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Medical Applications of Nuclear Radiation and Isotopes

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Lecture delivered at the KIVI-NNS Symposium entitled, " 75 Years of Nuclear Reactors: A Chain Reaction of Applications", held at Science Centre, TU Delft, The Netherlands, 3 November 2017

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Outline

- **Introduction: Historical and general**
- **Radiation therapy**
- **Internal use of radionuclides**
  - **- Diagnosis**
  - **- Therapy**
- **Research oriented radionuclides**
- **New directions in radionuclide applications**
- **Conclusions**

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Introduction

Radioactivity in Medicine

Historical Development

1920s	**Biological experiments with natural radioactivity** - use of ThB(^{212}Pb) to study movement of Pb in plants (1923) - use of RaE(^{201}Bi) to study metabolism of Bi in rabbits (1924) (G. v. Hevesy)
1930s	**Biological experiments with artificial radioactivity** • First use of Ra/Be neutrons to induce radioactivity (1934) (E. Fermi) - Production of ^{32}P via ^{32}S(n,p)-reaction (1935) *Studies on phosphorus metabolism in rats (^{32}P)* (O. Chievitz, G. v. Hevesy) ***(Tracer principle)*** • Development of cyclotron (1932) (E.O. Lawrence) - Cyclotron production of ^{11}C, ^{99m}Tc, ^{131}I (late 1930s) • Discovery of fission (1938) (O. Hahn and F. Straßmann)

Radioactivity in Medicine

Historical Development (Cont´d)

1940s	• Construction of first nuclear reactor (1942) (E. Fermi) - Medical application of cyclotron radionuclides *Use of ^{131}I in therapy (1939)* (J.G. Hamilton, M.H. Soley) *Inhalation studies using ^{11}CO (1945)* (C.A. Tobias, J.H. Lawrence, F. Roughton)
1946 onwards	Availability of many long-lived reactor produced radionuclides, e.g. ^{3}H, ^{14}C, ^{32}P, ^{60}Co, $^{125,131}I$ for studies in biochemistry, pharmacology, therapy
1960 onwards	Production of large number of short-lived radionuclides using cyclotrons for in-vivo studies
Today	• ***About 400 research reactors and 500 cyclotrons partly used for radionuclide production.*** • ***Radioisotope applications as big an enterprise as nuclear energy production.***

Radioactivity in Medicine

General

Diagnostic investigations

- Perfusion rates
- Metabolic turnover rates
  - oxygen - glucose - fatty acids - amino acids
- Receptor occupancy
- Immuno reactions

Radiation dose should be minimum.

Radiotherapy

- External radiation therapy (with γ, n, p or heavy ion)
- Internal radionuclide therapy (using highly-ionising radiation)

Selective specific dose needs to be applied.

External Radiation Therapy

Types of Therapy

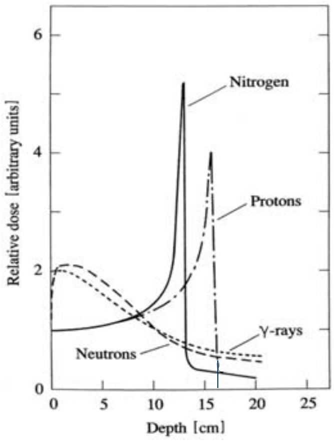
- ***Photon therapy***: use of ^{60}Co or linear accelerator (*low-LET radiation*) — **most common**
- ***Slow neutron capture therapy*** (use of reactor neutrons) — **seldom**
- ***Fast neutron therapy***: accelerator with E_p or E_d above 50 MeV (*high-LET radiation*) — **being abandoned**
- ***Proton beam therapy***: accelerator with E_p = 70 - 250 MeV (*treatment of deep-lying, tumours*) — **increasing significance**
- ***Heavy-ion beam therapy*** (*rather specialized)* — ***limited application***

A large number of patients worldwide undergo photon therapy.

Charged-Particle Therapy

• Charged particles used: p, α, ^{12}C, ^{14}N, etc.

Depth-dose relationship



Kraft et al., Advances in Hadrontherapy, Elsevier, 1997

- Charged-particle dose increases with the penetration depth, reaching a maximum in the Bragg peak area.
- Major advantage of charged-particle therapy is the capability to treat deep-lying tumours, close to critical structures.
- Heavy-ion therapy is specialized; proton therapy is more common.

Patient care studies are done still mostly through photon therapy.

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Internal Use of Radionuclides in Medicine

Criteria

- **Physical properties**
  - detection efficiency
  - radiation dose
- **Biochemical properties**
  - selectivity
  - suitable kinetics

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Radioactive Tracers in Medicine

Radiotracer is a radionuclide in a well defined chemical form, e.g. $^{22}NaCl$, [^{99m}Tc] labelled compound

Problems

- Small amount of material (< 10^{-10} g)
- High level of radioactivity
- Short half-life

Advantages

- Dynamic studies from outside of the body
- Biological equilibrium undisturbed (no toxicity effect) (organ imaging at real molecular level)
- Study of physiological function

Fast, efficient, remotely controlled working methods mandatory

Radionuclides Commonly used in Nuclear Medicine

Diagnostic Radionuclides

- **For SPECT**
  γ-emitters (100 – 250 keV)
  ^{99m}Tc, ^{123}I, ^{201}Tl
  (used worldwide)

- **For PET**
  β^+ emitters
  ^{11}C, ^{13}N, ^{15}O, ^{18}F,
  ^{68}Ge (^{68}Ga), ^{82}Sr (^{82}Rb)
  (fast developing technology)

Therapeutic Radionuclides (in-vivo)

- β^--emitters (^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu)
- α-emitter (^{211}At, ^{223}Ra)
- Auger electron emitters (^{111}In, ^{125}I)
- X-ray emitter (^{103}Pd)

(increasing significance)

Production methods are generally well developed.

Commonly Used SPECT Radiopharmaceuticals

Radiopharmaceuticals	Function
^{99m}Tc – HMPAO	Brain blood flow
^{99m}Tc – ECD	Brain blood flow
^{99m}Tc – sestamibi	Heart blood flow
^{99m}Tc – tetrofosmin	Heart blood flow
^{99m}Tc – DMSA	Renal function
^{99m}Tc – TRODAT	Dopamin–transporter
^{111}In – DTPA-D-Phe-1-octreotide	Somatostatin receptor ligand
^{111}In – pentetreotide	Somatostatin receptor ligand
^{123}I – IMP	Brain blood flow
^{123}I – IBZM	Dopamin2–receptor–ligand
^{123}I – iomazenil	Benzodiazepine receptor ligand
^{123}I – epidepride	Dopamin2–receptor–ligand
^{123}I – β – CIT	Dopamin–transporter
$^{201}TlCl$	Heart blood flow

Security of Supply of $^{99}Mo/^{99m}Tc$

Observations and Comments

- Due to ageing reactors, production via $^{235}U(n,f)$-route in jeopardy.
- Enhanced use of accelerators suggested (Ruth, 2009).
- Several processes under consideration: (p,f), (γ,f), (p,xn), (γ,n)
- All routes evaluated ***(Van der Marck, 2010; Qaim, 2014; Wolterbeek, 2014)***
- Direct production of ^{99m}Tc via $^{100}Mo(p,2n)$-reaction is promising. Considerable development work underway. However,
  - large effort • low yield • low specific activity

This route may solve local problem but not global shortage.

Potentially promising approaches

- Development of low specific activity ^{99}Mo generators
- Fission of ^{nat}U with spallation type neutrons

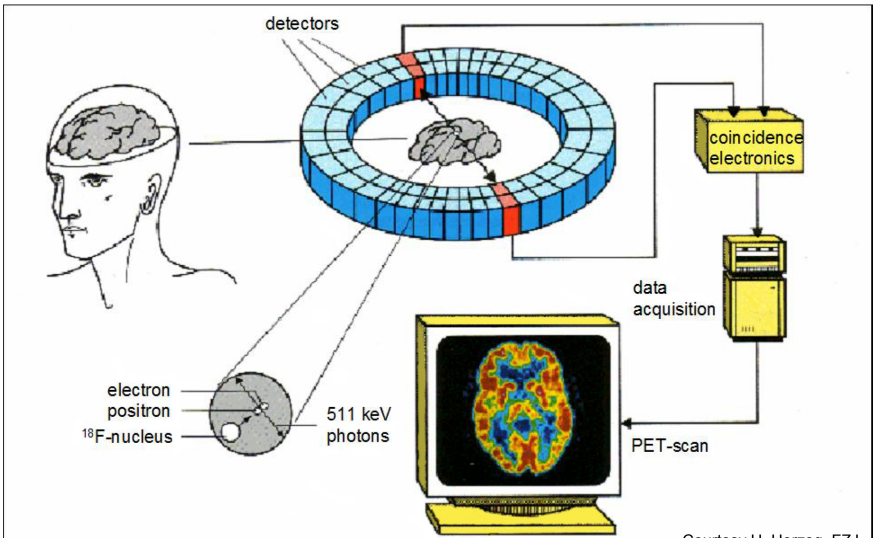
Security of Supply of ^{99}Mo/^{99m}Tc (contd.)

Analysis of present status

- ***NEA-High Level Group on the Security of Supply of Medical Isotopes (Paris)***
  Analysis of supply/demand situation (2017) indicates
  - more effective use of existing facilities
  - some new emerging facilities (Australia, China)
  - adequate level of supply capacity till 2022

Nonetheless, continuous development efforts are needed for security of supply of this very important radionuclide also in the future.

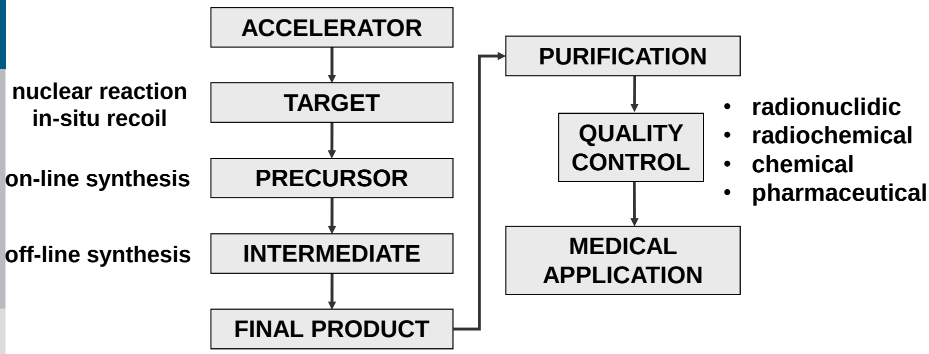
Positron Emission Tomography (PET)



Courtesy H. Herzog, FZJ

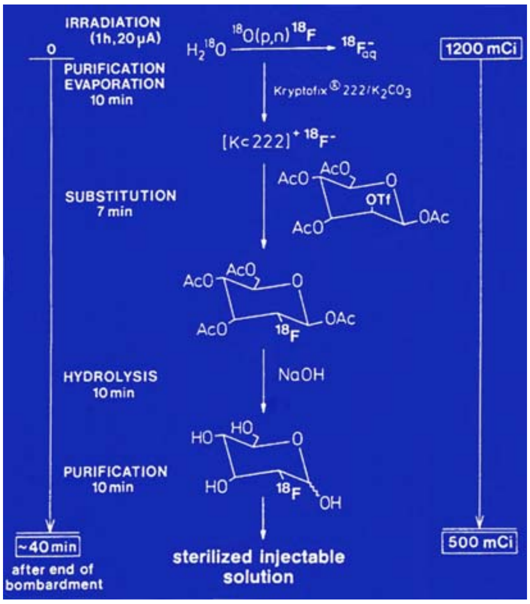
Quantitative imaging

Flow Sheet of Production of Short-lived PET Radiopharmaceuticals



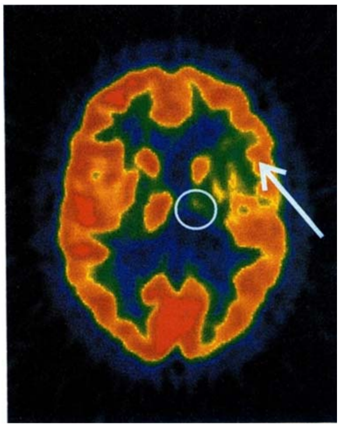
Fast, automated methods of production are absolutely necessary

Synthesis of 2-[^{18}F]FDG



Hamacher et al., JNM **27**, 235 (1986)

PET Imaging of Brain of a Stroke Patient administered with ^{18}FDG



Decreased uptake of ^{18}FDG in infarct region (circle) as well as in the brain skin (arrow)

An important information for the neurologist for therapy planning

Recent Progress in Medical Application of Radiotracers

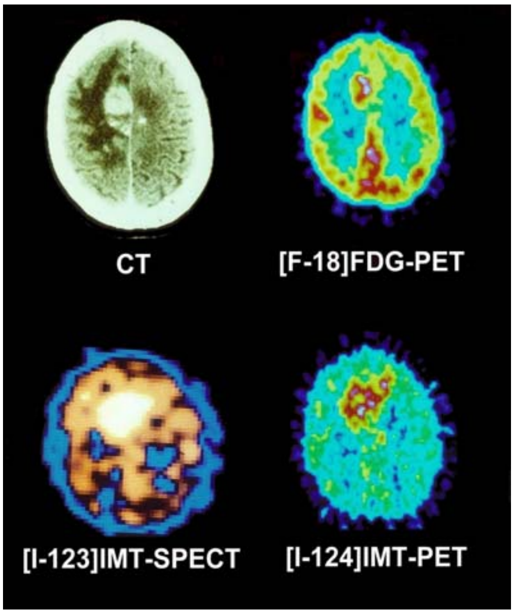
- New efficient automated production methods
- High intensity dedicated accelerators
- Fast labelling, separation and purification methods (GC, HPLC)
- High resolution emission tomographs (SPECT, PET)

For routine PET applications, complete technology *(cyclotron, radiosynthesis apparatus, tomograph)* is commercially available.

Major applications in neurology, cardiology and oncology.

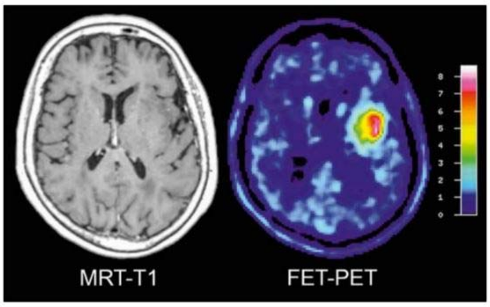
Multimode Imaging

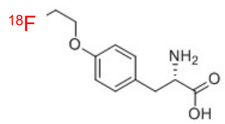
Brain Tumour Mapping



Langen et al., JNM **31**, 281 (1990).

Diagnosis of Brain Tumour





2-[^{18}F]Fluoroethyl-L-tyrosine

Methodology established at FZ Jülich

Pauleit et al., Brain **128**, 678 (2005).

Amino acids are more suited for diagnosis of brain tumour.

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Internal Radionuclide Therapy

- **Brachytherapy**
  (insertion of sealed sources near the tumour)
  Examples: ^{192}Ir as wire
  ^{103}Pd and ^{125}I as seeds
- **Administration in cavities**
  (for pain palliation)
  Examples: ^{32}P colloid for arthritis
  ^{90}Y, ^{186}Re and ^{188}Re complexes for joint inflammation
- **Metabolic therapy**
  (incorporation of radionuclide via a biochemical path)
  Examples: ^{131}I for thyroid cancer
  ^{89}Sr, ^{186}Re and ^{153}Sm are bone seekers
- **Radioimmunotherapy**
  (administration of a radionuclide chemically conjugated to antibodies)
  Examples: low-energy high-LET value radionuclides

Therapeutic radionuclides are generally produced in nuclear reactors, but use of accelerators is increasing.

Summary of Present Status of Use of Radionuclides in Medicine

Diagnosis

- 40 million diagnostic investigations/year using ^{99m}Tc and SPECT
- 5 million patients/year investigated using [^{18}F]FDG and PET

Therapy

- Several million treatments/year via external radiation therapy
- A sizeable number of patients/year undergo internal radionuclide therapy, e.g. thyroid cancer with ^{131}I.

Research Oriented Radionuclides

- Non-standard positron emitters
  - to study slow metabolic processes
  - to quantify targeted therapy
- Novel low-range highly ionising radiation emitters for internal radiotherapy
  - for targeted therapy

Continuous development work is underway.

Emphasis is on metal radionuclides.

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Non-standard Positron Emitters for Medical Applications Produced via Low-energy Reactions

Qaim, RCA **99**, 611 (2011)

Nuclide	Major production route	Energy range [MeV]	Application
^{52}Mn (5.6 d)	^{52}Cr(p,n)	14 → 9	Multimode imaging (PET + MRI)
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 → 8	Tumour localisation; immuno-PET
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	^{82}Kr(p,n)	14 → 10	Cardiology
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Theranostic approach
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 → 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 → 8	Tumour targeting; dosimetry

Novel Radionuclides for Therapy

Examples :

^{67}Cu ($T_{½}$ = 2.6 d; E_{β^-} = 577 keV)

^{186}Re ($T_{½}$ = 3.7 d; E_{β^-} = 1070 keV)

^{225}Ac ($T_{½}$ = 10.0 d; E_{α} = 5830 keV)

^{193m}Pt ($T_{½}$ = 4.3 d; Auger electrons)

Applications in targeted therapy.

For production, large-sized multiple particle accelerators are needed.

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Targeted α-Radiation Therapy

Example: ^{213}Bi ($T_{½}$ = 46 min; E_{α} = 5900 keV) from ^{225}Ac generator

Prostate-specific membrane antigen radioligand therapy (PSMA-RLT)

- ^{177}Lu-PSMA successfully applied, but some patients show radioresistance to β^- radiation
- **New approach**: ^{213}Bi-PSMA

M. Sathekge et al., EJNMMI **44**, 1099 (2017)

^{68}Ga-PSMA (PET-CT scan)
Pre-therapy

^{68}Ga-PSMA (PET-CT scan)
Post-therapy
(11 months after ^{213}Bi-PSMA)

Targeted α-radiation therapy appears promising.

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New Directions in Radionuclide Applications

- **Theranostic approach**

  (combination of PET/Therapy)

  $^{64}Cu/^{67}Cu$, $^{86}Y/^{90}Y$, etc.

- **Multimode imaging**

  (combination of PET/CT and PET/MRI)

- **Radioactive nanoparticles**

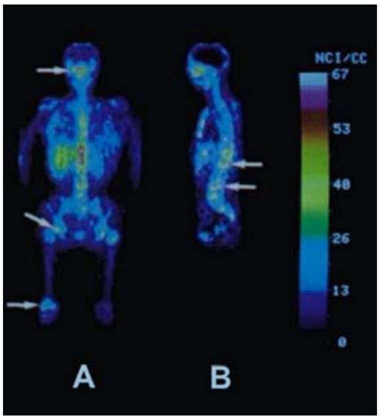
  Possible improvement in delivery of radionuclide to tumour

Continuous radionuclide research is underway.

Theranostic Approach

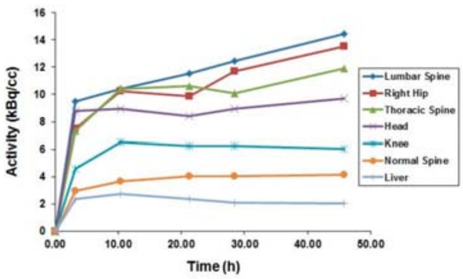
- Addition of β^+ emitting ^{86}Y analogue to the therapy nuclide ^{90}Y
- Uptake of [^{86}Y]Citrate determined using PET

Herzog et al., JNM **34**, 2222 (1993).



(A) Anterior (B) Sagittal

Arrows show metastases



Accurate dose calculation possible

Rösch, Herzog, Qaim, Pharmaceuticals **10**, 56 (2017)

Conclusions

- Nuclear reactors and accelerators have revolutionised medicine.
- Radiotracer and imaging technologies are well established. Patient care studies are routinely performed (diagnosis and therapy).
- Biological functions can be investigated dynamically at real molecular level (study of disease development at early stage).
- Combination of radioactivity with other emerging technologies is opening up new vistas in medical research.
- Development work involves nuclear, chemical and biological research as well as technological innovation; interdisciplinary cooperation is vital.

Interesting science and human-health related technology; future perspectives are bright.

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