon Emission Computed Tomography

PET: Positron Emission Tomography



How is imaging done with radio-tracers ?

SPECT

PET

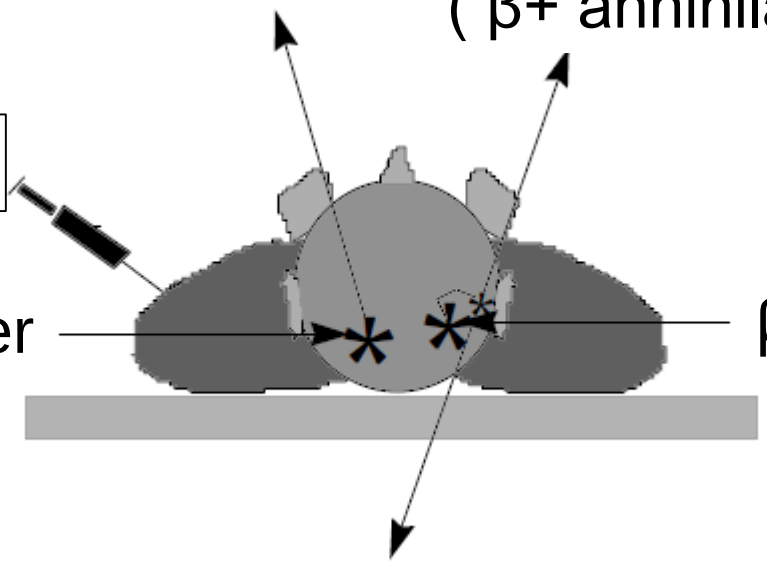
Single photon

2 photons of 511keV
(β+ annihilation)

Radio-isotope

γ emitter

β+ emitter



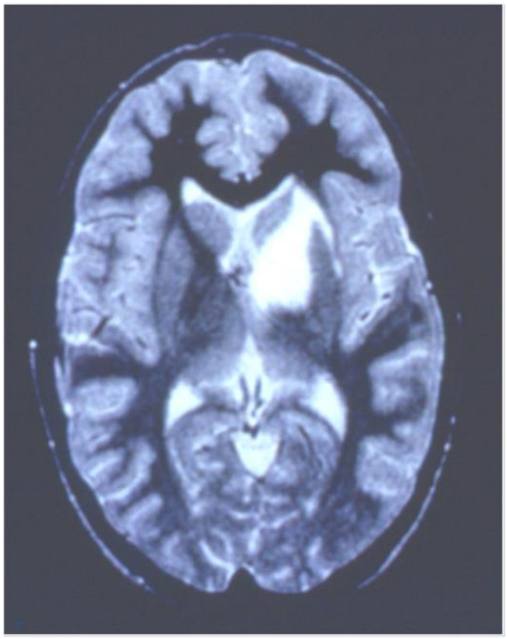
A camera (Gamma or PET) detects the photons emitted from the body and computes 3D distributions of the radio-activity

The use of Radio Isotopes for medical imaging

- Radio tracers can be used to label a specific bio-chemical molecule.
- They allow to see metabolism
  - X-ray scan or MRI are better to see the anatomy (structure)
- Nuclear medicine (imaging of metabolism using molecules labeled with an appropriate radioisotope) is therefore not in competition, but in complement of imaging techniques such as X-ray, X-ray CT-scan or MRI.

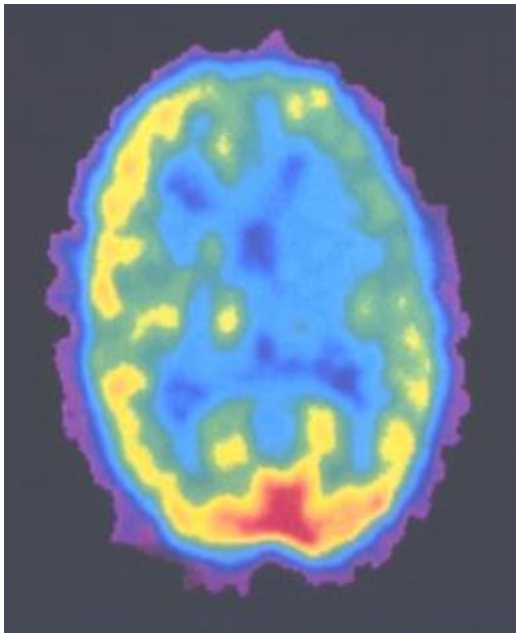
Metabolic versus anatomic imaging

MRI



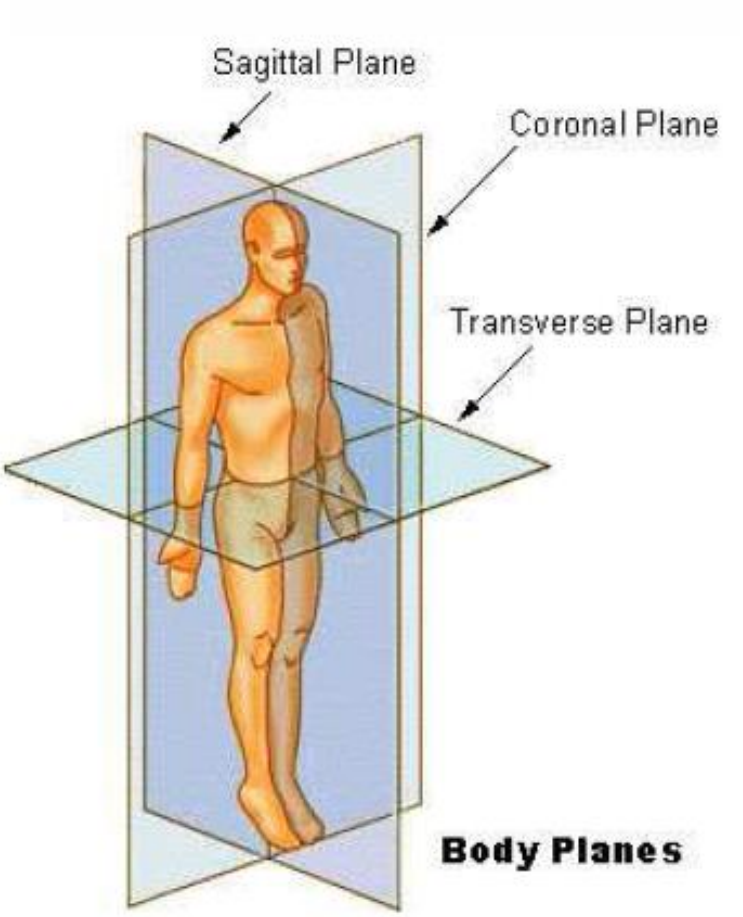
Anatomic View
(Tissue-structure)

PET



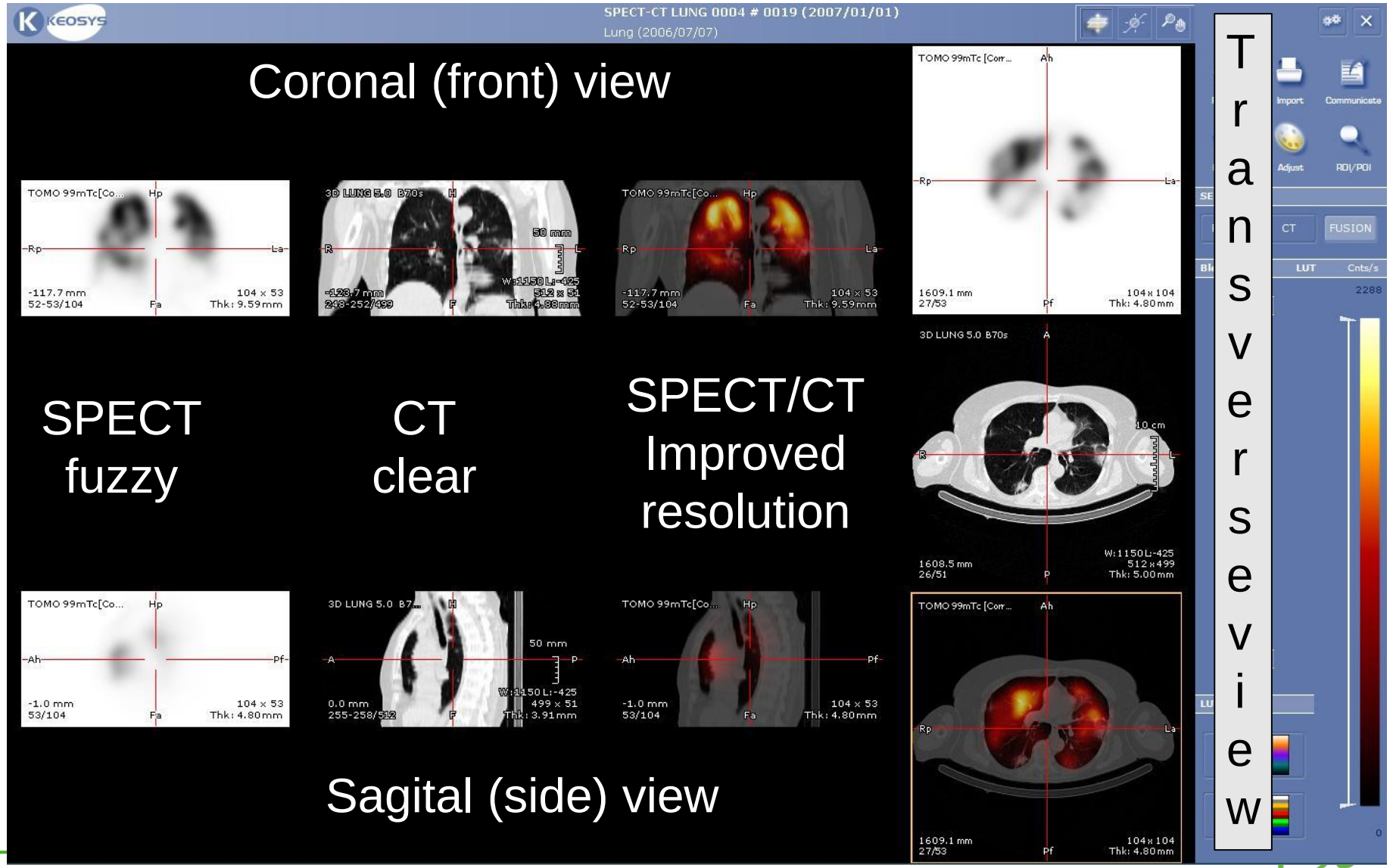
Metabolic imaging
(Biological-function)

The three body planes



- Coronal => frontal
- Sagital => side
- Transverse

Metabolic and anatomic imaging combined: fusion of SPECT and CT to improve image quality



How is imaging done with radio-tracers ?

Single photon isotopes (SPECT)

- The imaging of single photons emitters requires:
  - a collimator (causes a loss of efficiency !).
  - a position-sensitive detector (with good detection efficiency): the Gamma (or Anger) camera.

- The image obtained is a projection.
- Multiple (perpendicular) projections can be mathematically correlated to produce a 3D representation.
- SPECT (Single Photon Emission Computed Tomography).

How is imaging done with radio-tracers ?

Positron emitting radio-isotopes (PET)

- The emitted positron travels a few millimeters, then meets an electron and annihilates, emitting two anti-parallel photons of 511keV.
- These two photons can be detected in **coincidence** by a ring of detectors surrounding the region of interest.
- One knows then that the origin of the photons is on the line connecting the two detectors.
- Several detections allow to locate the source.
- By mathematical reconstruction, a 3D representation of the activity can be obtained.
- PET (Positron Emission Tomography).

How to select a good single-photon radio-tracer?

1. The energy of the emitted photon
   - Low enough to keep a good detector efficiency
   - Low enough in order to achieve good collimation
   - High enough to cross the body tissue
   - 100 keV $\leq$ E $\leq$ 300 keV is generally the optimum

How to select a good single-photon radio-tracer ?

2. The half-life:
   - Short enough to minimize the patient's exposure
   - Long enough to allow industrial production and distribution to the hospitals
   - Practically 10h $\leq T_{1/2} \leq$ 100h is roughly best
   - Generators are great too !

^{99}Mo (66 hours) = $^{99}Tc_m$ (6 hours)

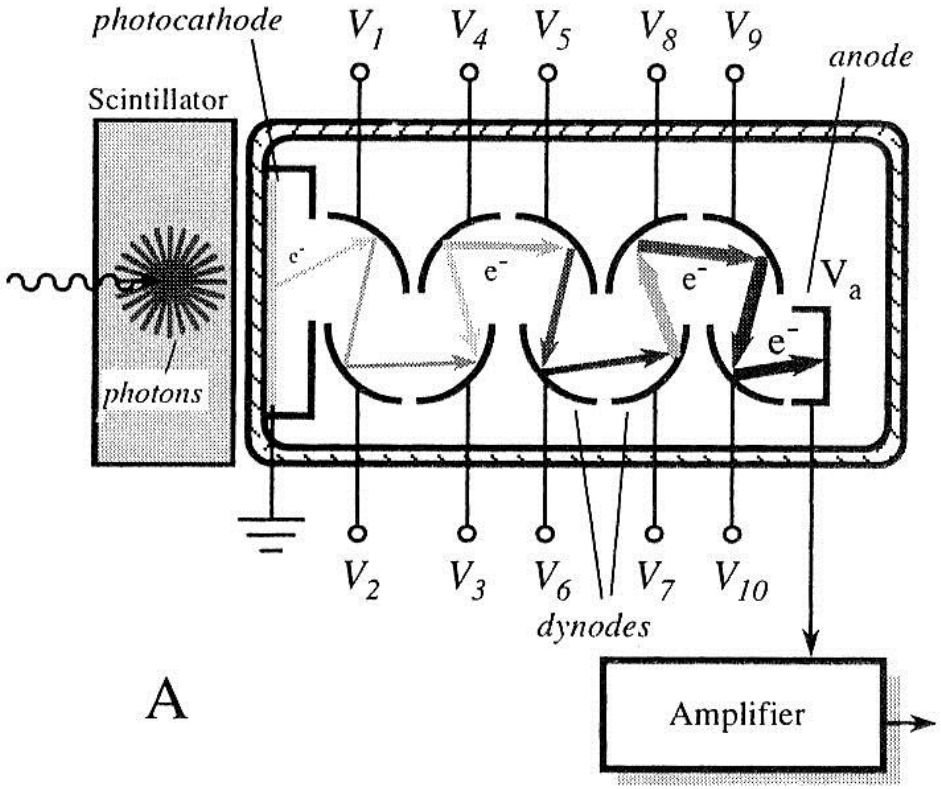
^{81}Rb (4.6 hours) => $^{81}K_r$ (13sec)

How to select a good single-photon radio-tracer

3. The chemistry
   - The radio-tracer should bind easily to organic bio-molecules of interest
   - Essential bio-chemical behavior of the molecule shoud remain intact after labeling
     - Halogens (Fluor, Iodine), Technetium ⇒good;
     - Noble metals (Gold) ⇒ difficult

Detecting the radiation

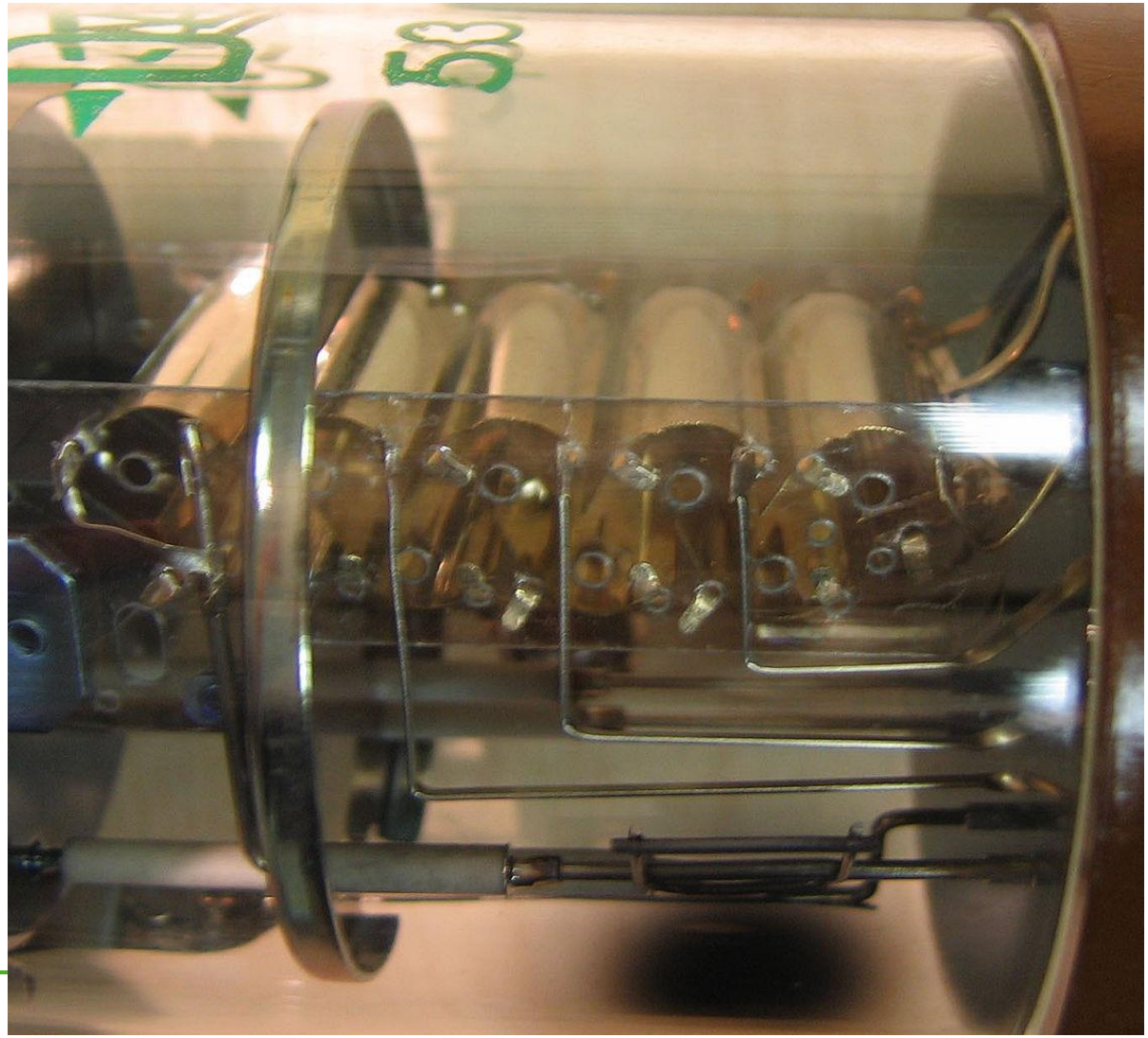
Scintillator with photomultiplier tube



The incoming gamma ray interacts with the scintillator to produce photons. These photons dislodge electrons from the photocathode in the photomultiplier tube. These electrons are accelerated to the first nearest dynode where they dislodge further electrons. This process continues down the tube, resulting in a cascade of electrons. Multiplication factor can be up to 10^8

Detecting the radiation

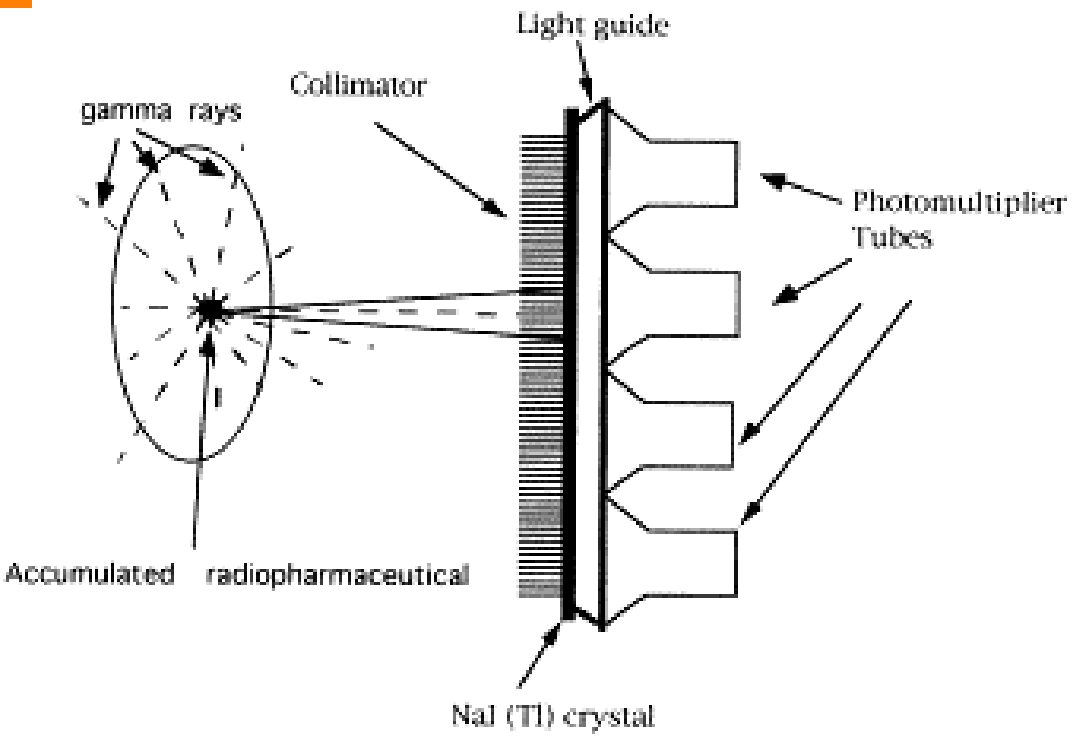
Scintillator with photomultiplier tube



The SPECT gamma camera (Anger camera)

Anger camera

The collimator prevents photons that are not approximately perpendicular to the collimator holes from interacting with the detector.

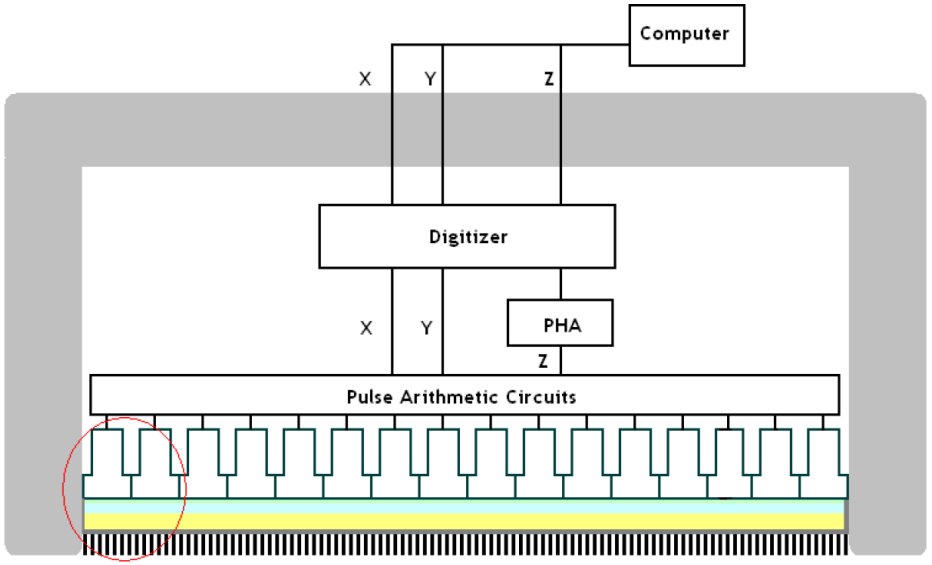


The field of view for the detector element behind each hole of the collimator is divergent, so that in a gamma camera, spatial resolution degrades as the distance to the distance to the object is increased. Collimators are usually made of lead.

Typical dimensions: holes 3mm, walls 1mm, depth 40mm.

The SPECT gamma camera (Anger camera)

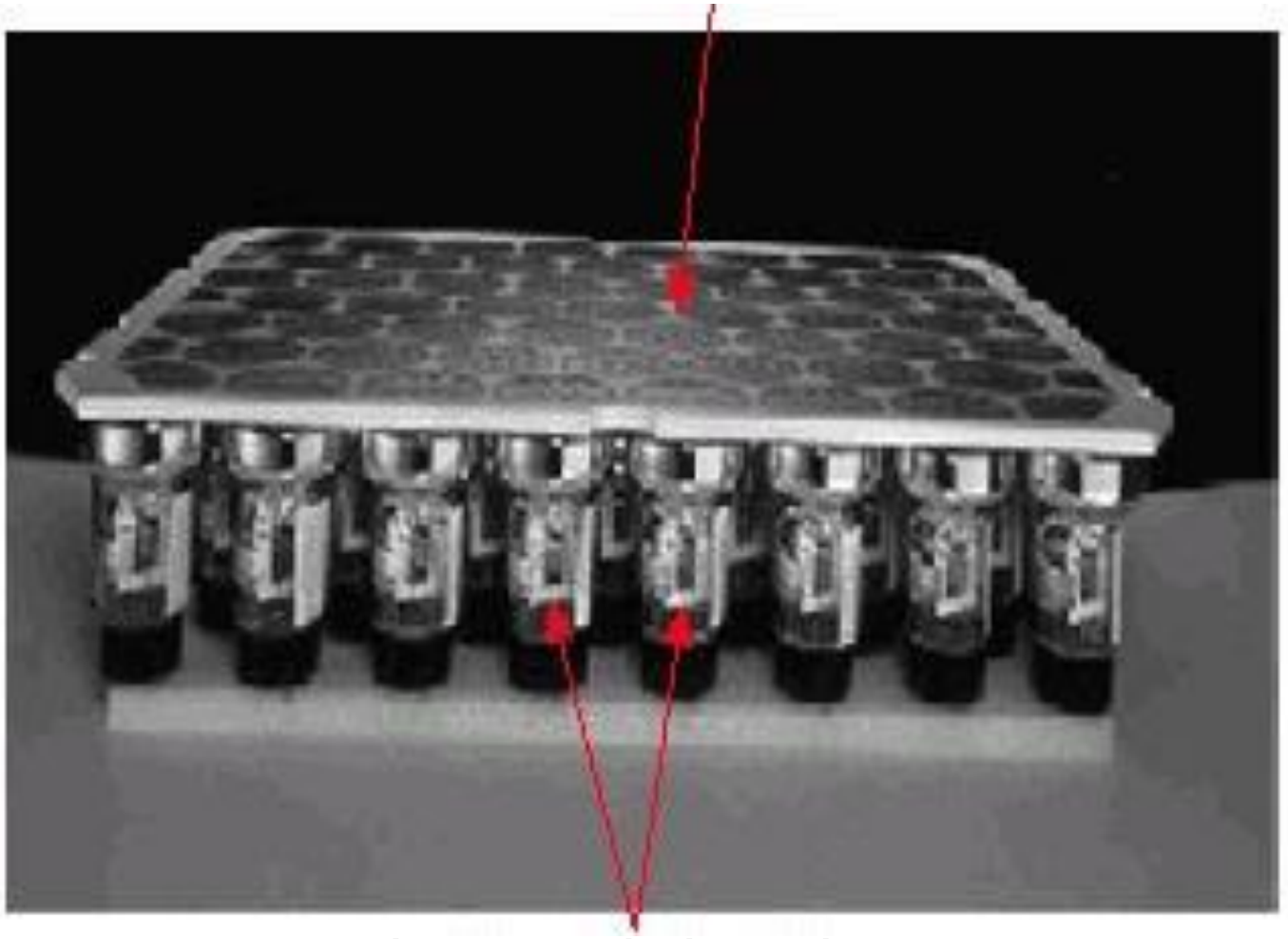
- The location of the interaction between the gamma ray and the crystal can be determined by processing the voltage signals from the photomultipliers; in simple terms, the location can be found by weighting the position of each photomultiplier tube by the strength of its signal, and then calculating a mean position from the weighted positions. between scattered and direct photons.



- The total sum of the voltages from each photomultiplier is proportional to the energy of the gamma ray interaction, thus allowing discrimination between different isotopes or between scattered and direct photons.

The SPECT gamma camera (collimator removed)

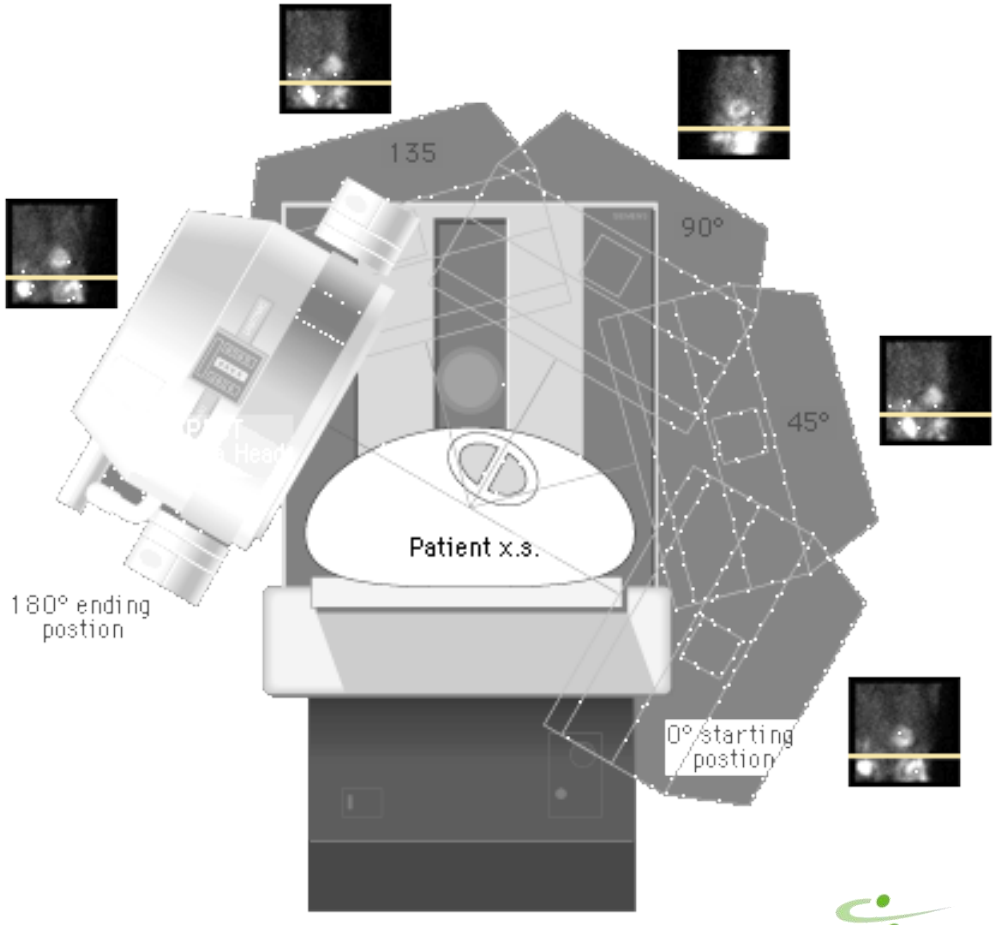
Scintillator



Photomultiplier tubes

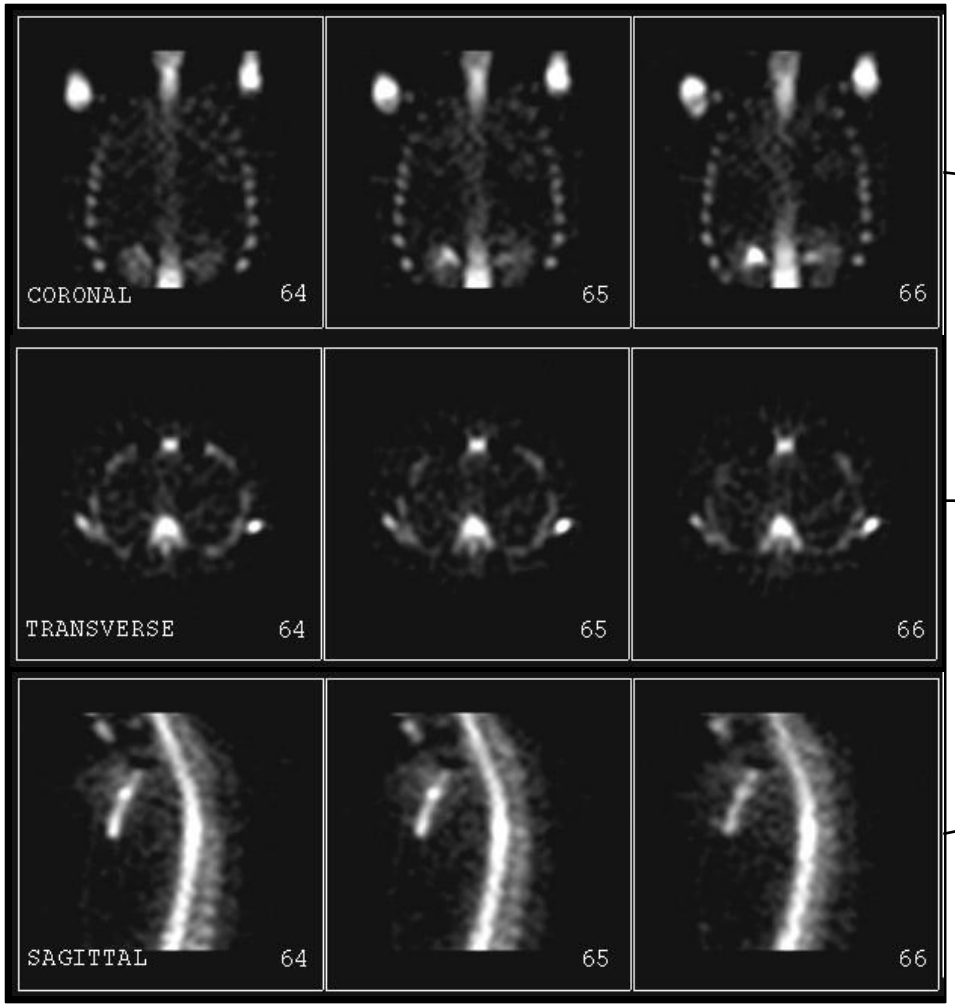
The SPECT gamma camera

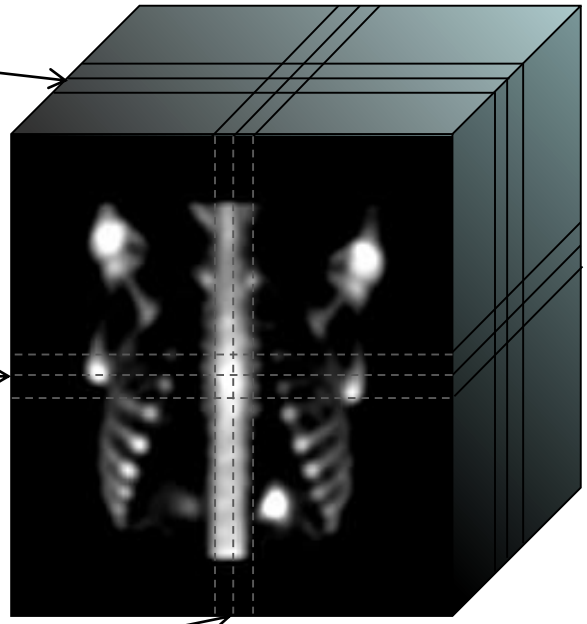
Projections from different angles are taken by rotating the camera around the patient



The SPECT gamma camera

3D Reconstruction





multipleperpendicular projections
=> mathematical deconvolution
=> 3D distribution

Nuclear reactions used for the production of medical isotopes

1. Nuclear Reactors $\Rightarrow$ neutrons
   - Neutron capture, as well as fission is performed in nuclear reactors (famous example: Mo-Tc generator)
2. Accelerators (often cyclotrons) $\Rightarrow$ charged particles
   - To bring a positive charged particle into a nucleus requires to overcome the Coulomb barrier and requires therefore the use of accelerators
   - The compound nucleus formed is unstable, and immediately cools off by emitting neutrons or alpha particles (more rarely protons)
   - Typical reactions are: (p, xn) , (p, α) , (d, xn)….

Nuclear reactions for Radio-Isotopes production

Radioisotope	Half-life	Reaction	Energy (MeV)
^{201}Tl	73.1 h	^{203}Tl (p,3n) => ^{201}Pb => ^{201}Tl	17~28
^{67}Ga	78.3 h	^{68}Zn (p,2n) => ^{67}Ga	12~28
^{111}In	67.4 h	^{112}Cd (p,2n) => ^{111}In	12~28
^{123}I	13.2 h	^{124}Te (p,2n) => ^{123}I	20~25
		^{124}Xe (p,2n) => ^{123}Cs => ^{123}I	20~30
		^{124}Xe (p,pn) => ^{123}I	
		^{127}I (p,5n) => ^{123}Xe => ^{123}I	45~68

A 30 MeV cyclotron can often do the job

“Traditional” nuclear medicine

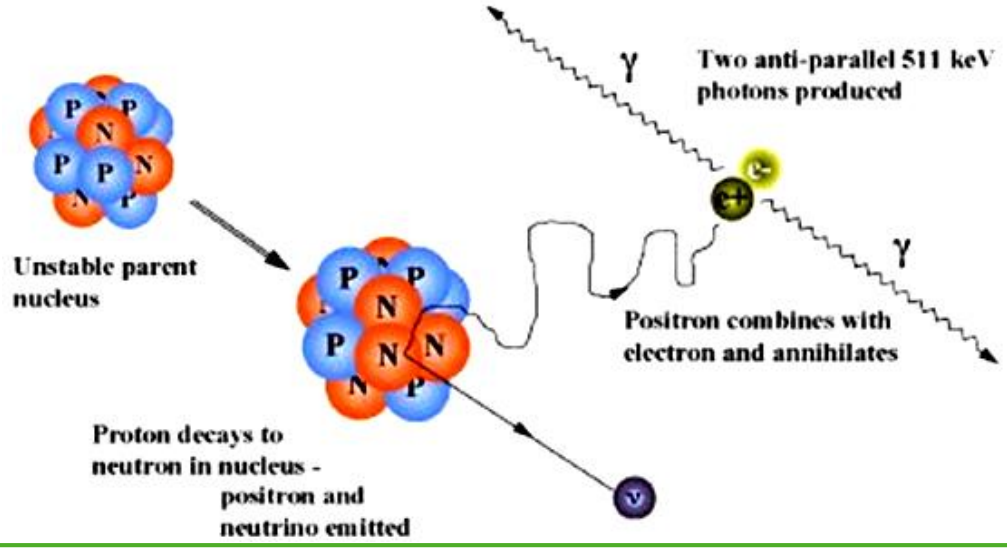
- Technetium 99m, the most commonly used radio-isotopes in nuclear medicine is produced in reactors.
  - 90% of diagnostic studies in hospitals is done with ^{99m}Tc !
- But a number of other, very important nuclear medicine radio-isotopes are produced with cyclotrons of higher energy.
  - ^{201}Tl (Cardiac studies).
  - ^{123}I (Thyroid, Various examinations).
- For these longer life isotopes, international distribution is possible.
- Large, very powerful cyclotrons are owned by radiopharmaceutical companies.

The Cyclone 30

The cyclotron used by all radiopharmaceutical producers

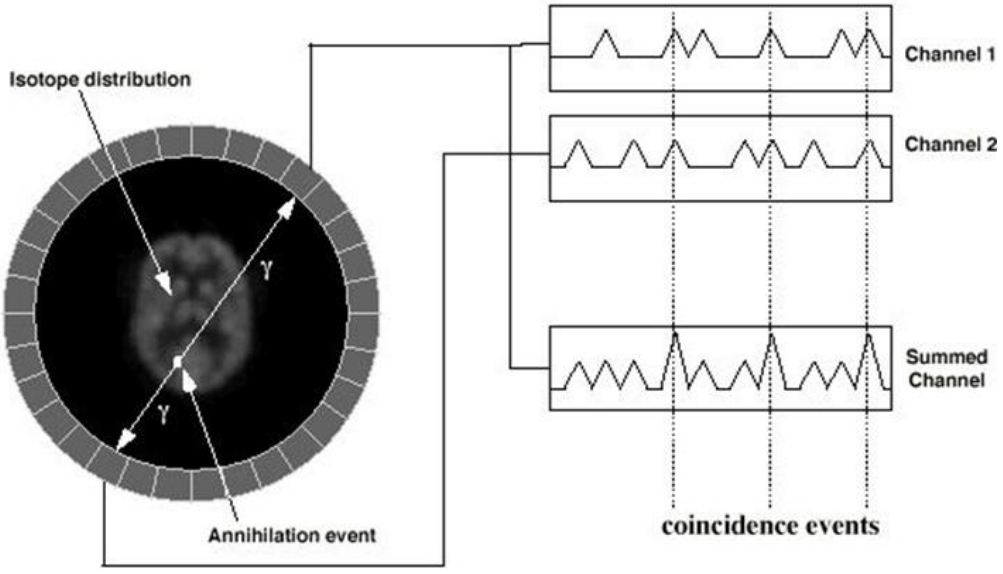
The positron (anti-electron)

- Proton rich nucleus decays: proton → positron + neutrino.
- Positron cools off by Coulomb interaction with electrons.
- At thermal energy: positron annihilates producing two anti-parallel 511keV photons. (within 4mrad due to momentum conservation)
- The finite positron range and the non-collinearity of the annihilation photons give rise to positional inaccuracy (±5mm).

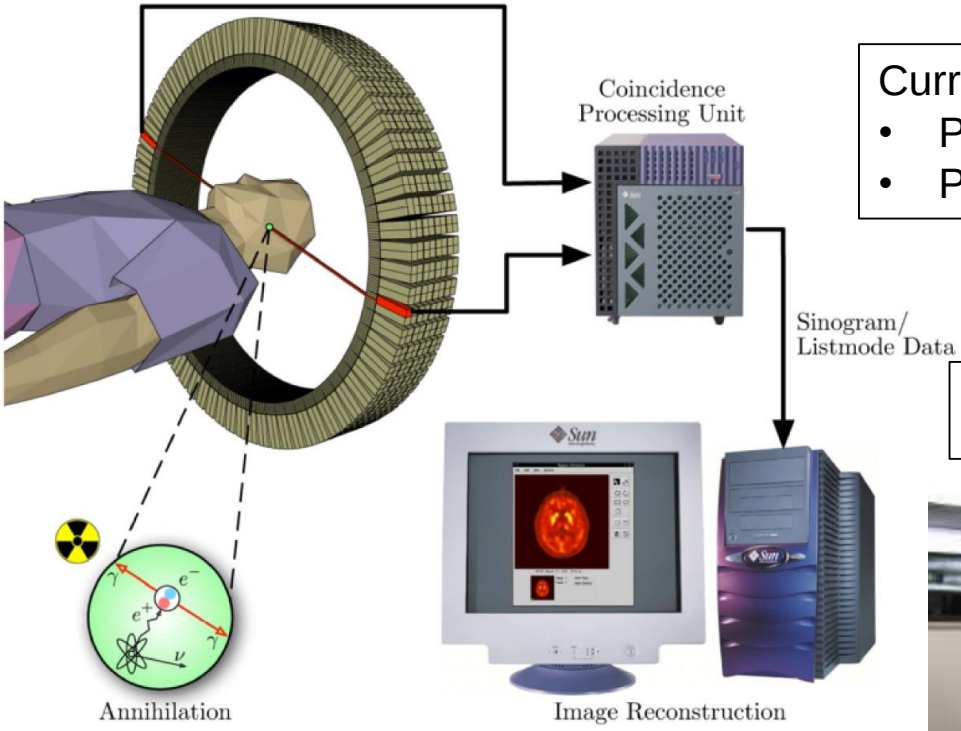


Coincidence detection in a PET scanner

In a PET camera, each detector generates a timed pulse when it registers an incident photon. These pulses are then combined in coincidence circuitry, and if the pulses fall within a short time-window, they are deemed to be coincident. A coincidence event is assigned to a line of response joining the two relevant detectors. In this way, positional information is gained from the detected radiation without the need for a physical collimator.



The PET scanner



Currently available are
- PET scanners integrated with CT: PET-CT
- PET scanners integrated with MRI: PET-MRI

PET scanner in a hospital

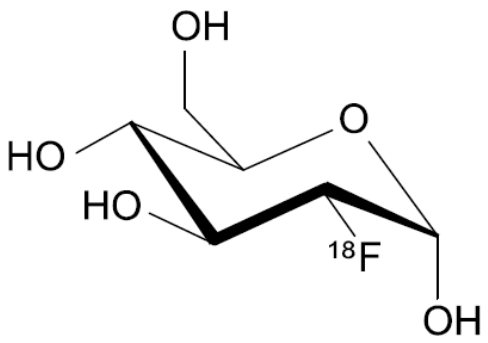
- Coincidents events are grouped into projected images (sinograms) and sorted by the angle of view
- Analogous to the projections obtained with Computed Tomography (CT) scanners
- 3D image re-construction is similar

Common positron emitting radioisotopes for PET

Radioisotope	Half-life (min)	Positron energy (MeV)	Reaction	Energy (MeV)
^{11}C	20.4	1.0	^{14}N (p,a)=> ^{11}C	5=>16
^{13}N	9.96	1.2	^{16}O (p,a)=> ^{13}N	8=>16
			^{12}C (d,n)=> ^{13}N	3=>8
^{15}O	2.07	1.7	^{15}N (p,n)=> ^{15}O	5=>14
			^{14}N (d,n)=> ^{15}O	3=>8
^{18}F	109.8	0.6	^{18}O (p,n)=> ^{18}F	5=>14

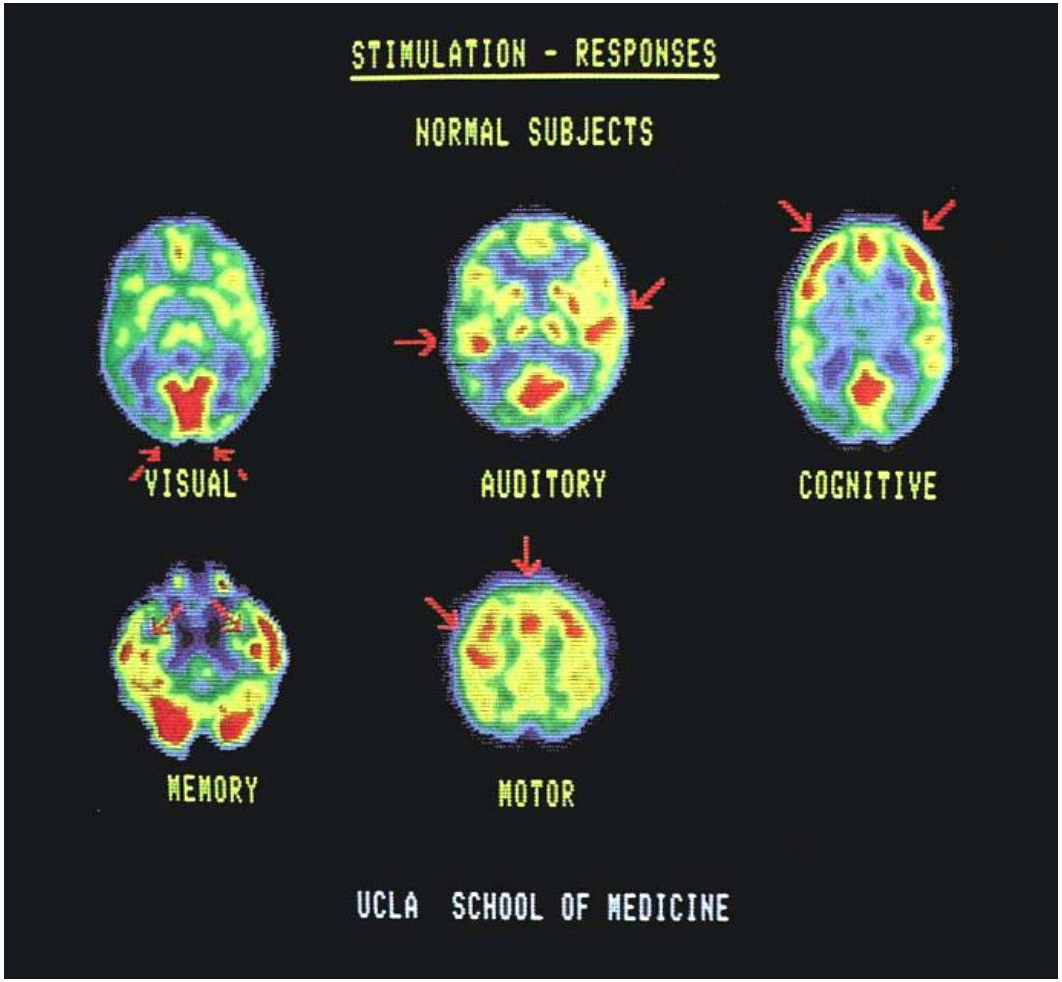
FDG = Fluoro-Deoxy-Glucose

- Most commonly made PET scan (90% of cases) is done with 18F-FDG (Fluoro-Deoxy-Glucose)
- Metabolic activity by virtue of glucose uptake in tissue
- This tracer is mainly used to explore the possibility of cancer metastasis



- In glucose one OH-group is replaced by a 18-F atom
- Both atoms have about the same size =>
- Bio-chemical behaviour almost not altered

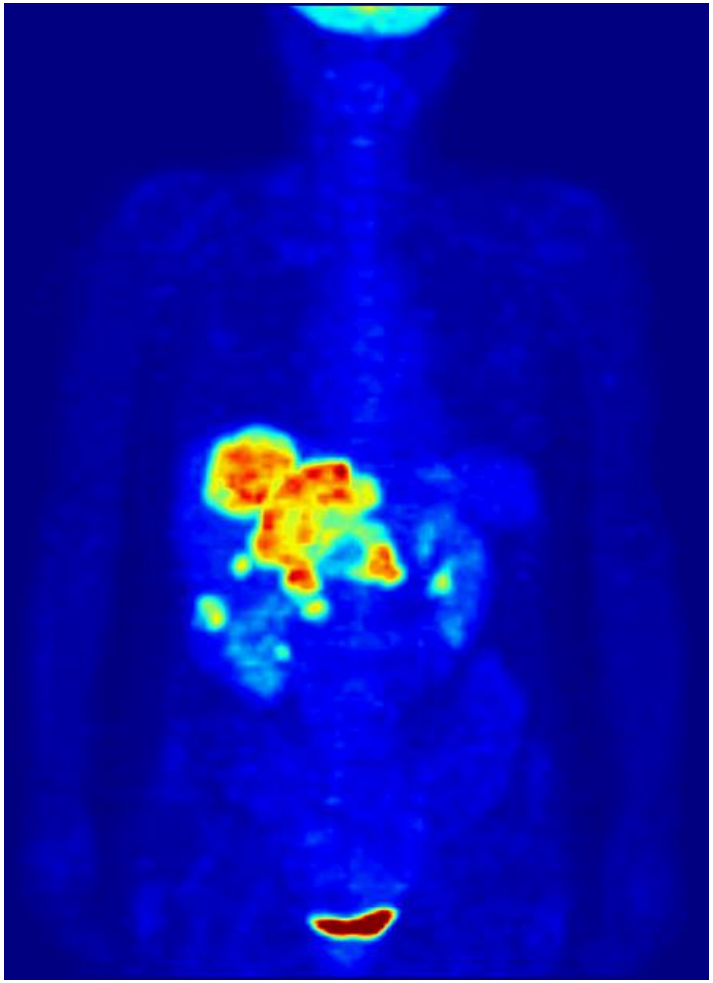
FDG was used to study brain function



PET also allowed for fundamental medical research

Iba Particle Therapy

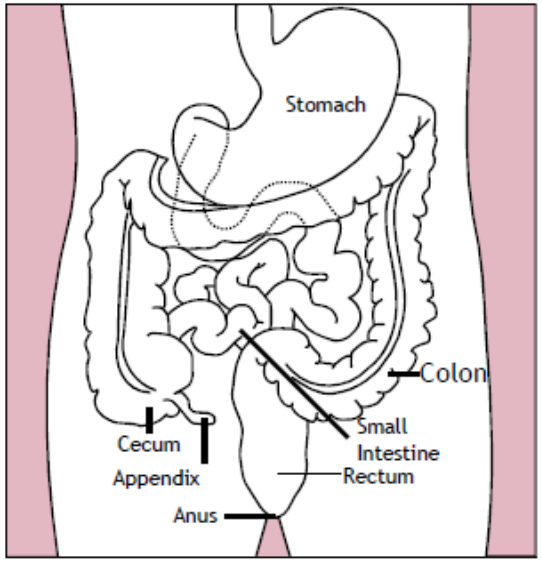
Cancer imaging with PET



^{18}F FDG

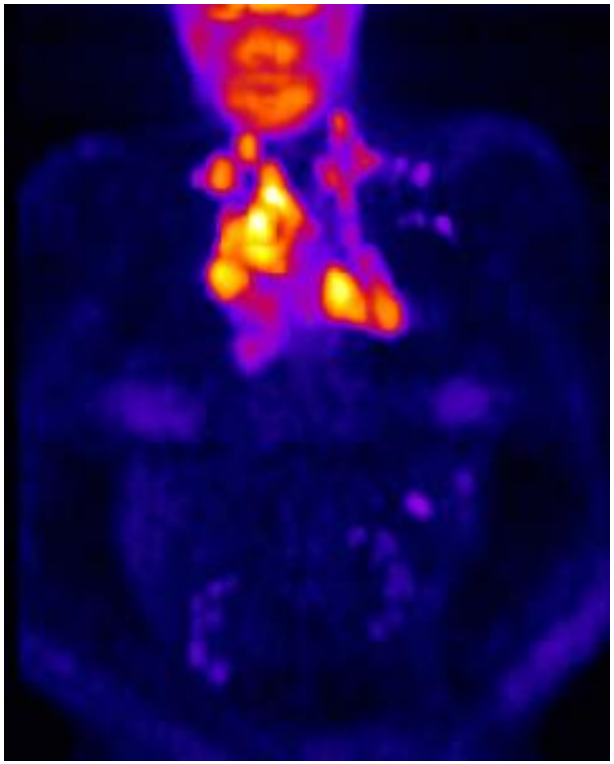
- 45 minute scan time

- normal heart, bladder.
- normal kidney, brain.
- colon tumor.
- metastatic liver lesions.

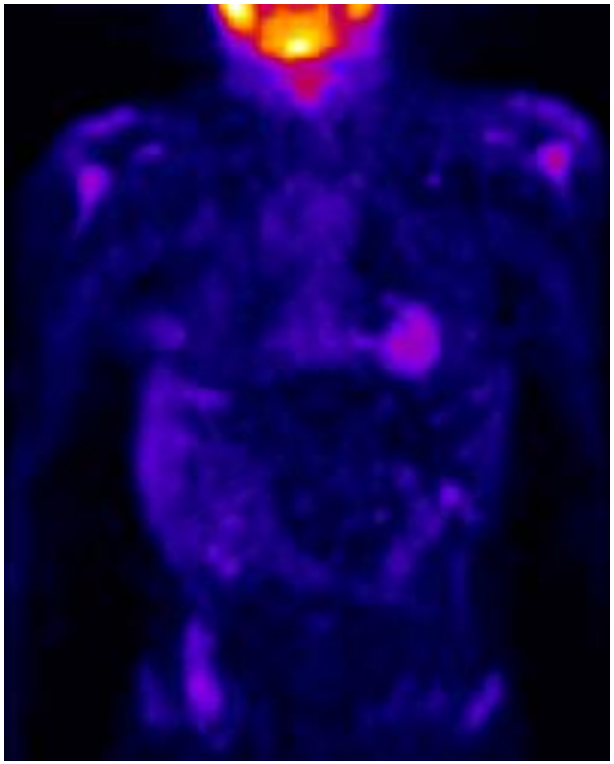


PET Scan - Response to therapy => cancer staging

31 yo female with newly diagnosed Non-Hodgkin‘s Lymphoma



Staging PET Scan



Post Chemotherapy

Production and Application of PET radio-isotopes

Cyclotron Beam

Target

Target materials

$H_2{}^{18}O$ enriched ($\rightarrow {}^{18}F$)

$H_2{}^{16}O$ natural ($\rightarrow {}^{13}N$)

^{14}N natural ($\rightarrow {}^{11}C$)

^{14}N natural ($\rightarrow {}^{15}O$)

Radioactive products

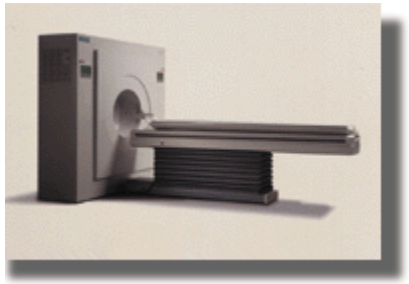
^{18}F, ^{13}N, ^{11}C, ^{15}O

Labeled compounds

^{18}FDG, $^{13}NH_3$, $^{11}CO_2$, $^{15}O_2$

Injection

PET Scan



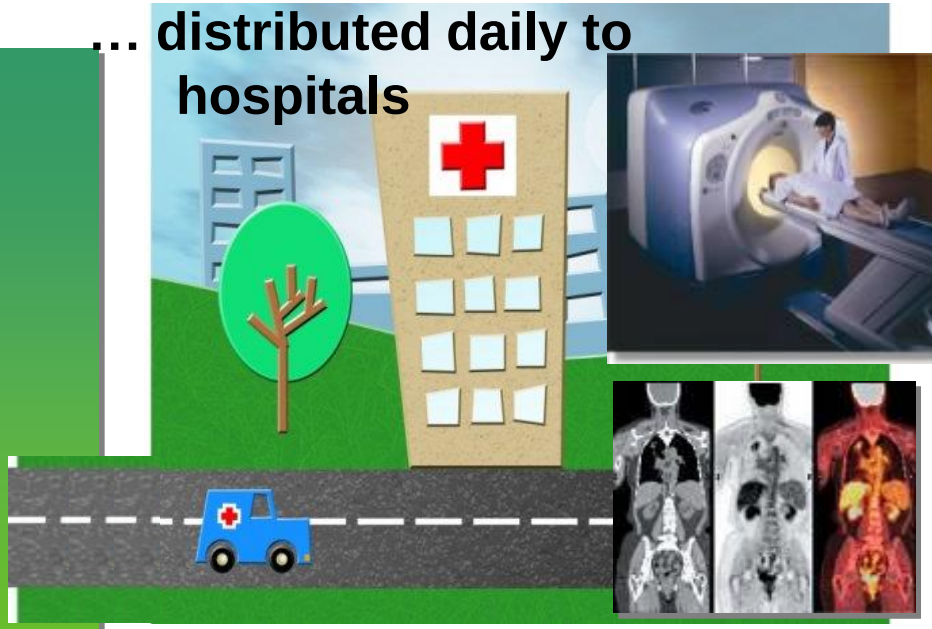
iba Particle Therapy

IBA Molecular

➢ **200 PET & SPECT Cyclotrons sold worldwide to Hospitals, R&D centers, Radiopharma. companies**

33 facilities Worldwide producing Radiopharmaceuticals…

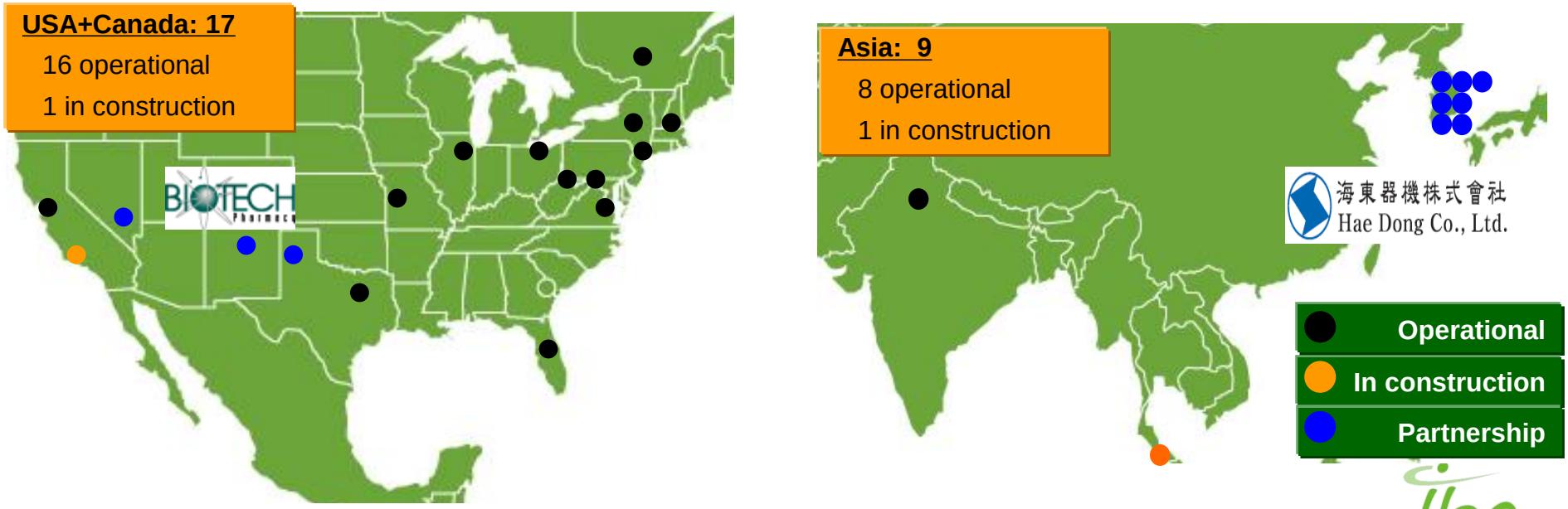
… distributed daily to hospitals



iba Particle Therapy

52 PET Radiopharmaceuticals Production Facilities

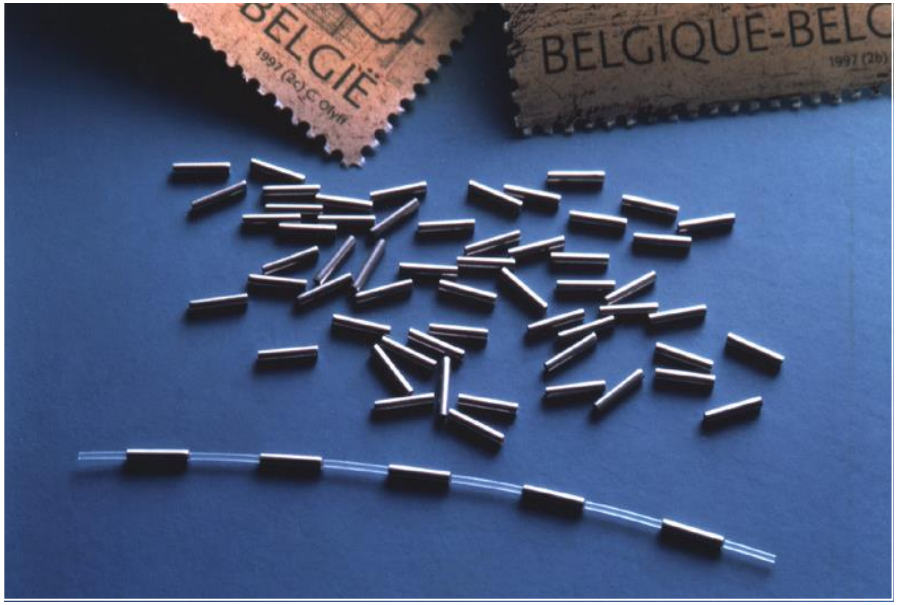
IBA realized many facilities and made alliances to enlarge network for distribution of future new drugs. These facilities were sold last year but presently IBA is still connected via share-holding



Part I-B: Cancer therapy with radio-isotopes

Systemic radio-isotope therapy

Brachytherapy



iba Particle Therapy

Three different types of radiation therapy

1. External beam radiation therapy (teletherapy)
   - Radiation source is external (like proton therapy)
2. Brachy therapy:
   - Sealed radioactive sources placed precisely in the tumor
   - Can use temporary or permanent placement of radioactive sources
3. Systemic radiation therapy
   - Radioistopes are given by infusion or by oral ingestion

Systemic radiation therapy

- When the cancer is not limited to a well defined, primary tumor, systemic therapies can be used.
- A form of targeted therapy. Targeting can be obtained by:
  - Isotope chemical property. Example: iodine => thyroid gland
  - Attach isotope to molecule or antibody that finds the target
    - Iodine labeled MIBG to treat neuroblastoma (brain tumor-children)
    - Hormone-bound Lutetium-177 or Yttrium-90 for neuroendocrine tumors
- Injection of Yttrium-90 radioactive glass microspheres
    - Liver tumors or metastatis. Sphere diameter about 30 μm
- Treatment of bone-metastasis with Stronium-89
- Alpha-particles or Auger electron emitting radio-isotope are often preferred because of short range of dose delivery.

Pairs of radioisotopes for systemic therapy

Diagnostic (PET) RI	Therapy RI
^{124}I	^{131}I
^{86}Y	^{90}Y
^{64}Cu	^{67}Cu
Etc!	

Problem of dosimetry and treatment planning: how to assess the radiation dose received by the tumor and by the healthy organs at risk.

- Biochemical properties of pairs are exactly the same
- PET-study allows quantitative diagnostics of distribution and uptake of the labelled molecule
- With this information the actual delivered dose of therapeutic treatment can be predicted

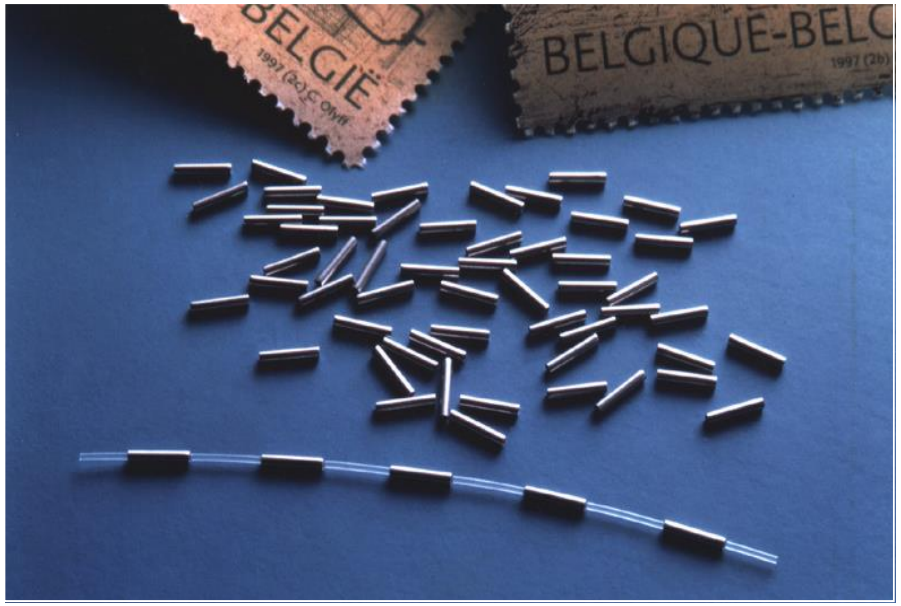
Brachy therapy

- Dose is delivered by placing the radiation source directly inside the area requiring treatment
- Commonly used for cervical (uterus), prostate, breast and skin cancer
- Irradiation affects only a very localized area => healthy tissues are spared
- Much higher doses can be delivered. For comparison:
  - Proton therapy: about 40 Gray
  - Prostate brachytherapy: about 100 to 150 Gray
- Brachytherapy can often be completed in less time
  - Reduce the possibility of recovery of cancer cells between treatment intervals

Brachytherapy

Local irradiation of tumors by sealed radioactive implants placed directly inside the cancerous tissue

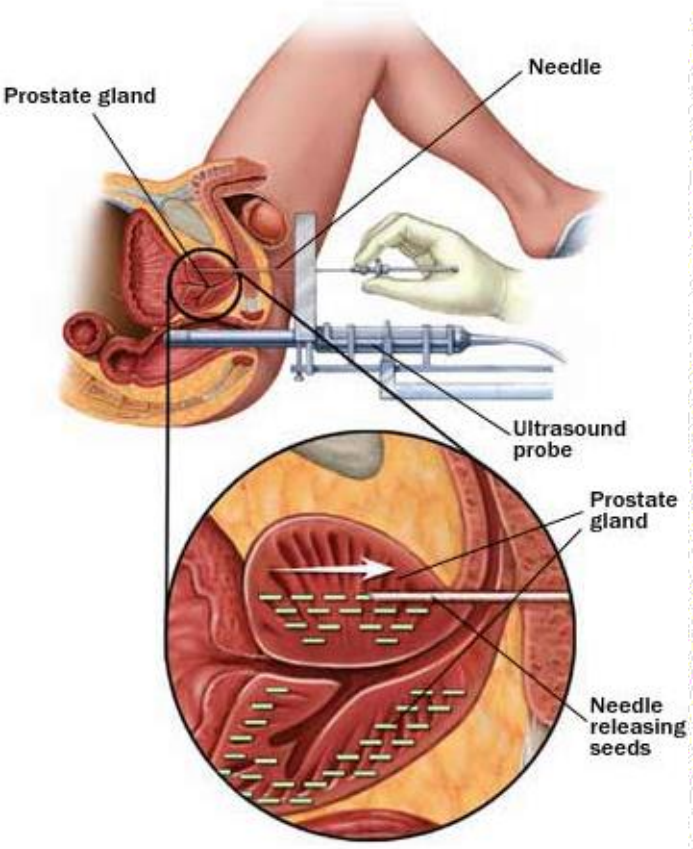
Theragenics

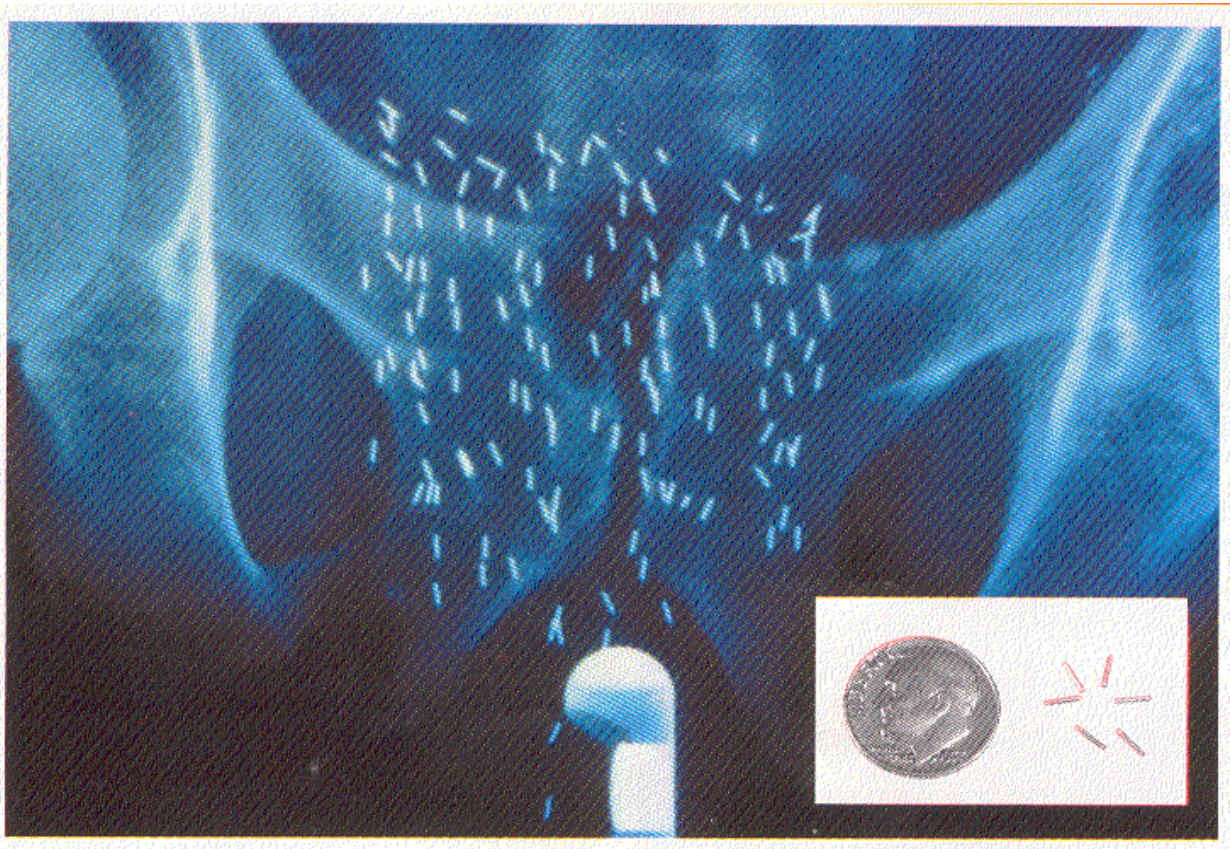


IBt

Prostate brachytherapy with Pd-103 or I-125

Seeds placed with 3D precission verified with ultrasound probe
Seeds are not harmfull and can stay in place after treatment





Pd-103 vs. I-125

	^{103}Pd	^{125}I
Half-life (days)	16.97	60
Photon energy (keV)	20~23	27~35
Half-value-layer (mm.Pb)	0.008	0.02
Total delivered dose (Gy)	115	160
Initial dose rate (cGy/hr)	20~24	6~10